Title Page

Protocol Title:		A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer
Short Protocol Title:		A Phase 1b Study of AMG 160 in Subjects with Non-Small Cell Lung Cancer
Protocol Number:		20180273
Investigational Product:		AMG 160
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:	To be determined
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Data Elements Standards Version:	7.0

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer, dated **25 March 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

_____
Title and Role of Investigator

_____
Institution Name

_____
Address and Telephone Number of Institution

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer
Short Protocol Title: A Phase 1b Study of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Study Phase: Phase 1b

Indication: Non-Small Cell Lung Cancer (NSCLC)

Rationale

AMG 160 (acapatamab) is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®) molecule designed to redirect T effector cells to lyse prostate-specific membrane antigen (PSMA)-expressing cells, with a single chain fragment crystallizable (scFc) moiety for half-life extension. Immunohistochemistry (IHC) studies demonstrate that PSMA is expressed on the surface of endothelial cells within the tumor vasculature of many tumor types, including non-small cell lung cancer (NSCLC), and is not expressed on normal vasculature (Schmidt et al, 2017; Wang et al, 2015; Chang, et. al 1999). PSMA-targeted radioligands have also shown the potential to identify PSMA-positive lung cancer (Shetty et al, 2016; Milowsky et al, 2007). Previous studies have shown that angiogenesis inhibitors can inhibit tumor growth by blocking new blood vessel formation and depriving the tumor of critical nutrients. More recent studies suggest anti-angiogenesis treatments may enhance immune responses by altering the tumor microenvironment (Fukumura et al, 2018). Given the selective expression of PSMA on the neovasculature in lung tumors, AMG 160 may lead to anti-tumor activity by disrupting the tumor neovasculature and by facilitating immune cell infiltration. This is a phase 1b study to assess safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of AMG 160 in adult subjects with NSCLC.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 160 • To evaluate the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D)	• Dose-limiting toxicities (DLT) • Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs and clinical laboratory tests
Secondary	
• To 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, and half-life ($t_{1/2}$)
• To evaluate the preliminary anti-tumor activity of AMG 160	• Objective response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Overall Survival • Progression-free survival (radiographic [rPFS], clinical) • Time to response • Time to progression (radiographic, clinical) • Duration of response • Time to subsequent therapy

Overall Design

This is an open label phase 1b study evaluating the safety, tolerability, PK, and efficacy of AMG 160 monotherapy in subjects with relapsed, refractory non small cell lung cancer (NSCLC).

AMG 160 monotherapy will be administered as a short-term IV infusion every 2 weeks after the target dose is reached in a 28-day cycle in subjects with relapsed, refractory NSCLC. [redacted]. The starting dose of AMG 160 will be 1 dose

level below the recommended phase 2 dose (RP2D) as determined in the ongoing first in human (FIH) study of AMG 160 in subjects with metastatic castration-resistant prostate cancer (mCRPC; 20180101). A safety cohort of 2 to 4 subjects will initially be enrolled to assess the tolerability of AMG 160. If the dose is tolerated (based on target dose-limiting toxicity [DLT] rate < 30%), the dose level will be increased to the RP2D (or RP2D+1) identified in Study 20180101. Alternative dosing schedules, including further dose escalation may be explored based on emerging safety and PK data. Additional subjects (up to 20) may be enrolled at 1 or more monotherapy dose levels that have been shown to be safe and tolerable (defined as backfill enrollment). This backfill enrollment may be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and [redacted] of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

Number of Subjects

Approximately 10 subjects will initially be enrolled in Part 1 (dose exploration) of the study. Additional subjects (up to 20) 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 may be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and [redacted] of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD. If 1 or more objective responses (OR) are observed (per modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) in Part 1, additional subjects (up to 40) will be enrolled in Part 2 (dose expansion) of the study.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years of age) with relapsed/refractory (RR) NSCLC with a histological or cytological diagnosis of non-squamous NSCLC (stage 4 or recurrent) are eligible to participate in Part 1. In Part 2, adult subjects with RR NSCLC with a histological or cytological diagnosis of NSCLC (stage 4 or recurrent) are eligible to participate. Subjects without a driver mutation are required to have had disease progression following at least 1 line of prior chemotherapy and anti-programmed cell death protein 1 (PD1)/programmed death-ligand 1 (PDL1) therapy to be eligible. Subjects with a driver mutation (epidermal growth factor receptor [EGFR] mutation [exon 19 deletion, L858R point mutation or T790M], BRAF V600E mutation, RET gene fusion, anaplastic lymphoma kinase [ALK] gene rearrangement, MET exon 14 skipping mutation or neurotrophic tropomyosin-related kinase [NTRK] gene fusion) must experience disease progression on at least 1 targeted therapeutic agent to be eligible.

Subjects are required to have disease with detectable PSMA assessed by ^{68}Gallium (^{68}Ga)-PSMA-11 positron emission tomography (PET)/computed tomography (CT) imaging [redacted] to be eligible (see inclusion criteria for full details). Eligible subjects must have measurable disease per modified RECIST 1.1 criteria, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, and adequate organ function (see inclusion criterion 112).

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Investigational product (AMG 160) will be administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks after the target dose is reached. The starting dose and dosing schedule of AMG 160 [redacted] will be 1 dose level below the RP2D from the ongoing FIH monotherapy study (20180101) in subjects with mCRPC.

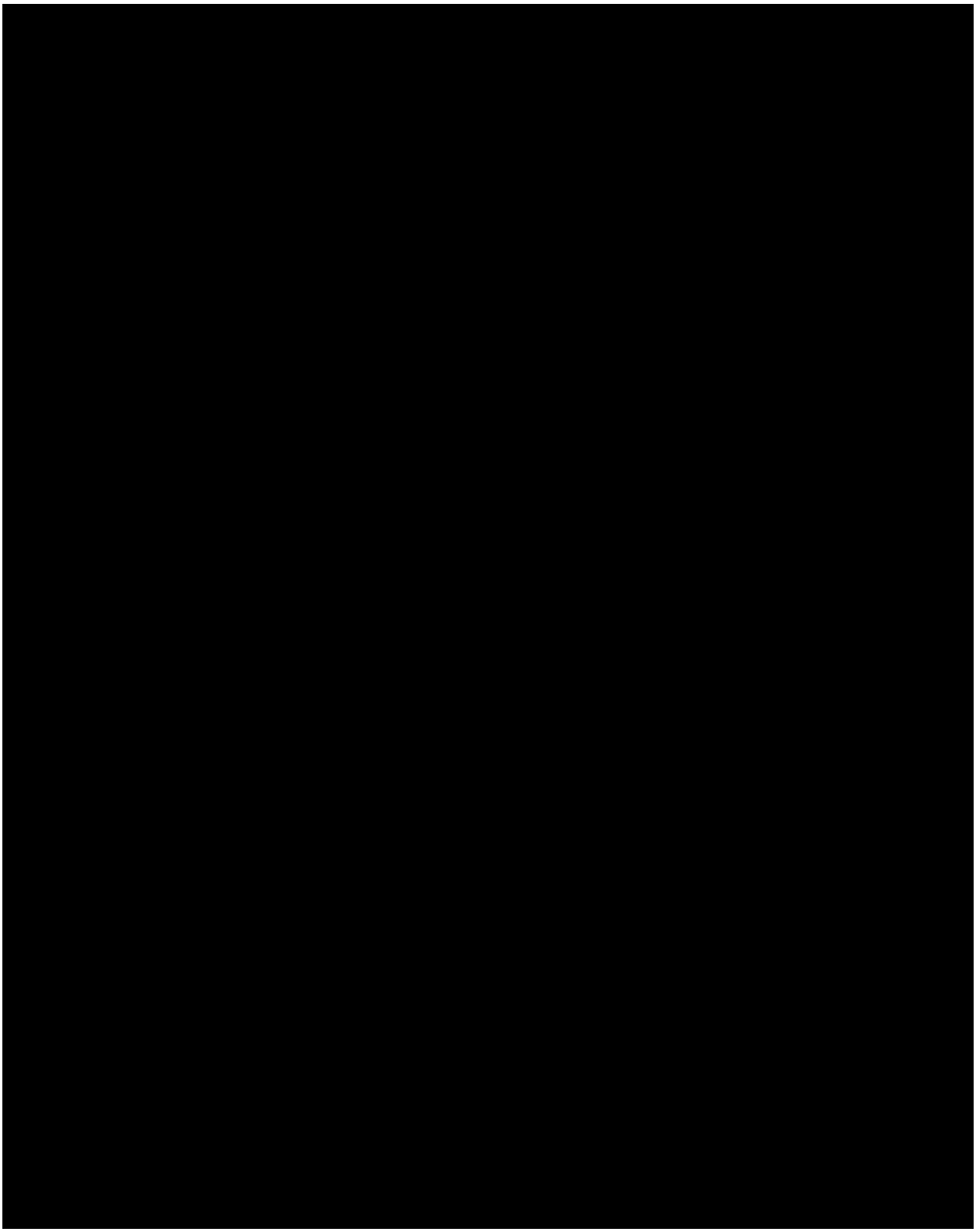
[redacted]

Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS.

[redacted]

In addition to the approaches listed above, per DLRT recommendations additional prophylaxis may be implemented, [redacted]

To reduce the potential of CRS, the cycle 1 dosing schedule will be initiated with one or more of the following measures as the study continues, as per the emerging cumulative data from the ongoing FIH monotherapy study (20180101) in subjects with mCRPC.



To further assess the safety of the subjects, the subject must return for safety follow-up visit approximately 30 (+3) days after the last dose of AMG 160 or prior to initiation of other therapy, whichever occurs first. Long-term follow-up will be conducted every 6 months up to 3 years from the first dose of AMG 160 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.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Section 1.3.

Statistical Considerations

All subjects who are enrolled and receive at least 1 dose of AMG 160 will be included in the analysis, unless otherwise specified. A formal interim analysis of available safety and efficacy data will occur when the first 10 evaluable subjects enrolled have had the opportunity to complete 4 months on study. This interim analysis will estimate maximum tolerated dose (MTD), support the determination of RP2D, conduct futility analysis of ORR, and support the evaluation of benefit/risk profile of AMG 160 as a monotherapy.

A futility analysis of ORR will be performed using Bayesian predictive probability (Lee and Liu, 2008) when the first 10 evaluable subjects reach month 4. If the predictive probability of observing objective response rate (ORR) response > 15% at the end of the study with 50 evaluable subjects is less than 30%, the study may stop early (pT = 0.25). Equivalently, if we observe ≥1 objective responder in the first 10 subjects, additional subjects (up to 40) will be enrolled into the expansion cohort. The predictive probability is calculated with a noninformative, Jeffreys prior, Beta (0.5, 0.5).

The primary analysis for the dose exploration phase will occur when target enrollment is complete and each subject either completes 6 months on the study or withdraws from the study.

The primary analysis for the study will occur when target enrollment is complete for the dose expansion phase and each subject either completes 1 year on study or withdraws from the study. The final analysis will occur when target enrollment is complete for both phases and all subjects have ended the study.

For a full description of statistical analysis methods, please refer to Section 9.

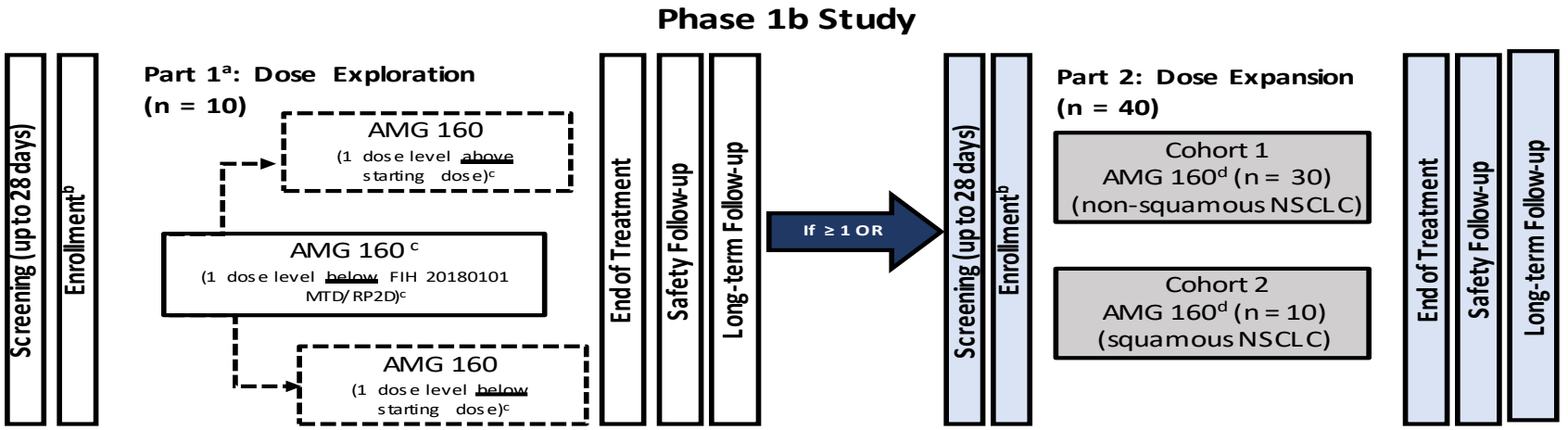
Statistical Hypotheses

AMG 160 will be safe and tolerated at a dose level with evidence of anti-tumor activity in subjects with NSCLC. No formal statistical hypotheses will be tested in this phase 1b study.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



CT = computed tomography; FIH = first in human; ^{68}Ga = ^{68}Gallium; IV = intravenous; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; OR = objective response; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RP2D = recommended phase 2 dose.

[a] Subjects with nonsquamous NSCLC. Up 20 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) to better estimate the RP2D and better characterize the safety, efficacy, PK, and [redacted] of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

[b] Subjects are required to have detectable PSMA expression by ^{68}Ga-PSMA-11 PET/CT imaging [redacted] to enroll (see Section 5.1).

[c] MTD/RP2D for Part 1 will be determined by the first in human AMG 160 study (Study 20180101).

[d] Part 2 will be determined by dose recommended in Part 1 of this study.

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks [redacted] treatment continues until confirmed progression
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of AMG 160
- Safety follow-up: approximately 30 (+3) days after 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 AMG 160 for all subjects who have not withdrawn consent

1.3 Schedule of Activities (SoA)

Quick link to SoA	Table Title
Table 1-1	Schedule of Activities if [redacted]
Table 1-2	Schedule of Activities if [redacted]
Table 1-3	Schedule of Activities if [redacted]
Table 1-4	Schedule of Activities (Cycle 2 and Beyond)
Table 1-5	Schedule of Pharmacokinetic Samples
Table 1-6	Schedule of Imaging Assessments (Cycle Independent)

Table 1-1. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/Treatment Cycle	SCR[a]	Cycle 1[b]														Infusion-free interval	Notes
Week[c]		1						2			3		4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	17	22	23	24	29	
GENERAL/SAFETY ASSESSMENTS																	
Informed consent	X																
Clinical evaluation	(X)	X	X	X	X			X	X	X	X	X	X	X	X	X	Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 8.2.1). (X): Additionally at screening: demographics, medical history, and height. [redacted]
Vital signs, pulse ox	X	X		X	X			X		X	X	X	(X)		X	X	(X): Refer to Section 8.2.3.1 for detailed vital sign collection time points. [redacted]
12-lead ECG	X (single read)	[X]						(X)					(X)				[X]: Collected pre-dose at baseline prior to start of infusion. Triplicate ECGs will only be collected if the dose being evaluated is higher than the MTD established in the monotherapy study in subjects with mCRPC. If the dose being evaluated is less than or equal to the MTD in subjects with mCRPC, single read ECGs are to be collected at the defined time points. [redacted] (X): Collected pre- and post-dose on days 8 and 22
ECHO or MUGA scan	X																
[redacted]																	
AE Review	[redacted]	Continually through SFU															
SAE Review		Continually throughout study															
Prior/concomitant medication		Continually through SFU															

Page 1 of 3

Abbreviations and footnotes defined on last page of table.

Table 1-1. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/Treatment Cycle	SCR[a]	Cycle 1[b]														Infusion-free interval	Notes
Week[c]		1						2			3		4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	17	22	23	24	29	
LOCAL LABORATORY TESTS[d]																	
CBC with differential	X	X	X	X	X	[redacted]		X	X	X	X	X	X	X	X	X	Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated. Blood samples must not be collected until at least 24 hours after PSMA PET/CT.
Coagulation	X	X	X		X			X	X		X	X	X	X			
Chemistry panel	X	X	X	X	X			X	X	X	X	X	X	X	X	X	[redacted]
Pregnancy test (serum)	X	(X)															(X): Collected pre-infusion of AMG 160.
Urinalysis	X																
CENTRAL LABORATORY TESTS																	
[redacted]																	
PK sample collection			(X)														(X): See Table 1-5 for detailed AMG 160 PK collection schedule during treatment period.

Abbreviations and footnotes defined on last page of table.

Table 1-1. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/Treatment Cycle	SCR[a]	Cycle 1[b]													Infusion-free interval	
Week[c]		1						2			3		4		5	
Day[c]		1	2	3	4	5	6	8	9	10	15	17	22	23	24	29	Notes
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES																	
Imaging	(X)																(X): See Table 1-6 – assessments are cycle independent
[redacted]																	

NOTE: This schedule of activities only applies to cycle 1. After cycle 1 day 28, there is a 1-week infusion-free interval. Then resume Table 1-4 Schedule of Activities beginning in cycle 2.

AE = adverse event; C1D1 = cycle 1 day 1; CBC = complete blood count; CT = computed tomography; [redacted] ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] EOI = end of infusion; IPIM = Investigational Product Instruction Manual; IV = intravenous; mCRPC = metastatic castration-resistant prostate cancer; MTD = maximum tolerated dose; MUGA scan = multigated acquisition scan; [redacted] PET = positron emission tomography; PK = pharmacokinetic; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SCR = screening; SFU = safety follow-up

[a] All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing. **Exception: serum pregnancy testing at screening is to be performed within 7 days of initiation of investigational product for females of childbearing potential.**

[b] All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.
[c] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified.
[d] Any blood samples collected during the screening window must be collected within 28 days of cycle 1 day 1.

Table 1-2. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]											Notes
Week[c]		1			2			3			4		
Day[c]		1	2	3	8	9	10	15	16	17	22	26	
GENERAL/SAFETY ASSESSMENTS													
Informed consent	X												
Clinical evaluation	(X)	X	X	X	X	X	X	X	X	X	X	X	Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 8.2.1). (X): Additionally at screening: demographics, medical history, and height.
Vital signs, pulse ox	X	X		X	X		X	X		X	X	X	(X): Refer to Section 8.2.3.1 for detailed vital sign collection time points.
12-lead ECG	X (single read)	(X)			(X)			(X)					(X): Collected pre- and post-infusion of AMG 160. Triplicate ECGs will only be collected if the dose being evaluated is higher than the MTD established in the monotherapy study in subjects with mCRPC. If the dose being evaluated is less than or equal to the MTD in subjects with mCRPC, single read ECGs are to be collected at the defined time points.
ECHO or MUGA scan	X												
[redacted]													
AE Review	[redacted]	Continually through SFU											
SAE Review	Continually throughout study												
Prior/concomitant medication	Continually through SFU												
LOCAL LABORATORY TESTING[d]													
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated. Blood samples must not be collected until at least 24 hours after PSMA PET/CT.
Coagulation	X	X	X	X	X	X	X		X	X	X	X	
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test (serum)	X	(X)											(X): Collected pre-infusion of AMG 160.
Urinalysis	X												

Abbreviations and footnotes defined on last page of table.

Table 1-2. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]											Notes
Week[c]		1			2			3			4		
Day[c]		1	2	3	8	9	10	15	16	17	22	26	
CENTRAL LABORATORY TESTS													
[redacted]													
PK sample collection		(X)											(X): See Table 1-5 for detailed AMG 160 PK collection schedule during treatment period.
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES													
Imaging		(X)											(X): See Table 1-6 – assessments are cycle independent
[redacted]													
AMG 160 IV infusion		X			X			X					
Hospitalization/monitoring		X			X			X					See Table 6-1 for additional guidance regarding hospitalization.

NOTE: This schedule of activities only applies to cycle 1. Then resume Table 1-4 Schedule of Activities beginning in cycle 2.

AE = adverse event; CBC = complete blood count; CT = computed tomography; [redacted] ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; IPIM = Investigational Product Instruction Manual; IV = intravenous; mCRPC = metastatic castration-resistant prostate cancer; MTD = maximum tolerated dose; MUGA scan = multigated acquisition scan; [redacted] PET = positron emission tomography; PK = pharmacokinetic; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SCR = screening; SFU = safety follow-up

[a] All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing. **Exception: serum pregnancy testing at screening is to be performed within 7 days of initiation of investigational product for females of childbearing potential.**

[b] All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[c] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified (except for PK and [redacted] collections days).

[d] **Any blood samples collected during the screening window must be collected within 28 days of cycle 1 day 1.**

Table 1-3. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]												Infusion-free interval	Notes
Week[c]		1			2			3			4			5	
Day[c]		1	2	3	8	9	10	15	16	17	22	23	24	29	
GENERAL/SAFETY ASSESSMENTS															
Informed consent	X														
Clinical evaluation	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 8.2.1). (X): Additionally at screening: demographics, medical history, and height.
Vital signs, pulse ox	X	(X)		X	(X)		X	(X)		X	(X)			X	(X): Refer to Section 8.2.3.1 for detailed vital sign collection time points.
12-lead ECG	X (single read)				(X)			(X)			(X)				(X): Collected pre- and post-infusion of AMG 160. Triplicate ECGs will only be collected if the dose being evaluated is higher than the MTD established in the monotherapy study in subjects with mCRPC. If the dose being evaluated is less than or equal to the MTD in subjects with mCRPC, single read ECGs are to be collected at the defined time points.
ECHO or MUGA scan	X														
[redacted]															
AE Review	[redacted]	Continually through SFU													
SAE Review	Continually throughout study														
Prior/concomitant medication	Continually through SFU														
LOCAL LABORATORY TESTING[d]															
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated. Blood samples must not be collected until at least 24 hours after PSMA PET/CT.
Coagulation	X	X	X		X	X		X	X		X	X			
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test (serum)	X	(X)													(X): Collected pre-infusion of AMG 160.
Urinalysis	X														

Abbreviations and footnotes defined on last page of table.

Table 1-3. Schedule of Activities if [redacted] is Initiated (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]												Infusion-free interval	Notes
Week[c]		1			2			3			4			5	
Day[c]		1	2	3	8	9	10	15	16	17	22	23	24	29	
CENTRAL LABORATORY TESTS															
[redacted]															
PK collection		(X)													(X): See Table 1-5 for detailed AMG 160 PK collection schedule during treatment period.
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES															
Imaging	(X)														(X): See Table 1-6 – assessments are cycle independent
[redacted]															
AMG 160 IV infusion		X			X			X			X				
Hospitalization/monitoring		X			X			X			X				See Table 6-1 for additional guidance regarding hospitalization.

NOTE: This schedule of activities only applies to cycle 1. Then resume Table 1-4 Schedule of Activities beginning in cycle 2.

AE = adverse event; CBC = complete blood count; CT = computed tomography; [redacted] ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; IPIM = Investigational Product Instruction Manual; IV = intravenous; mCRPC = metastatic castration-resistant prostate cancer; MTD = maximum tolerated dose; MUGA scan = multigated acquisition scan; [redacted] PET = positron emission tomography; PK = pharmacokinetic; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SCR = screening; SFU = safety follow-up

[a] All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing. **Exception: serum pregnancy testing at screening is to be performed within 7 days of initiation of investigational product for females of childbearing potential.**

[b] All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[c] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified.

[d] Any blood samples collected during the screening window must be collected within 28 days of cycle 1 day 1.

Table 1-4. Schedule of Activities (Cycle 2 and Beyond)

Study Period/ Treatment Cycle	Cycle 2[a]						Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	Notes
Week[e]	1		2	3		4	1	3				
Day[e]	1	2	8	15	16	22	1	15				
GENERAL/SAFETY ASSESSMENTS												
Clinical evaluation	X	X	X	X	X	X	X	X	X	X		Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 8.2.1).
Vital signs, pulse ox	(X)		X	(X)		X	X	X	X	X		(X): Refer to Section 8.2.3.1 for detailed vital sign collection time points.
12-lead ECG	(X)¥			(X)			(X)	(X)				(X): Collected pre- and post-infusion of AMG 160. ¥ Triplicate ECG on C2D1 will only be collected if the dose being evaluated is higher than the MTD established in the monotherapy study in subjects with mCRPC (Study 20180101). If the dose being evaluated is less than or equal to the MTD in Study 20180101, single read ECGs are to be collected at the defined time points.
[redacted]												
AE review	Continually through SFU											
SAE review	Continually throughout study										X	
Prior/concomitant medication	Continually through SFU											
Survival status and/or subsequent cancer therapy											X	
LOCAL LABORATORY TESTS												
CBC with differential	X	X	X	X	X	X	X	X	X	X		Blood samples must not be collected until at least 24 hours after PSMA PET/CT scans.
Coagulation	X	X	X	X	X	X	X	X	X	X		
Chemistry panel	X	X	X	X	X	X	X	X	X	X		
Pregnancy test (serum)	(X)						(X)			X		(X): Collected pre-infusion of AMG 160.
Urinalysis	X						(X)					(X): Collected D1 of every other cycle (C2, C4, C6, etc.)

Abbreviations and footnotes defined on last page of table.

Table 1-4. Schedule of Activities (Cycle 2 and Beyond)

Study Period/ Treatment Cycle	Cycle 2[a]						Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1		2	3		4	1	3				
Day[e]	1	2	8	15	16	22	1	15				Notes
CENTRAL LABORATORY TESTS												
[redacted]												
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES												
PK sample collection	X											See Table 1-5 for detailed AMG 160 PK collection schedule during treatment period.
Imaging	(X)											(X): See Table 1-6 – assessments are cycle independent
[redacted]												
Hospital stay	X			X			X	X				See Table 6-1 for additional guidance regarding hospitalization. In cycles 3 and 4, subject should be monitored in hospital or outpatient clinic for at least 4 hours post-infusion.
AMG 160 IV infusion	X			X			X	X				

AE = adverse event; C = cycle; CBC = complete blood count; CT = computed tomography; [redacted] D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; IPIM = Investigational Product Instruction Manual; IV = intravenous; LTFU = long-term follow-up; mCRPC = metastatic castration-resistant prostate cancer; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; [redacted] PET = positron emission tomography; PK = pharmacokinetic; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SFU = safety follow-up

[a] Please follow Table 1-1, Table 1-2, and Table 1-3 for the procedures/activities for cycle 1 and Table 1-4 for cycle 2 and subsequent cycles. [redacted] All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[b] For subjects who discontinue investigational product, an end of treatment visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

[c] 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 investigational product or prior to initiation of other therapy, whichever occurs first.

[d] Assessed every 6 months up to 3 years from the first dose of AMG 160 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. During the long-term follow-up phase, serious adverse events **regardless of causality** (including fatal events) will be reported to Amgen.

[e] Each visit week and day is relative to day 1 of each cycle. Cycle 2 visits have a ± 1-day window from designated time point unless otherwise specified. All subsequent visits beginning in cycle 3 will have a ± 3-day window.

Table 1-5. Schedule of Pharmacokinetic Samples (All time points relative to AMG 160 dosing)

	Preinfusion [a]	End of infusion [b]	Hours after end of infusion [c]							
			2	6	24	48	72	96	120	168
AMG 160 PK Sample Collection										
Cycle [redacted] only (days 1, 8, and 15)	X	X		X		X				
Cycle 1 [redacted] only (days 1, 8, 15, and 22)	X	X		X		X				
Cycle 1 [redacted] (day 1)	X[e]									
Cycle 1 [redacted] (day 1)	X[f]									
Cycle 1 [redacted] (day 1)	X[g]									
Cycle 1 [redacted] - target dose only (days 8 and 22)	X	X		X		X				X
Cycle 2 (days 1 and 15)	X	X		X		X				X
Cycle 3 (day 1)	X	X								
Cycle 4 (day 1)	X	X								
Cycle 5 (day 1)	X	X								
Cycle 6 through C12[d] (day 1)	X									

eCRF = electronic case report form; IV = intravenous; PK = pharmacokinetic

[a] For pre-infusion, PK can be collected up to 30 minutes prior to dosing of AMG 160.

[b] For end of infusion, PK samples to be collected within 30 minutes after AMG 160 infusion.

[c] **The samples for [redacted] need to be collected as close to the sampling time point for the infusion duration.** For any samples after end of infusion time point, PK can be collected ± 30 minutes within the scheduled sample collection time. Date and time of collection should be recorded in eCRF. Samples collected outside of the collection window will not be considered as a protocol deviation.

[d] PK samples to be collected until end of cycle 12 only.

[e] For the [redacted] in cycle 1, PK samples should be collected pre-infusion and 2, 6, 24, 48, and 72 hours after start of infusion.

[f] For the [redacted] in cycle 1, PK samples should be collected pre-infusion and 2, 6, 24, and 48 hours after start of infusion.

[g] For the [redacted] in cycle 1, PK samples should be collected pre-infusion and 2, 6, 24, 48, 72, 96, and 120 hours after start of infusion.

Table 1-6. Schedule of Imaging Assessments (Cycle Independent)

	SCR	Treatment Period[a]		EOT	SFU	LTFU	Notes
MRI brain	X						All subjects must have MRI of the brain performed within 28 days prior to the first dose of AMG 160. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.
CT/MRI and tumor burden assessment (chest, abdomen and pelvis)	X	Weeks 1-24 Every 8 weeks	Weeks 25+ Every 8 weeks	X	X	X[b]	Radiologic imaging (CT/MRI) is required at the EOT or SFU visit if the subject has not had radiologic imaging performed within 6 weeks of the visit.
^{68}Ga-PSMA-11 PET/CT	X	At week 8 and week 16		X			[redacted]

CT = computed tomography; EOT = end of treatment; ^{68}Ga = 68-Gallium; [redacted]; LTFU = longterm follow-up; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SCR = screening; SFU = safety follow-up;

[a] Timing is based on first dose of AMG 160 (cycle 1 day 1) ± 7 days for imaging assessments.

[b] For subjects who discontinued treatment for any reason other than confirmed disease progression, every effort should be made to perform radiographic imaging (CT/MRI) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed disease progression per modified RECIST 1.1, clinical progression, start of new anticancer therapy, or up to 3 years after the first dose of AMG 160, whichever occurs first.

2. Introduction

2.1 Study Rationale

AMG 160 (acapatamab) is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®) molecule designed to redirect T effector cells to lyse prostate-specific membrane antigen (PSMA)-expressing cells, with a single chain fragment crystallizable (scFc) moiety for half-life extension. AMG 160 induces potent T cell redirected lysis of prostate cancer cells, with half-maximal effective concentrations of 6-55 pM against prostate cancer cell lines in vitro that express as low as 6881 PSMA copies per cell (Bailis et al, 2019). The BiTE mechanism of action is effective against even very low levels of target (< 1000 copies per cell; Owen et al, 2019). PSMA has been shown to be highly expressed in metastatic and castration-resistant prostate cancer (von Eyben et al, 2018). Immunohistochemical analysis has shown intense and homogenous expression of PSMA on prostate cancer cells within metastatic lesions localized to the bones, lymph nodes, soft tissue and the lungs (Chang et al, 2001; Sweat et al, 1998; Murphy et al, 1996). Numerous PSMA-targeted therapies in prostate cancer are currently under development. PSMA has also been shown to be expressed on the surface of endothelial cells within the tumor vasculature of many tumor types, including non-small cell lung cancer (NSCLC), and is not expressed in the vasculature of normal endothelial tissues (Chang et al, 1999). Several recent reports confirm PSMA expression on the tumor vasculature of NSCLC, with recent studies showing 49-77% of NSCLC samples noting PSMA expression in the tumor vasculature (Schmidt et al, 2017; Wang et al, 2015). PSMA-targeted radioligands have also shown the potential to identify PSMA-positive lung cancer. (Shetty et al, 2016; Milowsky et al, 2007). In vitro, PSMA expression can be induced on endothelial cells cultured in conditioned media from cancer cell lines (Nguyen et al, 2016; Liu et al, 2011). In vivo, angiogenesis was significantly impaired in PSMA-null mice or PSMA wild-type mice treated with a PSMA inhibitor, suggesting that PSMA participates in tumor-specific neovasculature growth (Nguyen et al, 2016; Conway et al, 2006). Targeting of PSMA with a radiolabeled PSMA-ligand demonstrates selective killing of PSMA-positive neovasculature in preclinical models (Morgenroth et al, 2019). Previous studies have shown that angiogenesis inhibitors can inhibit tumor growth by blocking new blood vessel formation and depriving the tumor of critical nutrients. More recent studies suggest anti-angiogenesis treatments may enhance immune responses by altering the tumor microenvironment (Fukumura et al, 2018). AMG 160 has the potential both to redirect T cells to lyse any PSMA-positive endothelial cells in tumor vasculature, and to promote

T cell proliferation. This is a phase 1b study to assess safety, tolerability, pharmacokinetics (PK) and anti-tumor activity of AMG 160 in adult subjects with NSCLC.

2.2 Background

2.2.1 Disease

Lung cancer is the leading cause of cancer-related mortality world-wide, with NSCLC accounting for 85% of lung cancer cases (Brahmer et al, 2018). In the United States, lung cancer-related deaths will account for an estimated 142 670 deaths in 2019. NSCLC accounts for approximately 85% of all primary lung cancers, with most patients presenting with advanced, unresectable disease at the time of diagnosis (Arbour et al, 2019). Until recently, cytotoxic chemotherapy has been considered the mainstay of treatment for advanced NSCLC. More recently, however, the development of immunotherapy treatments that disrupt the programmed cell death-1 (PD-1) and PDL1 pathway, commonly referred to as immune checkpoint inhibitors, have changed the therapeutic landscape of advanced NSCLC. Developed to target self-tolerance pathways that tumors use to escape immune-mediated recognition and destruction, immune checkpoint inhibitors stimulate T cell-mediated immunity to recognize and destroy cancer cells (Pennock et al, 2015; Reiss et al, 2014). Currently, 4 PD-1 and PDL1 immune checkpoint pathway inhibitors have demonstrated an overall survival (OS) benefit and have been approved either by the United States Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for use in patients with NSCLC: nivolumab and pembrolizumab, both targeting the PD-1 receptor, as well as atezolizumab and durvalumab, both targeting the programmed death-ligand 1 (PDL1) (Atezolizumab United States Prescribing Information [USPI]; Pembrolizumab USPI; Nivolumab USPI). Pembrolizumab is approved by the FDA and EMA for patients with metastatic NSCLC whose tumors express PDL1 (tumor proportion score [TPS] ≥ 1% per FDA requirements and TPS ≥ 50% per EMA requirements), with no epidermal growth factor receptor (EGFR) or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC (Pembrolizumab USPI). Pembrolizumab is also approved by the FDA and EMA for use in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations and in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC (Pembrolizumab USPI). Atezolizumab is approved by the FDA and the EMA for use in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of adult patients with metastatic

non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (Atezolizumab USPI). In the second line and beyond setting, nivolumab, pembrolizumab (in adults whose tumors express PDL1 with a ≥ 1% TPS), and atezolizumab are all approved by the FDA and the EMA after chemotherapy in patients with metastatic NSCLC (Atezolizumab USPI; Pembrolizumab USPI; Nivolumab USPI).

Molecularly targeted agents have also dramatically altered the therapeutic landscape for a subset of NSCLC patients with EGFR, ALK, NTRK, RET, BRAF, MET mutation, or ROS1 mutations, with multiple tyrosine kinase inhibitors approved by the FDA and/or the EMA for these indications (Russo et al, 2020; Pakkala et al, 2018).

In addition to these recent approvals, anti-angiogenesis inhibitors have demonstrated clinical benefit in patients with NSCLC. Previous studies have shown that tumor angiogenesis plays a key role in supporting tumor growth, the tumor microenvironment and metastatic dissemination (Folkman, 1971). Currently, 3 anti-angiogenesis agents, bevacizumab, ramucirumab and nintedanib, have demonstrated an overall survival benefit and are approved by the FDA and/or EMA for treatment in patients with NSCLC (Ramucirumab USPI; Bevacizumab USPI). Based upon higher rates of hemoptysis associated with squamous cell histology, bevacizumab is currently approved for use in patients with non-squamous NSCLC (Reck et al, 2012; Bevacizumab USPI).

Despite these recent advances, long-term durable responses remain uncommon for the majority of patients with advanced NSCLC, with an estimated 5 year survival of 24%, and remains an unmet need (American Cancer Society, 2020).

2.2.2 Amgen Investigational Product Background: AMG 160

BiTE® molecules are designed to direct T effector cells to kill target cells. The BiTE® molecule triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation. Blinatumomab (BLINCYTO®), cluster of differentiation (CD)19 BITE® molecule, is approved for the treatment of acute lymphoblastic leukemia (ALL).

AMG 160 is an HLE BiTE® molecule designed to direct T effector cells (via CD3 binding) to prostate cancer cells expressing PSMA. In addition to binding domains specific for CD3 and PSMA, AMG 160 contains the N-terminus of an immunoglobulin (Ig)G scFc region. The fusion to the Fc domain is a well-established strategy to prolong the half-life of protein therapeutics, such as cytokines, growth factors, and bispecific antibodies, with several approved for the treatment of cancer (Kontermann, 2011).

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 160 is provided in the AMG 160 Investigator's Brochure.

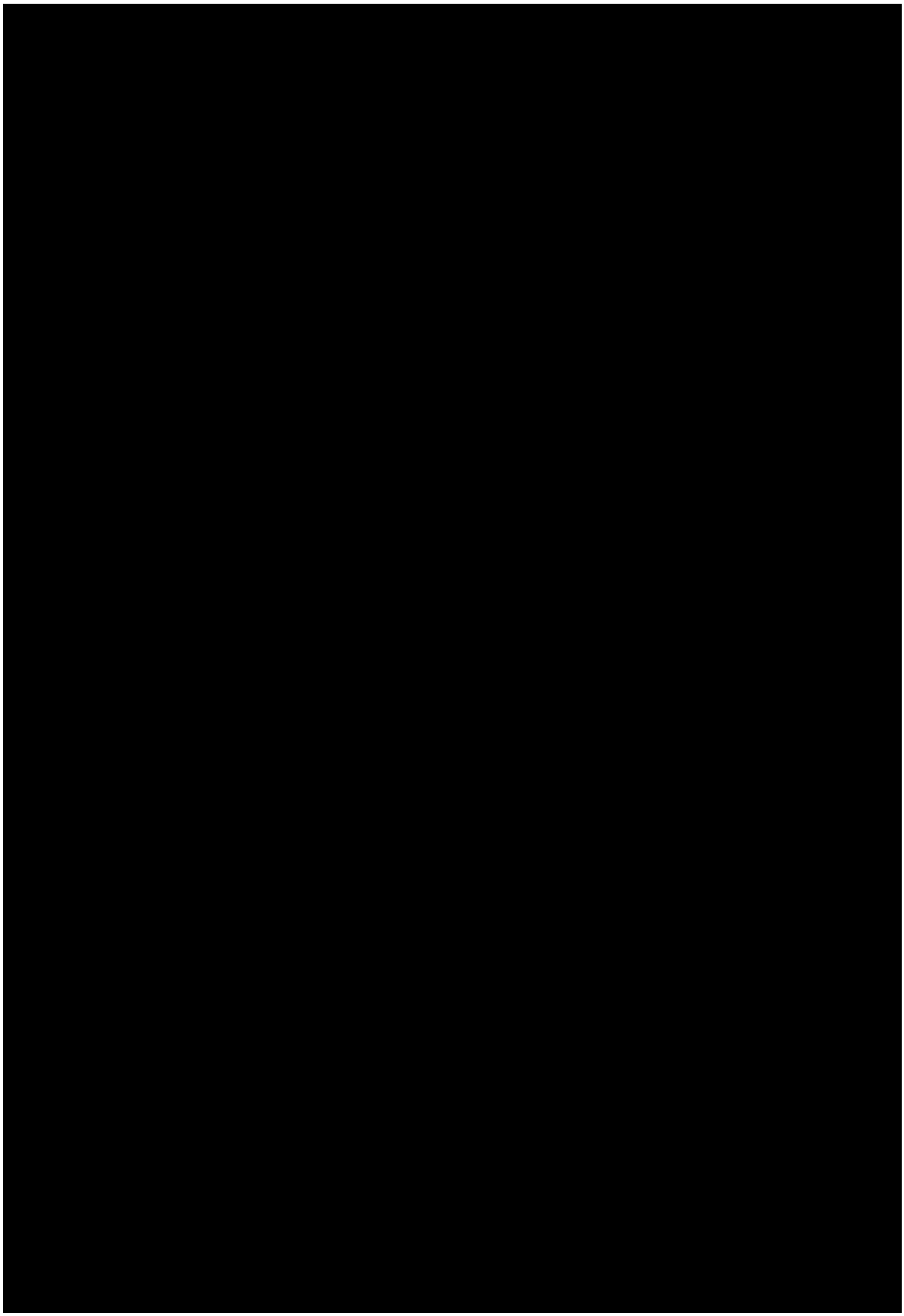
2.2.2.1 Nonclinical Pharmacology

In vitro experiments demonstrated that AMG 160 activity requires the simultaneous binding to PSMA-positive cells and T cells. The pharmacological effect of AMG 160 is mediated by specific redirection of previously primed cytotoxic CD3 positive T lymphocytes to kill PSMA expressing cells. AMG 160 is a potent molecule showing mean half maximal lysis of human tumor cell lines by human effector cells in vitro over a range of 6 to 55 pM (0.636 to 5.83 ng/mL).

AMG 160 monotherapy significantly inhibited the growth of established subcutaneous (SC) PSMA expressing human prostate cancer cell line (22Rv1) tumors in mouse xenograft studies with reconstituted human T cells.

2.2.2.2 Nonclinical Toxicology

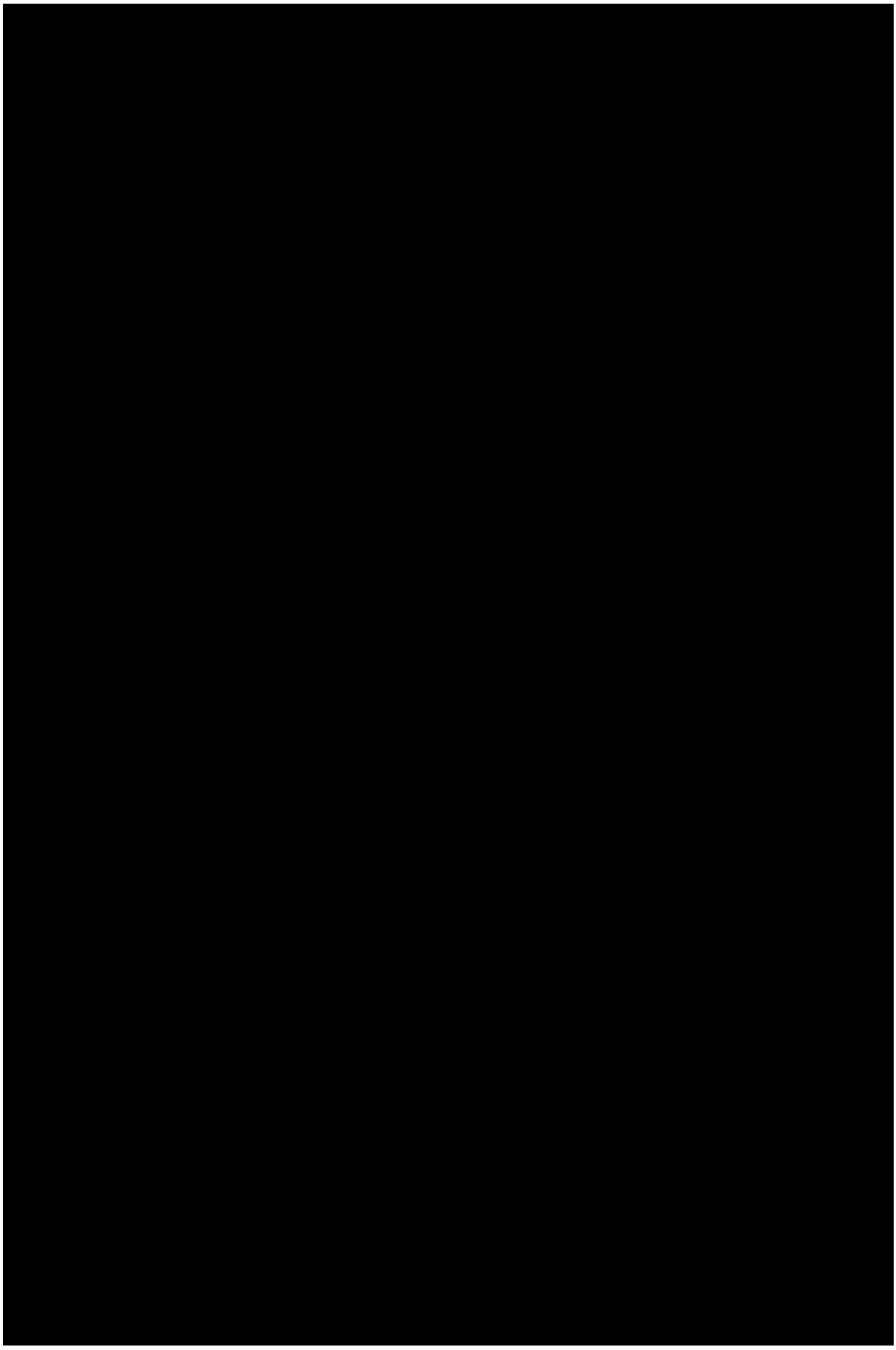
The nonclinical safety assessment of AMG 160 was conducted in male cynomolgus monkeys by intravenous (IV) administration in a 33-day GLP study.

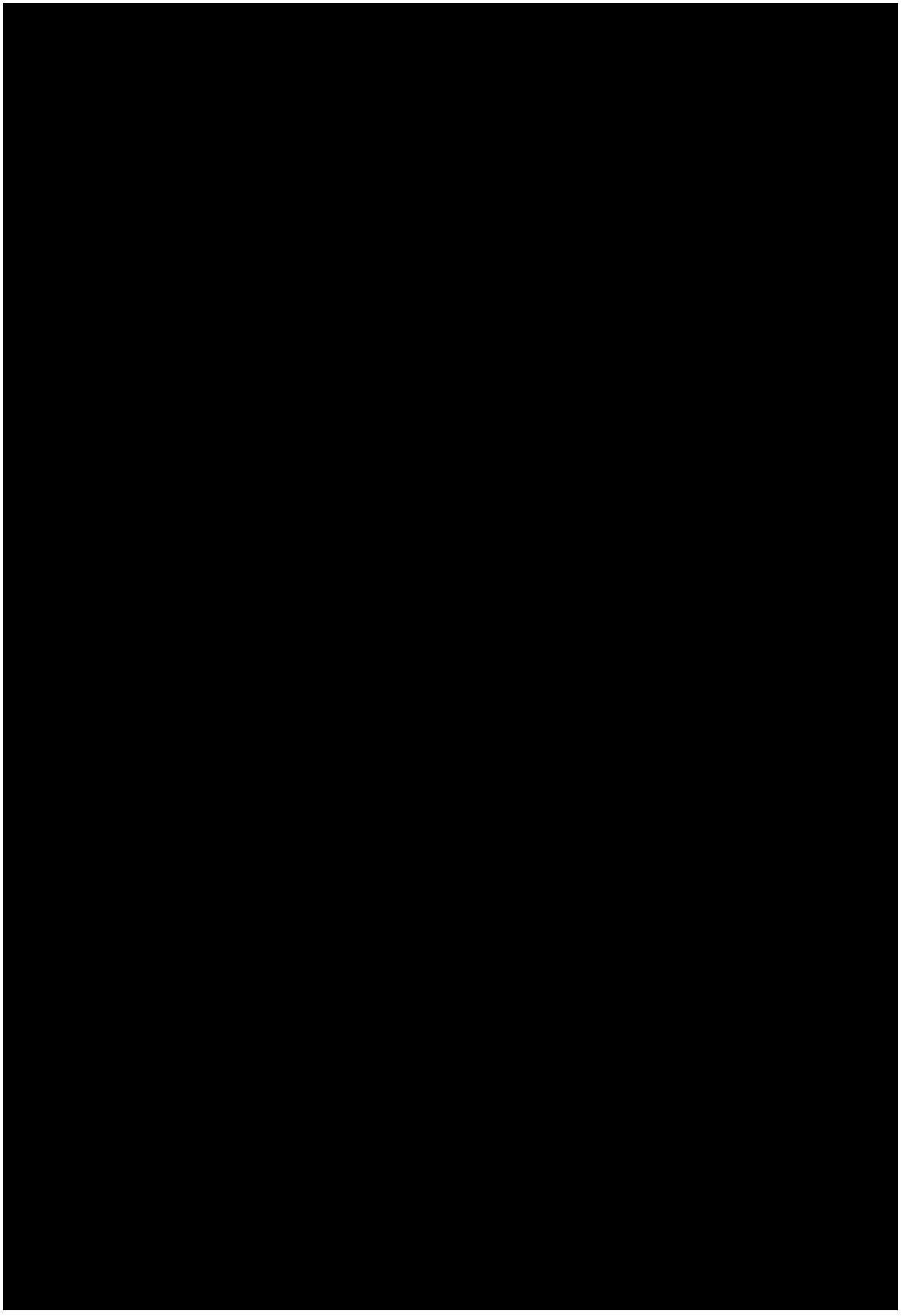


[redacted]

2.2.2.3 Clinical Experience

[redacted]





[redacted]

2.3 Benefit/Risk Assessment

This is a phase 1b study of AMG 160 monotherapy in adult subjects with NSCLC.

Based on nonclinical toxicity studies of AMG 160, and clinical experience with AMG 160

in patients with metastatic castration-resistant prostate cancer (mCRPC), the anticipated benefit/risk profile favors clinical development of AMG 160 for subjects with NSCLC. The following benefit risk assessment supports the conduct of this clinical trial. Please refer to the Investigator's Brochure for further data on AMG 160.

2.3.1 Therapeutic Context

PSMA targeted therapies have recently shown promise in mCRPC. In a phase 2 study involving mCRPC patients refractory to standard of care therapies, 177Lu-PSMA-617 demonstrated evidence of clinical activity as well as improvements in quality of life assessments (Hofman et al, 2018). Key outstanding issues for PSMA radiopharmaceuticals involve grade 3 to 4 bone marrow toxicities driven by the radioactive moiety as well as primary resistance to therapy and lack of response durability. While PSMA has been established as a therapeutic target for mCRPC, it is currently not an established therapeutic target in NSCLC. Given PSMA expression on the tumor vasculature of NSCLC and the limited therapeutic options for patients with advanced NSCLC following progression on standard of care treatments, there is a need for new PSMA targeted therapies with novel modalities that permit improved safety, patient access, and durability of responses.

The development of immunotherapy treatments that disrupt the programmed cell death 1 (PD-1) and PDL1 pathway, commonly referred to as immune checkpoint inhibitors, have changed the therapeutic landscape of advanced NSCLC. Currently, 4 PD-1 and PDL1 immune checkpoint pathway inhibitors have demonstrated an overall survival (OS) benefit and have been approved either by the United States Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for use in patients with NSCLC. Despite these recent advances, long-term durable responses remain uncommon for the majority of patients with advanced NSCLC. There is a need for novel immunotherapies that are active in the advanced NSCLC population.

BiTE® molecules exert a common mechanism of action involving engagement of T cells and target cells leading to redirected lysis of the target cells. Therefore, experiences with other BiTE® molecules provide a therapeutic context for AMG 160.

The most advanced BiTE® molecule is blinatumomab, which is FDA approved for the treatment of B-cell precursor ALL in first or second complete remission with minimal residual disease greater than or equal to 0.1% and relapsed or refractory B cell precursor ALL. Blinatumomab targets CD3 and CD19 and is administered by extended IV infusion. Clinical trials in late-stage hematological malignancies demonstrated an

acceptable safety profile with clinical responses, leading to breakthrough designation and accelerated approval by the FDA (BLINCYTO United States Prescribing Information, 2018). In the European Union, conditional license for blinatumomab was granted in 2015 and full license approved in 2018. The most common adverse reactions (≥ 20%) are infections, pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. According to the US prescribing information (BLINCYTO United States Prescribing Information, 2018), additional adverse reactions included CRS, neurological toxicities, infections, TLS, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, pancreatitis, leukoencephalopathy, and preparation/administration errors.

Several other BiTE® molecules have entered clinical trials. Adverse events common to these constructs and blinatumomab include fatigue and CRS (particularly fever).

2.3.2 Key Risks

Based on biological mechanism, nonclinical toxicity studies of AMG 160, and**/or** clinical experience, CRS [redacted]

Other potential safety concerns based on preclinical studies and experience with other BiTE® molecules include gastrointestinal and neurologic toxicities, and tumor lysis syndrome (TLS) (see Table 2-1).

Table 2-1. Key Safety Risks for AMG 160

Safety Risk	Description
Identified Risk	
Cytokine release syndrome (CRS)	Signs and symptoms may include the following: • constitutional - fever, rigors, fatigue, malaise • neurologic – confusion, headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure (refer to immune-effector cell associated neurologic syndrome [ICANS] guidance in Section 11.10) • respiratory - dyspnea, tachypnea, hypoxemia • cardiovascular - tachycardia, hypotension • gastrointestinal - nausea, vomiting, diarrhea • hepatic - transaminitis, hyperbilirubinemia • hematology - anemia, bleeding, hypofibrinogenemia, elevated D-dimer • skin - rash
[redacted]	
Potential Safety Concerns	
Gastrointestinal toxicities	Signs and symptoms may include nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal inflammation and ulceration; mostly associated with CRS.
Neurologic toxicities (Section 11.10)	Signs and symptoms include confusional state, headache, dizziness, encephalopathy, tremor, aphasia, syncope; mainly observed with CRS.
Tumor lysis syndrome	Signs and symptoms may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure.

BiTE = bi-specific T-cell engagers; CD = cluster of differentiation

Clinical signs and symptoms of CRS and [redacted] gastrointestinal and neurologic toxicities, TLS, along with other safety labs, will be monitored during the study and at the appropriate time points to ensure subjects' safety. Refer to Table 6-3, Section 6.1.4, and Section 11.10 for specific recommendations regarding the mitigation and management of these risks.

Coronavirus disease 2019 (COVID-19) infection may theoretically increase the signs and symptoms of CRS. Subjects with acute symptoms of COVID-19 disease within 10 days prior to first dose of AMG 160 (counted from day of positive test for asymptomatic subjects) are excluded from study. See Section 11.13 for additional guidance related to COVID-19.

Please refer to the AMG 160 Investigator's Brochure for further description of the key safety risks.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 160 • To evaluate the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D)	• Dose-limiting toxicities (DLT) • Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs and clinical laboratory tests
Secondary	
• To 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, and half-life ($t_{1/2}$)
• To evaluate the preliminary anti-tumor activity of AMG 160	• Objective response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Overall Survival

	• Progression-free survival (radiographic [rPFS], clinical) • Time to response • Time to progression (radiographic, clinical) • Duration of response • Time to subsequent therapy
Exploratory	
[redacted]	

4. Study Design

4.1 Overall Design

This is an open label phase 1b study evaluating the safety, tolerability, PK, and efficacy of AMG 160 monotherapy in subjects with relapsed, refractory non--small cell lung cancer (NSCLC).

AMG 160 will be administered as a short-term IV infusion every 2 weeks after the target dose is reached in a 28-day cycle as monotherapy therapy in subjects with relapsed, refractory NSCLC. The starting dose of AMG 160 will be 1 dose level below the recommended phase 2 dose (RP2D) as determined in the ongoing first in human (FIH) study of AMG 160 in subjects with mCRPC. To mitigate the risk of CRS [redacted] Based on the maximum tolerated dose (MTD) or RP2D and the associated dosing schedule selected in Study 20180101, one of the following [redacted] (see Table 6-1 for further details). A safety cohort of 2 to 4 subjects will initially be enrolled to assess the tolerability of AMG 160. If the dose

is tolerated (based on target DLT rate > 28%), the dose level will be increased to the RP2D (or RP2D+1) identified in Study 20180101. Alternative dosing schedules, including further dose escalation as per the ongoing mCRPC trial (Study 20180101), may be explored based on emerging safety and PK data. Additional subjects (up to 20) 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 may be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and [redacted] of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

If 1 or more objective responses (OR) are observed (per modified RECIST 1.1 criteria) in Part 1, additional subjects (up to 40) will be enrolled in Part 2 (dose expansion) of the study at the MTD/RP2D identified in Part 1. In Part 2, 2 cohorts will be opened: Cohort 1 (up to 30 subjects with non-squamous NSCLC) and Cohort 2 (up to 10 subjects with squamous NSCLC). Based on emerging safety and tolerability data in Cohort 2, the dose of AMG 160 could be lowered 1 dose level below the starting dose identified in Part 1 if necessary.

Based on emerging safety and efficacy data from Part 1 and/or Part 2, the protocol may be amended (and sample size increased) to include a combination of AMG 160 with an anti-programmed cell death protein 1 (PD1)/programmed death-ligand 1 (PDL1) agent.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately 10 subjects will initially be enrolled in Part 1 (dose exploration) of the study. If 1 or more objective responses (OR) are observed (per modified RECIST 1.1 criteria) in Part 1, additional subjects (up to 40) will be enrolled into an expansion cohort in Part 2 (dose expansion) of the study. The protocol may be amended to increase enrollment based on emerging clinical data.

Participants in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non evaluable for dose escalation decisions and MTD determination and may be replaced by an additional

subject at that same dose level, as necessary, to ensure that all dose escalation decisions are made with sufficient safety data (eg, safety data from at least 2 evaluable subjects in a multi subject cohort).

Subjects who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs may be replaced at the discretion of the medical monitor or DLRT.

4.2.2 Number of Sites

Approximately 5 investigative sites in the United States**,** Australia, and/or Europe will be included in the study in Part 1. Approximately 7 additional sites in Europe, United States, and Australia will be included in Part 2. Sites that do not enroll subjects within 4 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

AMG 160 dose and dosing schedule (regimen) for this study in males and female subjects with NSCLC will be based on the dose levels that have been deemed safe and tolerable (with evidence of preliminary efficacy) in the ongoing AMG 160 phase 1 monotherapy study (20180101) in subjects with mCRPC. It is anticipated that AMG 160 at the RP2D regimen in subjects with NSCLC will demonstrate a comparable safety and tolerability profile to that determined in subjects in mCRPC. In addition, this regimen is expected to show clinical activity in subjects with NSCLC based on the preliminary evidence of efficacy in subjects with mCRPC. Safety and tolerability data for AMG 160 thus far is only available in male subjects with mCRPC. Based on the published literature for approved biologics, after adjusting for bodyweight, no clinically meaningful differences in exposures have been reported between males and females (Dirks and Meibohm, 2010). Although expression levels of PSMA may differ between subjects with mCRPC and NSCLC, the safety and tolerability profile for AMG 160 in female subjects is expected to be similar to that of male subjects at the same dose levels. Therefore the starting dose in this study for both males and female subjects with NSCLC will be 1 dose level below the RP2D established in male subjects with mCRPC.

Based on Study 20180101, it is expected that the MTD/RP2D regimen will include [redacted] followed by the maintenance dosing every 2 weeks thereafter. These dosing approaches have been implemented to mitigate the risk of CRS. The potential doses of AMG 160 to be used for [redacted]

[redacted] which are under evaluation in Study 20180101.

4.3.1 Justification for Non-investigational Product Dose

^{68}Gallium (^{68}Ga)-PSMA-11 is a non-Amgen investigational product administered as part of positron emission tomography/computed tomography (PET/CT) imaging assessments in this study and will be used to enroll patients who are PSMA positive defined as at least 1 site of disease exceeding blood pool activity by visual assessment [redacted].

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date 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).

The study-specific primary completion date is the date when data for the primary endpoint are last collected.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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, additional antibody testing), as applicable.

4.4.2 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to 3 years.

This includes a screening period lasting up to 28 days, a treatment period lasting until disease progression and a follow-up period lasting up to 3 years from the first dose of AMG 160.

4.5 Patient Input on Study Design

There was no patient input on study design.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

102 Subject is ≥ 18 years of age at the time of signing the informed consent.

103 Part 1 only: have a histologically or cytologically confirmed diagnosis of stage 4 or recurrent non-squamous NSCLC.

104 Part 2 only: have a histologically or cytologically confirmed diagnosis of stage 4 or recurrent NSCLC (squamous cell histology/cytology allowed in Part 2).

105 Subjects without a driver mutation are required to have disease progression following at least one line of prior chemotherapy (or are deemed unsuitable to be treated with chemotherapy or have actively refused treatment with chemotherapy) and at least 1 prior anti-PD1/PDL1 therapy. This includes subjects who have experienced disease progression during or after combination treatment with platinum-based chemotherapy plus anti-PD1/PDL1 therapy and subjects who have developed recurrent or metastatic disease after definitive chemoradiation followed by anti-PD1/PDL1 therapy. Subjects who have received adjuvant or neoadjuvant platinum-based chemotherapy and developed recurrent or metastatic disease within 12 months of completing therapy and have received prior anti-PD1/PDL1 therapy are eligible. Subjects who developed recurrent or metastatic disease greater than 12 months after completing adjuvant or neoadjuvant platinum-based chemotherapy are required to receive at least 1 line of additional chemotherapy and at least 1 line of prior anti-PD1/PDL1 therapy to be eligible.

106 Subjects with a driver mutation (EGFR mutation [exon 19 deletion, L858R point mutation or T790M], BRAF V600E mutation, RET gene fusion, ALK gene rearrangement, MET exon 14 skipping mutation or NTRK gene fusion, KRAS G12C mutation) must experience disease progression on at least 1 approved targeted therapeutic agent to be eligible.

107 Subjects with treated brain metastases are eligible provided they meet the following criteria:

- Treatment (surgery or radiation, including stereotactic radiation) was completed at least 2 weeks prior to the first dose of AMG 160.
- There is no evidence of radiographic central nervous system (CNS) progression following treatment and by the time of study screening. Subjects with new brain metastases detected or progression of previously treated lesions at the time of screening must receive therapy (surgery or radiation) to be eligible. Following definitive treatment, subjects may then be eligible without the need for additional brain imaging.
- Any CNS disease is clinically stable for at least 7 days and the subject is off high-dose steroids [redacted] for at least 7 days (physiologic doses of steroids are permitted).

[redacted]

109 Measurable disease by modified RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression at that site.

110 Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2

111 Life expectancy of greater than or equal to 3 months

112 Adequate organ function, defined as follows:

- absolute neutrophil count $\geq$ 1 x 10^9/L (without growth factor support within 7 days from screening assessment)
- platelet count $\geq$ 100 x 10^9/L (without platelet transfusion within 7 days from screening assessment)
- hemoglobin $>$ 9 g/dL (90 g/L) (without blood transfusion within 7 days from screening assessment)
- estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 30 ml/min/1.73 m^2
- AST and ALT $<$ 3 x upper limit of normal (ULN) (or $<$ 5 x ULN for subjects with liver involvement)
- TBL $<$ 1.5 x ULN (or $<$ 2 x ULN for subjects with liver metastases)
- Cardiac function:
  - left ventricular ejection fraction $>$ 50% (2-D transthoracic echocardiogram [ECHO] is the preferred method of evaluation; multi-gated acquisition scan is acceptable if ECHO is not available)
  - baseline electrocardiogram (ECG) QTcF ≤ 470 msec

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Radiographic evidence of intratumor cavitation.

202 Radiographic evidence of major blood vessel invasion or encasement by cancer.

203 Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period

Other Medical Conditions

204 Unresolved toxicities from prior anti-tumor therapy not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 1, with the exception of alopecia or toxicities that are stable and well-controlled and there is agreement to allow by both the investigator and sponsor.

205 Untreated (includes new lesions or progression in previously treated lesions) or symptomatic brain metastases and leptomeningeal disease.

206 Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures once or more per month. Indwelling catheters are permissible.

207 History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 3 months prior to first dose.

208 History or evidence of gastrointestinal inflammatory bowel disease (ulcerative colitis or Crohn disease).

209 Myocardial infarction, unstable angina, cardiac arrhythmias requiring medication, and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months prior to start of dosing.

210 Vasculitis or grade 3/4 gastrointestinal bleeding within 3 months prior to first dose.

211 History of significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months of first dose.

212 Gastrointestinal (GI) perforation and/or fistulae within 6 months prior to start of dosing.

213 Interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with treatment.

214 Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).

215 Serious, non-healing would, active ulcer, or untreated bone fracture.

Prior/Concomitant Therapy

216 Needing chronic systemic corticosteroid therapy [redacted] or any other immunosuppressive therapies (including anti-tumor necrosis factor-alpha [TNF-α] therapies) unless stopped 7 days prior to first dose.

217 Any biological therapy or immunotherapy within 3 weeks of start of first dose.

- Subjects who received conventional chemotherapy or a targeted therapeutic agent are eligible if at least 14 days have elapsed and if all treatment-related toxicity has been resolved to Grade ≤1.

218 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study.

219 Radiation therapy within 2 weeks of first dose.

220 Major surgery within 4 weeks of first dose (thoracentesis, indwelling catheter placement or line placement is permissible).

221 Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to first dose.

- The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalized ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the enrolling institution) and the subject has been on a stable dose of anticoagulants for at least 2 weeks prior to start of dosing.
- Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR prolongation and aPTT is within normal limits within 14 days prior to start of dosing
- Prophylactic use of low-molecular-weight heparin (ie, enoxaparin 40 mg/day) is permitted

222 Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials for management within 7 days of dosing.

NOTE: Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with sponsor. Screening for chronic infectious conditions is not required.

223 Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed), or hepatitis B infection (subjects with hepatitis B surface antigen [SAg] or core antibody that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed). Screening for these conditions is not required.

224 Active autoimmune disease or any other diseases requiring immunosuppressive therapy (ie, with the use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal insufficiency or pituitary insufficiency, etc) is allowed.

225 Current or recent (within 10 days of first dose) use of high-dose aspirin (≥ 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol.

Other Exclusions

226 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 4 months after the last dose of AMG 160.

227 Female subjects of childbearing potential unwilling to use 1 acceptable method of effective contraception during treatment and for an additional 4 months after the last dose of AMG 160. Refer to Section 11.5 for additional contraceptive information.

228 Female subjects of childbearing potential with a positive pregnancy test assessed at screening by a serum pregnancy test.

229 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 4 months after the last dose of AMG 160. Refer to Section 11.5 for additional contraceptive information.

230 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 4 months after the last dose of AMG 160.

231 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 4 months after the last dose of AMG 160.

232 Subject has known sensitivity to any of the products or components to be administered during dosing.

233 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

234 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

235 Live vaccination is not allowed for at least 4 weeks prior to the start of AMG 160 treatment, during treatment, and until end of last study dose.

236 History or evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection unless agreed upon with Medical Monitor and meeting the following criteria:

- Negative test for SARS-CoV-2 RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) within 72 hours of first dose of AMG 160
- No acute symptoms of SARS-CoV-2 disease within 10 days prior to first dose of AMG 160 (counted from day of positive test for asymptomatic subjects)

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or their legally authorized representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and has received the enrollment confirmation from sponsor. The investigator, designee, or staff member is to document this decision and date in the subject's medical record and in/on the enrollment case report form (CRF). Following enrollment, study treatment should begin as soon as possible but no later than 7 days after enrollment.

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via interactive response technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Refer to Section 8.1.1.

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

	Amgen Investigational Product:[a]
Study Treatment Name	AMG 160
Dosage Formulation	[redacted]
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	**Part 1** The starting target dose of AMG 160 will be 1 dose level below the RP2D or otherwise the highest dose level deemed safe and tolerable as determined in the phase 1 monotherapy study (20180101). AMG 160 will be administered every 2 weeks after target dose is reached. [redacted] **Part 2** This is a dose expansion study. AMG 160 will be administered intravenously every 2 weeks 28-day cycle. The starting dose of AMG 160 will be the dose level that has been recommended as safe and tolerable in Part 1 of this study. To mitigate CRS, the cycle 1 dosing schedule may also be adapted the same way as Part 1 of this study.
Route of Administration	Short-term IV infusion (approximately 60 minutes). [redacted]

Study Treatment Name	Amgen Investigational Product:[a] AMG 160
Accountability	The planned dose, dose received, start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's eCRF(s).
Dosing Instructions	AMG 160 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment. [redacted] See pharmacy file for more detailed information regarding the storage, preparation, destruction, and administration of AMG 160.
Hospitalization Guidance	All subjects will be hospitalized for intensive monitoring for at least 48 hours post AMG 160 infusion during cycle 1[redacted]. The subjects may be discharged after the 48-hour period if there are no clinically significant symptoms of CRS or other acute toxicities. Minimum hospitalization times for subjects will be as follows: • cycle 1: 48 hours after each infusion [redacted] • cycle 2: – 24 hours after first infusion (48 hours in case a subject experienced grade ≥ 2 CRS or infusion reaction in cycle 1 (see Section 11.10.1 for grading of CRS) – 24 hours after each subsequent infusion • for cycles 1 and 2: study sites must have immediate access to a medical intensive care unit staffed by critical care providers • cycles 3 and 4: subject should be monitored in hospital or outpatient clinic for at least 4 hours after start of each infusion • cycle 5 and subsequent cycles: hospitalization not required unless a subject experiences an adverse event requiring hospitalization as described in Table 6-3, or if clinically indicated • re-start of treatment after an interruption due to adverse event: 8 hours Hospitalization beyond these recommended timelines based on adverse events may be allowed per investigator discretion.

C1D1 = cycle 1 day 1; CRS = cytokine release syndrome; DLRT = Dose Level Review Team; eCRF = electronic case report form; IPIM = Investigational Product Instruction Manual; IV = intravenous; IVSS = intravenous solution stabilizer; MTD = maximum tolerated dose; PK = pharmacokinetic(s); RP2D = recommended phase 2 dose; WFI = water for injection.
[a] AMG 160 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.1.1 Non-Amgen Investigational Imaging Products

^{68}Ga-PSMA-11 is a non-Amgen investigational product administered as part of PET/CT imaging assessments in this study.

6.1.2 Non-investigational Products

No non-investigational products will be used in this study.

6.1.3 Medical Devices

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies, including glucocorticoids and tocilizumab/siltuximab, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

[redacted]

For administration of [redacted] or tocilizumab/siltuximab after occurrence of CRS, follow guidance in Table 6-3. Tocilizumab should be administered according to warning and precautions guidelines for tuberculosis provided in the tocilizumab regional prescribing information. [redacted].

Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS. See Section 9.4.1.1.1 for siltuximab stopping rules.

6.1.5 Other Treatment Procedures

Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS.

6.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors and partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s) provisioned and/or repackaged/modified by Amgen (ie, AMG 160).

Any product complaint(s) associated with an investigational or non-investigational product supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments and/or procedures are excluded during the treatment period of the study (unless approved by Amgen medical monitor):

- any anticancer therapy other than AMG 160, such as:
  - cytotoxic and/or cytostatic drugs
  - radiation therapy (with the exception of radiotherapy for symptom control, such as bone or brain metastases after discussion with the medical monitor). The radiation therapy should not include the thoracic field and must have been completed at least 7 days before the subsequent dose of AMG 160.

  - immunotherapy
- chronic systemic corticosteroid therapy ([redacted]) or any other immunosuppressive therapies (except for the management of acute, treatment-related toxicities such as transient [ie, for up to 2 weeks] use of corticosteroids and tocilizumab)
  - high-dose corticosteroid therapy ([redacted]) is only allowed for up to 7 days
- any other investigational agent with the exception of ^{68}Ga-PSMA-11 (if applicable)
- any major surgery (exceptions can be discussed with the medical monitor and may be permissible)

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

6.2.1.1 Dose-exploration

The dose-exploration part of the study will estimate the MTD/RP2D of AMG 160 in NSCLC. The starting dose of AMG 160 will be 1 dose level below the RP2D or otherwise the highest dose level deemed safe and tolerable as determined in the phase 1 monotherapy study (20180101; planned dose levels show in Table 6-2).

Table 6-2. Study 20180101 Planned Doses per Dose Cohort Level

Cohort Number	Dose (mg) IV Every 2 Weeks
[redacted]	

IV = intravenous

Dose Level Determination

Dose exploration will begin with 2 to 4 subjects. The study DLT window is 28 days (see Section 6.2.1.3). To be DLT evaluable, subjects must receive all planned cycle 1 doses of AMG 160. After a minimum of 2 subjects enrolled at a certain dose level are DLT

evaluable, a DLRT meeting will be convened. Depending on observed safety data, the following may occur:

1. additional enrollment to dose Level 1; or
2. dose de-escalation to 1 dose below the starting dose; or
3. alternative dosing schedules, including further dose escalation, as per the ongoing mCRPC trial (Study 20180101), may be explored based on emerging safety and PK data.

Rules for dose-escalation/de-escalation are derived using a modified toxicity probability interval (mTPI) model with a target toxicity probability of 0.28.

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 $<$ 23%
- target TPI: DLT rate from 23% to 33%, inclusive
- over-dosing: DLT rate $>$ 33%

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 or stay at the current level. 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 MTD is the dose level with a DLT toxicity rate closest to 28%.

6.2.1.2 Dose Expansion

If 1 or more OR are observed in dose exploration, dose expansion will be conducted to confirm the safety and tolerability of the selected dose and to further evaluate the efficacy of AMG 160. Dose modification may occur as a result of interim analyses as described in Section 9.4.1.1.

6.2.1.3 Dose-limiting Toxicity

Dose-limiting toxicities are defined as any adverse event with an onset within first 28 days following first dose of AMG 160 with any of the following criteria unless clearly attributable to causes other than AMG 160 treatment:

- grade 5 toxicity (eg, death not due to disease progression)
- grade 3 adverse event lasting more than 3 days (with the exception of fatigue)
- grade 4 adverse event regardless of duration

- grade 3 nausea, vomiting, or diarrhea that do not improve to grade ≤ 1 within 72 hours despite maximum supportive care
- grade ≥ 3 neurologic events that do not improve to grade ≤ 1 within 7 days with treatment interruption and routine medical management
- grade 3 febrile neutropenia that cannot be attributed to CRS
- AST or ALT values of > 3 x ULN AND with serum TBL level of > 2 x ULN without signs of cholestasis or there is no other clear alternative to explain the observed liver-related laboratory abnormalities (ie, criteria for Hy's Law indicative of severe drug-induced liver injury [DILI])
- grade 4 neutropenia lasting > 7 days
- grade 4 thrombocytopenia lasting > 7 days
- grade 3 or higher thrombocytopenia with clinically significant bleeding regardless of duration of thrombocytopenia
- grade 4 anemia
- grade 4 non-hematologic laboratory abnormality of any duration

The following adverse events will NOT be adjudicated as DLT regardless of the duration:

- lymphopenia or lymphocyte count decreased of any grade
- grade 3 fever (defined as a temperature ≥ 40°C with a duration of ≤ 24 hours) occurring outside the context of CRS
- laboratory parameters of grade ≥ 3, not considered clinically relevant, and improved to grade ≤ 2 within 72 hours.
- grade ≥ 3 transaminitis associated with CRS that resolves to grade ≤ 1 within 5 days

Determination of whether a subject is evaluable for DLT assessment will be made in accordance with the following rules:

- Subjects who receive study treatment and remain on study through the DLT assessment window will be considered DLT-evaluable.
- Subjects who do not complete safety assessments during the DLT assessment window for reasons other than a DLT will be considered nonevaluable for dose escalation decisions and MTD determination and may be replaced by an additional subject at that same dose level.

Subjects who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs may be replaced at the discretion of the medical monitor or DLRT. See Section 9.4.1.1.1 for the stopping rules for siltuximab intervention.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: AMG 160

The reason for dose change of AMG 160 is to be recorded on each subject's electronic case report form (eCRF).

For treatment interruptions, delays, and discontinuations, refer to AMG 160 guidance in Table 6-3 in consultation with the Amgen medical monitor.

If any of the following events occur, further accrual will be suspended and a safety analysis conducted and submitted to FDA for review prior to resuming enrollment.

- any 1 treatment-related grade 5 adverse event or
- any 2 of the same treatment-related, clinically significant grade 4 adverse events at least possibly related to AMG 160

6.2.2.1.1 Infusion Interruptions/Delays/Withholding and Re-start in Case of Technical/Logistical Issues

Events leading to infusion interruption or delay for technical/logistical reasons may include: technical problem with the infusion pump or the investigational product is incorrectly prepared or administered.

Infusion Interruptions due to Technical/Logistical Issues

The administration of AMG 160 should not be interrupted for short-term (approximately 60 minute) or [redacted], if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible.

In case of infusion interruption, immediately consult with Amgen medical monitor to determine if:

- investigational product stability is sufficient to administer the remaining infusion or
- a new infusion can be administered or
- the dose should be withheld

For short-term (approximately 60 minute) infusions, if the remaining infusion can be administered, no specific precautions have to be taken. If a new infusion can be administered, follow the procedures in the Schedule of Activities (see Section 1.3) or the cycle day on which the original (interrupted) infusion was administered. [redacted] If the

infusion will need to be withheld, follow the instructions for re-start after interruptions due to adverse events described below for the next infusion.

Any interruption of an infusion should be recorded in the eCRF, providing the start and stop date/time of the infusion if the interruption is > 2 hours.

Infusion Delay due to Technical/Logistical Issues

If the infusion delay was ≤ 72 hours, the dose can be administered without specific precautions. Procedures performed will follow the schedule of assessments for the cycle day on which the infusion was originally planned. The following infusion should then be administered after 14 (± 1) days; eg, if the day 8 infusion needs to be delayed for logistical issues, and could only be administered on day 10, the next infusion should be administered on day 24 (± 1 day) rather than the regular day 22. The ± 1-day window is allowed until the original dosing schedule is met again.

If the delay of the next infusion was > 72 hours, the dose will need to be skipped and the instructions for re-start after interruptions due to adverse events described below should be followed.

6.2.2.1.2 Infusion Interruptions/Delays/Withholding and Re-start due to Adverse Events

6.2.2.1.2.1 General Guidelines

Subjects should be assessed for toxicity before each infusion of AMG 160. The severity of the toxicity will be graded using the CTCAE version 5.0, with the exception of CRS, which must be graded using the criteria referenced in the publication by Lee et al, 2014; TLS, which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008; and immune-effector cell associated neurologic syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al, 2019. Infusion modification and dose reduction due to a toxicity will be performed according to the instructions described below and outlined in Table 6-3.

[redacted]

6.2.2.1.2.2 Infusion Interruptions due to Adverse Events

Events occurring during the infusion and requiring treatment interruption will be managed by immediate infusion interruption. The site should record any unscheduled interruption of an infusion on the eCRF and provide the start and stop date/time of the infusion.

Events requiring an infusion interruption are listed in Table 6-3.

6.2.2.1.2.3 Delay of Subsequent Infusion due to Adverse Events

Events occurring after the end of the infusion and requiring a delay of treatment will be managed by delay of the subsequent infusion. The site should record any delay of an infusion on the eCRF and provide the start and stop date/time of the infusion.

Events requiring a delay of the subsequent infusion are listed in Table 6-3.

Infusion interruptions or delays for other reasons need to be discussed with the Amgen medical monitor.

6.2.2.1.2.4 Re-start of Infusion

Re-starting treatment after an interruption/delay due to an adverse event or if the interruption/ delay was > 72 hours, regardless of the reason, should be performed under medical supervision. [redacted]. The following assessments should be performed as for days 1, 2, and 3 per the Schedule of Activities for cycle 1 (see Section 1.3).

- vital signs, pulse oximetry
- physical examination
- neurological examination (only in case the treatment interruption was due to a neurologic event)
- weight
- ECOG
- safety labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for at least 48 hours after re-start of the infusion.

6.2.2.1.2.5 Dose Adjustments and Re-start at a Lower Dose Level

For adverse events for which restart of treatment is allowed according to the guidelines outlined in Table 6-3, treatment may be resumed at the same or lower dose.

Re-start at a lower dose level:

In the following cases, the next infusion administered should be at the previous (lower) dose level:

If the event occurred during the infusion and caused an interruption of the infusion for more than 72 hours and therefore the affected dose was withheld, or

If the event started after the end of an infusion and administration of the next infusion had to be delayed for more than 72 hours due to the event.

For specific events as outlined in Table 6-3.

In either case, re-escalation to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated with no events requiring dose interruption or delay as described in Table 6-3. After the dose re-escalation, the following assessments should be performed as for day 8 through day 11 per the Schedule of Activities for cycle 1 (see Section 1.3).

- vital signs, pulse oximetry
- physical examination
- neurological examination (only in case the treatment interruption was due to a neurologic event)
- safety labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for at least 48 hours after re-escalation.

In case an additional dose de-escalation is required, permanently discontinue treatment.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Description of Severity	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction					
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	N/A	Consider medication to control infusion reaction as deemed appropriate by the investigator according to local standard of care and institutional guidelines. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable	N/A	N/A
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Short-term infusion: Immediate interruption/delay until event has improved to grade ≤ 1 [redacted]		• Re-start possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. For short-term (approximately 60 minute) infusions, in case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion) • Delay of the next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the delayed infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose, if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Description of Severity	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction (continued)					
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Immediate interruption/ delay until event has improved to grade ≤ 1	Consider supportive therapy including steroids as clinically indicated. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.	• As for grade 2 infusion-related reaction, with the exception of mandatory dose modification: reduce to next lower dose	If subject missed more than 2 consecutive doses of AMG 160
4	Life-threatening consequences; urgent intervention indicated	N/A	As for grade 3 infusion-related reaction	N/A	Immediately stop the infusion (if applicable) and permanently discontinue AMG 160

Page 2 of **14**

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Cytokine Release Syndrome					
1	Symptoms are not life-threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	Avoid treatment interruption	Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.	N/A	N/A
2	Symptoms require and respond to moderate intervention • Grade 1 CRS symptoms, AND • Oxygen requirement < 40%, OR • Hypotension responsive to fluids or low dose of 1 vasopressor[b], OR • Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Immediately interrupt/ delay AMG 160 until event improves to CRS grade ≤ 1. [redacted]	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below. Persistent tachycardia with complications (eg, atrial fibrillation) should be managed with rate control medications (eg, metoprolol) along with cardiology consultation. [redacted]	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen medical monitor first. • In case of infusion interruption, continue treatment with next planned dose (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose, if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If there is no improvement to CRS ≤ grade 1 within 7 days OR If subject missed more than 2 consecutive doses of AMG 160

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Cytokine Release Syndrome (continued)					
3	Symptoms require and respond to aggressive intervention • Grade 1 CRS symptoms, AND • Oxygen requirement ≥ 40%, OR • Hypotension requiring high-dose[b] or multiple vasopressors, OR • Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Immediately interrupt / delay AMG 160 until event improves to CRS grade ≤ 1.	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines (unless related to asymptomatic elevation of liver enzymes). Administer [redacted] (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. AND/OR Investigators should also consider use of tocilizumab[c,d,e]as an additional therapy in this setting at a dose of 4 - 8 mg/kg IV as a single dose. Persistent tachycardia with complications (eg, atrial fibrillation) should be managed with rate control medications (eg, metoprolol) along with cardiology consultation. [redacted]	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult Amgen medical monitor. • In case of infusion interruption, continue treatment with next planned dose (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: reduce to next lower dose (continuation at same dose with [redacted] may be allowed – consult with medical monitor) Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If there is no improvement to CRS ≤ grade 1 within 7 days. OR If subject missed more than 2 consecutive doses of AMG 160 Decision to discontinue should be made in consultation with Amgen medical monitor.

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Cytokine Release Syndrome (continued)					
4	Life-threatening symptoms • Grade 1 CRS symptoms, AND • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria		Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer [redacted] (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, tocilizumab[c,d,e] should be administered if regionally available at a dose of 4 - 8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment. Persistent tachycardia with complications (eg, atrial fibrillation) should be managed with rate control medications (eg, metoprolol) along with cardiology consultation. [redacted]	N/A	Immediately stop the infusion (if applicable) and permanently discontinue AMG 160

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Cairo-Bishop Criteria				
2 (clinical TLS)	Immediate interruption/ delay until event has improved to grade ≤ 1	TLS should be managed according the local standard of care and institutional guidelines.	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days • Consult Amgen medical monitor. • In case of infusion interruption, continue treatment with next schedule infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and **f**ollow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: reduce to next lower dose • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160 OR In case of repeat grade 2 TLS event despite dose reduction.
≥ 3 (clinical TLS)	N/A	TLS should be managed according to the local standard of care and institutional guidelines	• N/A	Immediately stop the infusion (if applicable) and permanently discontinue AMG 160

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Neurological events related to AMG 160				
≥ 2	Interruption/ delay until event has improved to grade ≤ 1	For CRS-related neurological events, use ICANS grading and management system Consider administration of corticosteroids (and tocilizumab[c,d,e] if associated with CRS). Following a seizure: administer anti-seizure medication according to the local standard of care and institutional guidelines For grade ≥3 events, contrast-enhanced magnetic resonance imaging (MRI) of the head should be performed. A neurology consult is recommended.	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If grade 4 event OR In case of more than 1 seizure OR If resolution or improvement to ≤ grade 1 in > 14 days OR In case of repeat ≥ grade 2 event despite dose reduction

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events related to AMG 160				
2	Interruption/ delay required if deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1	GI toxicities should be managed according the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events related to AMG 160 (continued)				
≥ 3	Interruption/ delay until event has improved to grade ≤ 1	GI toxicities should be managed according the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160 OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any other AMG 160-related events not meeting DLT criteria				
≥ 3	Interruption/ delay required if deemed intolerable and/or clinically significant by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1		• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160 OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any Non-AMG 160-related events				
4	Interruption/ delay required if deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1		• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 28 days. • In case of infusion interruption, continue treatment with next scheduled infusion (do not resume prior infusion). • Delay of next infusion: – < 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: [redacted] and additional assessments as indicated in Section 6.2.2.1.2.4	If subject missed more than 2 consecutive doses of AMG 160 OR In case of reappearance of same event at grade 4

Page 11 of **14**

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
[redacted]				
Hepatotoxicity				
For Stopping and Rechallenge Rules please refer to Section 11.7.				
[redacted]				

Page 12 of 14

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

SARS CoV2 infection and COVID19 disease				
asympto matic	Interruption required until at least 10 days since positive SARS-CoV-2 test. UNLESS patient previously fully vaccinated against SARS-CoV-2. If patient previously vaccinated and tests positive, then discuss with Medical Monitor.	Follow local guidelines and standard of care for COVID-19 treatment and isolation Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities	• Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided: ○ There are no new findings on physical exam related to SARS-CoV-2, AND ○ Subject tests negative for SARS-CoV-2 by RT-PCR, OR ○ If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, or If subject initially tests positive in the setting of prior COVID vaccination, resume IP only after discussion with patient and reassessment of individual risk/benefit • Consider chest imaging, ECG, ECHO, and cardiology assessment prior to re-start • Consider hospitalization for re-start of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • [redacted] and assessments: follow guidance in Section 1.3	Immediately stop the infusion (if applicable) and permanently discontinue IP therapy, if: Subject required treatment interruption greater than 28 days and upon discussion with Amgen Medical Monitor the decision is made to permanently discontinue treatment OR Initial benefit/risk assessment for individual patient is not maintained any longer

Page **13** of **14**

Abbreviations and footnotes defined on last page of table.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events Including Dose Reductions

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS CoV2 infection and COVID19 disease (continued)				
symptomatic	Interruption required until at least 10 days since complete resolution of acute symptoms	Follow local guidelines and standard of care for COVID-19 treatment and isolation Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities	• Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided: ○ There are no new findings on physical exam and chest imaging, related to SARS-CoV-2 ○ Subject tests negative for SARS-CoV-2 by RT-PCR, OR ○ If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, resume IP only after discussion with patient and reassessment of individual risk/benefit • Consider chest imaging, ECG, ECHO, and cardiology assessment prior to re-start • Consider hospitalization for re-start of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • [redacted] and assessments: follow guidance in Section 1.3	Immediately stop the infusion (if applicable) and permanently discontinue IP therapy if: Subject required treatment interruption greater than 28 days due to severe or life-threatening COVID-19 OR Initial benefit/risk assessment for individual patient is not maintained any longer

CRS = cytokine release syndrome; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; GI = gastrointestinal; ICANS = immune-effector cell associated neurologic syndrome; IL-6 = interleukin 6; IP = investigational product; IV = intravenous; MRI = magnetic resonance imaging; N/A = not applicable; NSAIDS = non-steroidal anti-inflammatory drugs; PK = pharmacokinetics; Q2 = every 2; RT-PCR = real time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = tumor lysis syndrome; US = United States

[a] Revised grading system for CRS (Lee et al, 2014)

[b] High dose vasopressors (all doses are required for ≥ 3 hours): Norepinephrine monotherapy ≥ 20 μg/min; Dopamine monotherapy ≥ 10 μg/kg/min, Phenylephrine monotherapy ≥ 200 μg/min, Epinephrine monotherapy ≥ 10 μg/min; If on vasopressin, vasopressin + norepinephrine equivalent of ≥ 10 μg/min; If on combination vasopressors (not vasopressin), norepinephrine equivalent of ≥ 20 μg/min

[c] All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and (for sites in regions where tocilizumab is approved and available, eg, the US and Germany) 2 doses of tocilizumab per study subject

[d] If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of cytokine release syndrome, following the criteria outlined in the Management of Adverse Events table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 160. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

[e] A subgroup analysis for subjects treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding DILI guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and other protocol-required therapies during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with AMG 160.

6.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.5 Treatment Compliance

AMG 160 will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational product. Information regarding investigational product administration including date, time, dose, start and stop time of infusion, and other essential information are to be recorded on the individual subject's Investigational Product Administration eCRF per the eCRF completion guidelines. Please refer to IPIM for more details on treatment compliance.

6.6 Treatment of Overdose

The effects of overdose of this product are not known.

The administered AMG 160 dose may be up to 10% lower or higher than specified in the protocol. A dose of up to 10% higher than the intended dose may not require specific intervention.

In any case of overdose, consultation with the Amgen medical monitor is required for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also required even if there are no adverse events, in order to discuss further management of the subject. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved or returned to baseline and the adverse event(s) should be recorded/reported per Section 11.4.

A dose of > 10% higher than the intended AMG 160 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 11.4.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from 1 month prior to signing informed consent will be collected. For all prior therapies not taken for NSCLC, collect therapy name, indication, dose, unit, frequency, route, start and stop dates. All prior cancer treatment therapies will be collected.

For all prior therapies taken for NSCLC (eg, chemotherapy, immunotherapy, biological therapy or targeted therapy), collect (in the order they were administered):

- therapy name
- indication
- dose and schedule of the agent(s)
- unit
- frequency
- start and stop dates
- disease state in which it was administered
- reason for discontinuation (disease progression, clinical progression, toxicity, subject's decision, investigator's decision)

Additionally, details of the dates, portals, and total administered dose by portal should be recorded for all courses of radiation therapy, including those directed at the primary and metastatic site(s). Details of prior radioisotope therapy should also be recorded.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

[redacted]

Concomitant therapies are to be collected from informed consent through the end of the safety follow-up period.

For concomitant therapies being taken for the disease under study (eg, pain medication), collect therapy name, indication, dose, unit, frequency, start and stop dates. For all other concomitant therapies (including vaccines), collect therapy name, dose, start and stop dates (for SARS-CoV2 vaccines collect indication also).

6.7.2.1 Supportive Care

Subjects can receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, etc. Details of supportive care measures should be recorded for subjects in dose expansion phase.

6.7.2.2 Bone Disease Therapy

Treatment of lung cancer-related bone disease, hypercalcemia, and bone pain should be done according to institutional standards. This may include concurrent treatment with bisphosphonates or denosumab. Radiotherapy for palliative care such as bone pain is permitted after discussion with Amgen medical monitor and details should be recorded for subjects in dose expansion phase.

6.7.2.3 Growth Factors

The use of growth factors such as erythropoiesis-stimulating proteins as well as granulocyte colony stimulating factor (G-CSF) will be allowed during therapy per regional and investigator standard of care. However, growth factors are not allowed at inclusion (within 7 days of applicable screening assessment) and should be avoided, if subject`s condition allows, in the first treatment cycle for better assessment of safety parameters.

6.7.2.4 Tumor Lysis Syndrome

TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. Tumor lysis syndrome is characterized by a group of metabolic disorders caused by the massive and abrupt release of cellular metabolites into the blood including lactase dehydrogenase, uric acid, phosphorus, potassium, and calcium after lysis of the malignant cells (Coiffier et al, 2008). The metabolic complications predispose patients with cancer to various clinical complications included renal failure, seizures, cardiac arrhythmias, and even sudden death. To allow for early diagnosis, all subjects must be monitored closely for laboratory and clinical evidence of a possible TLS as outlined in Section 11.10.2.

To prevent TLS, ensure all subjects are well hydrated and provided supportive care measures before administration of AMG 160. To prevent TLS, before administration of AMG 160 all subjects should receive, at the discretion of the investigator, appropriate

hydration and supportive measures according to local standard of care and institutional guidelines. Monitor for evidence of TLS during treatment and manage promptly including interruption of AMG 160 infusion as outlined in Table 6-3. Subjects who experience TLS should be managed according to the local standard of care and institutional guidelines.

6.7.2.5 Nausea, Vomiting, and Diarrhea

The causes of nausea, vomiting, and diarrhea in subjects with cancer can be multifactorial. Therefore, a careful assessment which includes a detailed history, physical examination, and investigations for causes is vital. Management of nausea, vomiting, and diarrhea should be tailored to the individual subject's clinical situation.

6.7.2.5.1 Nausea and Vomiting

Antiemesis prophylaxis may be given according to local standard of care institutional standards if clinically indicated at the investigator's discretion. Treatment of nausea and vomiting with antiemetics such as metoclopramide should be considered according to the local standard of care and institutional guidelines. In cases with nausea and vomiting lasting for > 24 hours, additional treatment with corticosteroids ([redacted]) should be considered depending on tolerability/duration of previous [redacted] administration.

6.7.2.5.2 Diarrhea

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid, and electrolytes should be substituted via IV infusion. Consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.

Treatment with loperamide (starting dose of 4 mg, followed by 2 mg every 2 hours) should start after occurrence of the first episode of diarrhea. In cases with diarrhea lasting for > 24 hours, additional treatment with corticosteroids ([redacted] should be considered depending on tolerability/duration of previous [redacted] administration. Additional work-up and/or gastrointestinal (GI) consultation may be considered, as needed.

6.7.2.6 Vaccines

Every effort should be made to fully vaccinate subjects prior to 14 days from first dose of AMG 160. The use of vaccines except live and live-attenuated vaccines (live-attenuated vaccines for SARS-CoV-2 are allowed per local regulatory and institutional guidelines)

will be allowed during therapy per regional and institutional standard of care. If possible, SARS-CoV-2 vaccinations should be avoided during screening (within a minimum of 14 days from first dose of AMG 160) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the study, SARS-CoV-2 vaccination should be avoided within 3 days before and after the administration of AMG 160 due to the potential of CRS development. In the event where a subject requires steroids for CRS prophylaxis or treatment of adverse events, vaccination should be avoided while on steroids.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the

local country's regulatory mechanism, based on parameters consistent with Section 11.3.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Confirmed disease progression as defined by modified RECIST 1.1 criteria or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition
- Requirement for alternative therapy
- Pregnancy

7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not applicable for this study.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (Section 1.3).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure (standard of care radiographic assessments performed before signing of informed

consent may be used for screening purposes if performed within 28 days of subject enrollment) or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days. **Any blood samples collected during the screening window must be collected within 28 days of cycle 1 day 1.**

For a subject to be eligible for study participation, detectable PSMA expression by ^{68}Ga-PSMA-11 PET/CT imaging [redacted] must be demonstrated during screening. [redacted]

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). On-study visits may be completed within ± 1 day (except for PK collections days) during cycle 1 and cycle 2 and within ± 3 days cycle 3 onward. The date of the first dose of AMG 160 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Assessments are done pre-infusion unless otherwise specified in the schedule of activities.

8.1.3 End of Treatment

For subjects who discontinue investigational product, an end of treatment visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

8.1.4 Safety Follow-up

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 investigational product or prior to initiation of other therapy, whichever occurs first.

8.1.5 Long-term Follow-up

The procedures to be completed during long-term follow-up are indicated in the Schedule of Activities (Section 1.3). Long term follow-up will be conducted every 6 months up to 3 years from the first dose of AMG 160 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.

8.1.6 End of Study Visit

The end of study visit is defined as the date of the final study visit (eg, final long-term follow-up visit) when assessments and/or procedures are performed.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and PK of AMG 160.

8.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to enrollment through the time of consent. Medical history will include

information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

A complete medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved. Any unresolved medical history will be graded according to Common Toxicology Criteria for Adverse Events (CTCAE) version 5.0 (Section 11.4) unless specified otherwise.

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.5 Neurological Examination

If clinically indicated, subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).

The individual performing the neurological examination will characterize the findings as either normal or abnormal. Abnormal findings found pre-dose will be reported on the medical history page of the CRF. Abnormal findings found after the subject is dosed will be reported on the Event page of the CRF.

A more detailed neurological assessment may be performed in subjects at selected sites.

8.2.1.6 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes.

8.2.1.7 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

8.2.1.8 Performance Status

The subject's PS will be assessed using the ECOG performance scale (see Section 11.11).

8.2.2 Efficacy Assessments

Efficacy will be determined by radiographic assessments.

Radiographic assessments will be obtained as scheduled in Table 1-6 irrespective of cycle duration including dose delays and treatment discontinuation.

Standard radiological assessments should take place until clinically significant disease progression or deterioration, withdrawal of consent, or start of new anticancer therapy. Every assessment must include the chest, abdomen, and pelvis, all other known sites of disease and magnetic resonance imaging (MRI) of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. The same contrast and modality used at screening should be used for all subsequent assessments. [redacted].

Tumor burden assessments will be performed based on modified RECIST 1.1 criteria. To confirm PD, a second MRI/CT scan must be performed 4 to 6 weeks after the first detection of radiographical progression. Responses (PR and complete response [CR]) require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of radiographical response. Refer to the imaging manual for details on imaging assessments.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout

the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

After each AMG 160 monotherapy infusion for the first 2 cycles (during the 72-,48-, or 24-hour hospitalization), vital signs should be assessed accordingly during the following time points:

Table 8-1. Vital Sign Time Points

For [redacted] target doses	• Every 60 minutes during infusion and during first 4 hours after end of infusion (EOI) • Every 2 hours from 4 to 12 hours EOI • Every 4 hours from 12 to 24 hours EOI • Every 24 hours EOI, vital signs should be assessed per institutional standards
For cycle 1 [redacted] dosing	• Every 2 hours from 0 to 12 hours after start of infusion • Every 4 hours from 12 to 24 hours after start of infusion • After 24 hours after start of infusion, vital signs should be assessed per institutional standards

8.2.3.2 Pulse Oximetry

Oxygen saturation will be measured using a standard pulse oximeter. The subject must be in a rested and calm state for at least 5 minutes before pulse oximetry assessments are completed.

8.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate (where applicable), and run consecutively. Each triplicate, which consists of three 10-second tracings, should be completed within a total of five minutes from the start of the first to the completion of the third, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Triplicate ECGs (to be only performed if the dose being evaluated is higher than the MTD established in subjects with mCRPC [Study 20180101])

At pre-dose on cycle 1 day 1, baseline ECGs should be collected at 3 time points ≥ 5 minutes apart, with each baseline ECG performed in triplicate, and with at least

5 minutes between the end of each triplicate and the start of the next (total 9 ECGs). During cycle 1 and cycle 2 (at the time points per Schedule of Activities), each ECG should be performed in triplicate (total 3 ECGs). See Section 1.3 for ECG collection time points.

Safety ECGs

As listed in Section 1.3, single ECGs where applicable will be performed and will be referred to as safety ECGs.

The PI or designated site physician will review all ECGs. ECGs will be transferred electronically to an ECG central vendor per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

8.2.3.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.4 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 11.4. CRS, which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 11.10.1) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.10.2), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 11.10.3).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of AMG 160 through the safety follow-up visit are reported using the Event CRF.

8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the **safety follow-up visit** are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events (including fatal events) after the protocol-required reporting period (as defined in Section 8.2.4.1.2) is complete, these serious adverse events will be reported to Amgen (regardless of causality). The investigator will report **these** serious adverse events to Amgen within 24 hours following the investigator's **awareness** of the event **on the Events CRF**.

After end of study, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be

reported to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records if the subject ends the study.

8.2.4.1.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (any fatal event occurring outside the protocol required reporting period) that are study endpoints are reported on the Event CRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (refer to Section 11.4).

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional followup information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor holding the relevant Investigational New Drug/Clinical Trial Application for either AMG 160 or ^{68}Ga-PSMA-11 has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of AMG 160 or ^{68}Ga-PSMA-11, respectively, under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 4 months after the last dose of AMG 160.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

Pregnancy Testing

A high sensitive (serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and 4 months after the last dose of protocol-required therapies.

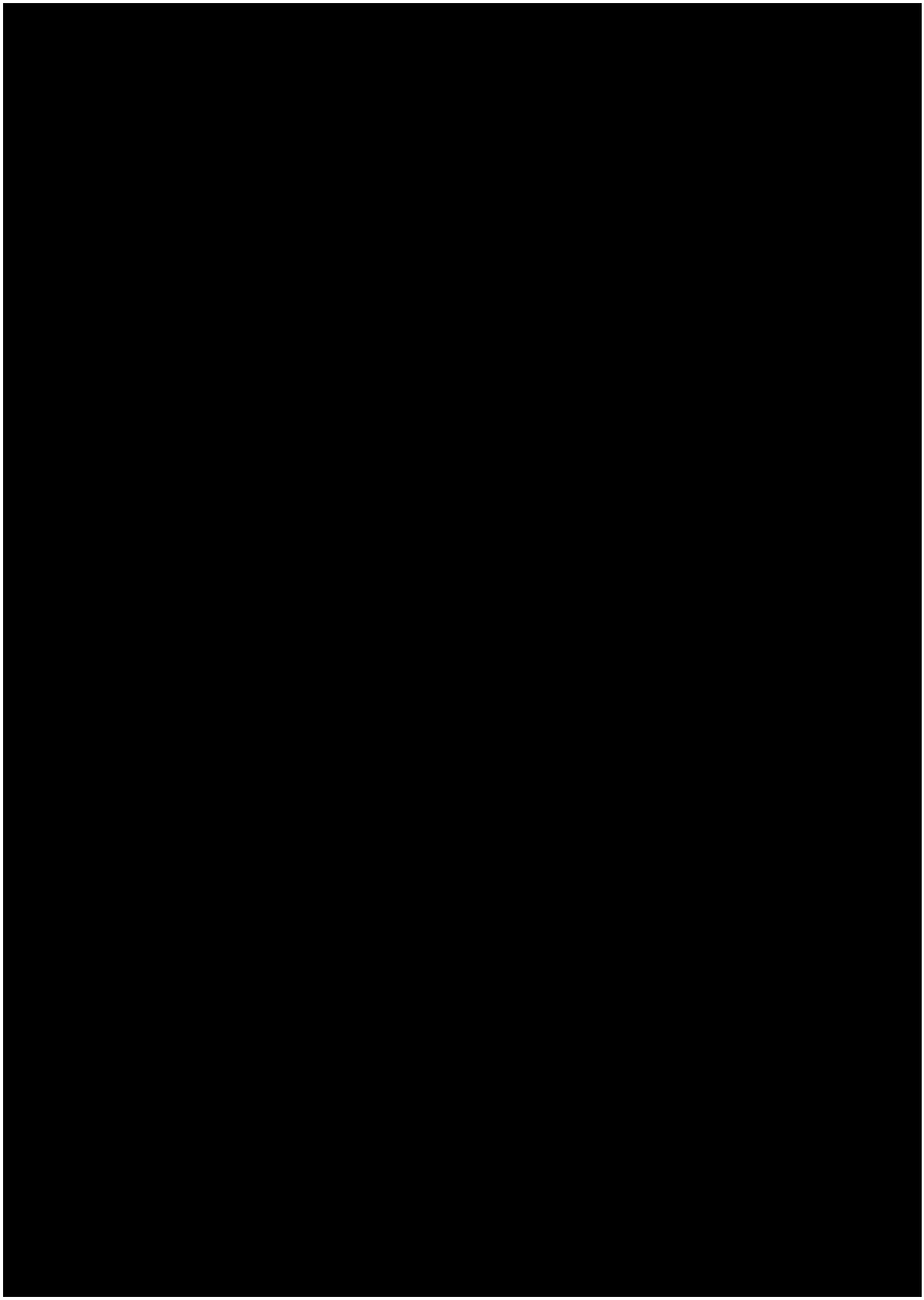
Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

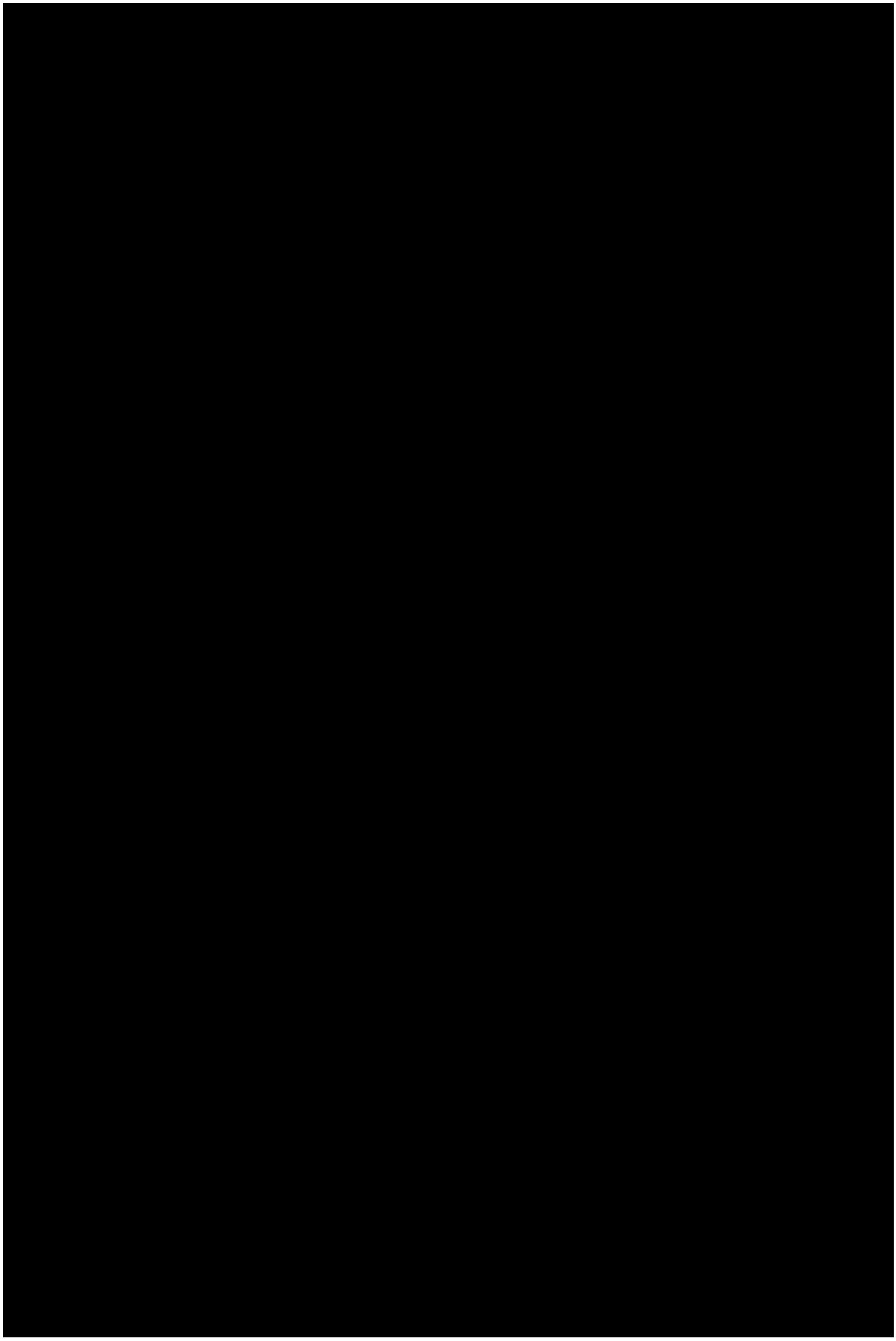
8.2.6 Pharmacokinetic Assessments

All subjects enrolled will have PK samples assessed.

Whole blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of AMG 160 as specified in the Schedule of Activities (Section 1.3) Instructions for the collection and handling of biological samples will be provided by the

sponsor. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF.





[redacted]

9. Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2 Sample Size Determination

Up to 50 subjects will be enrolled in the study (approximately 10 subjects in a dose exploration phase and up to 40 subjects in a dose expansion phase). Additional subjects (up to 20) 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 may be done to better estimate the RP2D and better characterize the safety, efficacy, PK, [redacted] of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

An initial 2 to 4 subjects will be enrolled and treated with Dose Level 1 (1 dose level below RP2D of AMG 160 Study 20180101). Rules for dose-escalation/de-escalation are derived using an mTPI model with a target toxicity probability of 0.28 (see Section 6.2.1.1). If the dose is not tolerated (based on target DLT rate > 28%), the dose level will be reduced 1 level below the starting dose. Alternative dosing schedules, including further dose escalation as per the ongoing mCRPC trial (Study 20180101), may be explored based on emerging safety and PK data. The sample size in the dose exploration phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD.

With 2 subjects in a cohort, there is a 19% to 55% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 4 subjects in a cohort, there is a 34% to 80% probability. With 6 subjects in a cohort, there is a 47% to 91% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 10 subjects in a cohort, there is a 65% to 98% probability.

In the dose expansion phase, a subject number of 40 will provide a 87% 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 the 40 subjects and 20% overall response rate, the expected 95% CI would be 9% to 36%.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

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.

The analysis of DLT will be conducted on the DLT Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 160 with an evaluable DLT endpoint. The DLT endpoint is evaluable if either: 1) the subject experiences a DLT; or 2) the subject does not experience a DLT after receiving all planned doses within the 28-day DLT window in cycle 1.

9.3.2 Covariates

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

[redacted]

9.3.4 Handling of Missing and Incomplete Data

Descriptive statistics will be used to identify the extent of missing data. Missing or incomplete dates that are critical to efficacy and safety analysis (eg, date of death, adverse event start date) will be imputed. Detailed imputation rules will be documented in statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis.

During dose exploration and formally during DLRMs, Amgen, in consultation with the site investigators, will review all available cumulative data by cohort prior to making dose escalation or dose de-escalation recommendations. 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. During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

1) Terminate the trial

2) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate [redacted])
3) Continue dose expansion without any changes

The stopping rules use a Bayesian approach proposed by Thall et al, 1995 to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in Table 9-1 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 9-2. The operating characteristics in Table 9-2 provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in Table 9-2 are based on situations where the empirical evidence would result in a posterior probability of ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 20%.

Table 9-1. Stopping Boundary for Dose Expansion With Posterior Probability of 80% and Grade 4 or Higher Treatment-related Adverse Event Limit of 20%

Number of Subjects	Stop Study if Observing These Many Grade 4 or Higher Treatment-related Adverse Events
10	≥ 4
20	≥ 6
30	≥ 9
40	Dose Expansion Complete

Table 9-2. Operating Characteristics With Batch Size of 10 Subjects

True Grade 4 or Higher Treatment-related Adverse Event Rate	Probability of Early Stopping of Dose Expansion	Average Dose Expansion Sample Size
0.10	2.0%	39.5
0.15	9.1%	37.6
0.20	23.2%	33.9
0.25	42.2%	28.8
0.30	61.6%	23.4

A formal interim analysis of available safety and efficacy data will occur when the first 10 evaluable subjects enrolled have had the opportunity to complete 4 months on study. This interim analysis will estimate MTD, support the determination of RP2D, conduct futility analysis of objective response rate (ORR), and support the evaluation of benefit/risk profile of AMG 160 as a monotherapy.

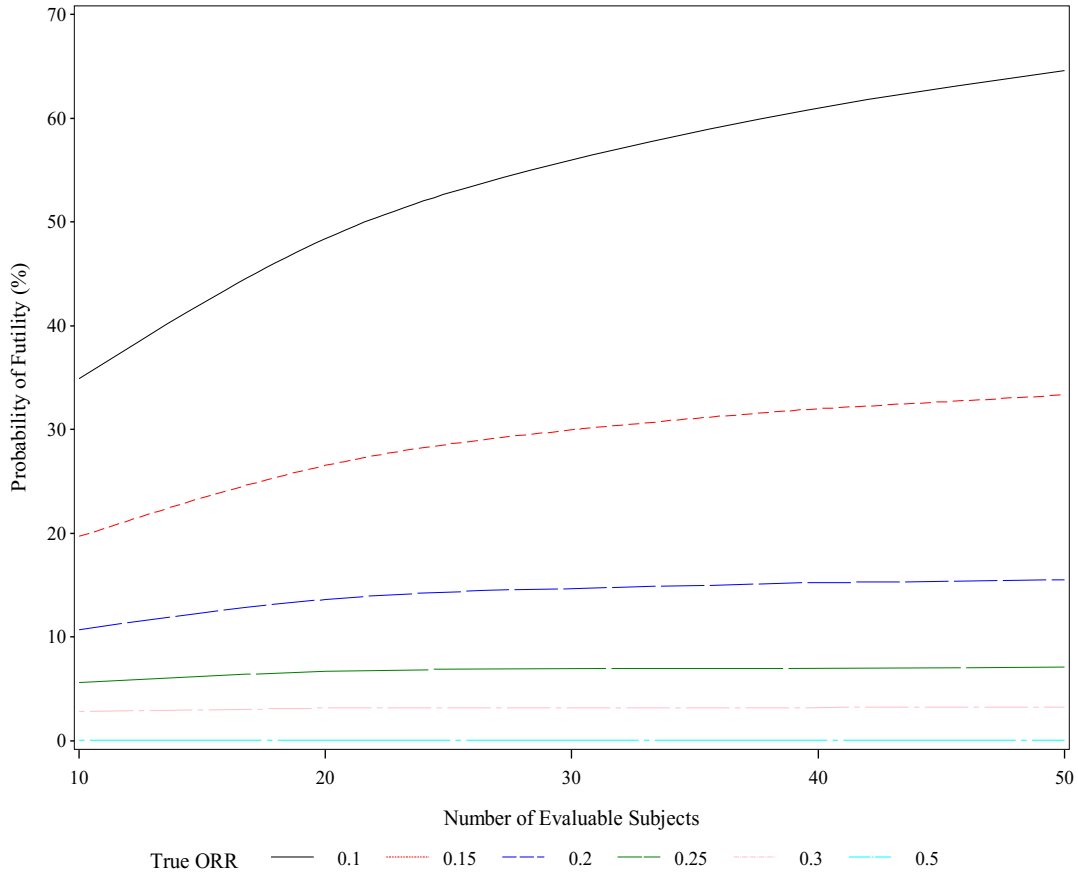
A futility analysis of ORR will be performed using Bayesian predictive probability (Lee and Liu, 2008) when the first 10 evaluable subjects reach month 4. If the predictive probability of observing ORR response > 15% at the end of the study with 50 evaluable subjects is less than 30%, the study may stop early (pT = 0.25). Equivalently, if we observe ≥ 1 objective responder in the first 10 subjects, an additional subjects (up to 40) will be enrolled into the expansion cohort. The predictive probability is calculated with a noninformative prior, Jeffreys prior, Beta(0.5, 0.5).

Similarly, futility analyses will also be conducted during the expansion cohort. The stopping boundaries are presented in Table 9-3. The operating characteristics in Figure 9-1 provide the probability of stopping the trial early for given hypothetical true rate of ORR.

Table 9-3. Objective Response Rate Stopping Boundary

Number of Evaluable Subjects Each Month 4	Stop Study if Observed Objective Response Rate (ORR) Response
10	< 1
20	< 2
30	< 3
40	< 4
50	Study Complete

Figure 9-1. The Probability of Stopping The Trial Early



9.4.1.1.1 Stopping Rules for Treatment With Siltuximab

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

frequently if necessary to address emerging safety concerns. If the triggered adhoc DLRM coincides with the regular DLRM, they may be combined.

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

9.4.1.2 Primary Analysis

The primary analysis for the dose exploration phase will occur when target enrollment is complete and each subject either completes 6 months on the study or withdraws from the study.

The primary analysis for the study will occur when target enrollment is complete for the dose expansion phase and each subject either completes 1 year on study or withdraws from the study.

9.4.1.3 Final Analysis

The final analysis will occur when target enrollment is complete for both phases and all subjects have ended the study.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, efficacy, [redacted] by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

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

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects. The proportion of subjects with an OR (per modified RECIST 1.1) and 95% CI will be tabulated by planned dose level. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate the time to event curve, median time to event and percentiles with 95% CI for 1) duration of response; 2) time to progression; 3) progression-free survival; 4) time to subsequent therapy; 5) overall survival; 6) time to response. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (eg, 1-year PFS) with 95% CI).
[redacted]	

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received AMG 160. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. The statistical analysis methods for other safety endpoints are in Section 9.4.2.3 below.

9.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term and grade. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. A subgroup analysis of safety with CRS outcome and PK will be performed for subjects who were administered siltuximab.

9.4.2.3.3 Laboratory Test Results

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject. 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

9.4.2.3.4 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.

9.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each subject.

9.4.2.3.6 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 cohort will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each cohort will be summarized. All on-study ECG data will be listed and select parameters of interest plotted.

[redacted]

9.4.2.3.8 Exposure to Investigational Product

Details of AMG 160 administration will be listed for every subject.

9.4.2.3.9 Exposure to Non-investigational Product

Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given. The number of days on non-investigational product, the daily dose, and the proportion of subjects receiving each dose level will be summarized using descriptive statistics.

Compliance with non-investigational product will summarized for each subject using descriptive statistics.

9.4.2.3.10 Exposure to Other Protocol-required Therapy

Descriptive statistics of total dose (mg/kg), total dose (mg), average daily dose, cumulative dose and number of cycles will be produced to describe the exposure to AMG 160 by planned dose level.

9.4.2.3.11 Exposure to Concomitant Medication

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

9.4.2.4 Other Analyses

Pharmacokinetic parameters will be determined from the time concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. [redacted].

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BiTE	bispecific T-cell engager
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CAR-T	chimeric antigen receptor T cells
CD	cluster of differentiation
CFR	U.S. Code of Federal Regulations
CI	confidence intervals
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTC0	circulating tumor cell zero
[redacted]	
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicities
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram

Abbreviation or Term	Definition/Explanation
EGFR	epidermal growth factor receptor
[redacted]	
EMA	European Medicines Agency
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
EOI	end of infusion
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FSH	follicle stimulating hormone
^{68}Ga	^{68}Gallium
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
GSO	Global Safety Officer
HIV	human immunodeficiency virus
HLE	half-life extended
HNSTD	highest nonseverely toxic dose
HRT	hormone replacement therapy
ICANS	immune-effector cell associated neurologic syndrome
ICE	immune effector cell associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
ICP	intracranial pressure
IEC	Independent Ethics Committee

Abbreviation or Term	Definition/Explanation
[redacted]	
Ig	immunoglobulin
IL-6	interleukin-6
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
IUD	intrauterine device
IV	intravenous
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA scan	multigated acquisition scan
NA	not available
NCT	National Clinical Trials
ND	not done
NTRK	neurotrophic tropomyosin-related kinase
NSCLC	non-small cell lung cancer
OR	objective response(s)
ORR	objective response rate
OS	overall survival
[redacted]	
PCWG3	Prostate Cancer Working Group 3
[redacted]	
PD	disease progression
PD1	programmed cell death protein 1
PDL1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PS	performance status
PSA	prostate specific antigen

Abbreviation or Term	Definition/Explanation
PSMA	prostate-specific membrane antigen
rPFS	progression-free survival (radiographic)
RECIST	Response Evaluation Criteria in Solid Tumors
RR	relapsed/refractory
RP2D	recommended phase 2 dose
RT-PCR	reverse transcriptase-polymerase chain reaction
SAg	surface antigen
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
scFc	single chain fragment crystallizable
SC	subcutaneous
SD	stable disease
SLD	sum of the longest diameters
Source Data	information from an original record or certified copy of the original record containing patient 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.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2}$	half-life
TBL	total bilirubin
TLS	tumor lysis syndrome
TPI	toxicity probability intervals
TPS	tumor proportion score
TNF	anti-tumor necrosis factor
UE	unable to evaluate
ULN	upper limit of normal

11.2 Appendix 2. Clinical Laboratory Tests

The tests will be performed by the local laboratory or by the central laboratory (Table 11-1). Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Laboratory Analyte Listing

<table>
<tr><td colspan="5">LOCAL LABORATORY</td></tr>
<tr><td colspan="2">Chemistry</td><td>Urinalysis</td><td>Hematology</td><td>Coagulation</td></tr>
<tr><td>sodium
potassium
chloride
bicarbonate
total protein
albumin
calcium
adjusted calcium
magnesium
phosphorus
glucose
BUN or urea</td><td>creatinine
uric acid
total bilirubin
direct bilirubin
AST (SGOT)
ALT (SGPT)
ALP
LDH
CRP
ferritin
eGFR[a]</td><td>specific gravity
pH
blood
protein
glucose
bilirubin
WBC
RBC
epithelial cells
bacteria
casts
crystals</td><td>RBC
hemoglobin
hematocrit
reticulocytes
platelets
WBC differential:
• neutrophils
•bands/stabs (if available)
•segmented neutrophils (if available)
• eosinophils
• basophils
• lymphocytes
• monocytes
ANC</td><td>aPTT
PT/INR
fibrinogen
D-dimer

Other Labs
Pregnancy test</td></tr>
<tr><td colspan="5">CENTRAL LABORATORY</td></tr>
<tr><td colspan="5">[redacted]</td></tr>
<tr><td colspan="5">PK collection</td></tr>
</table>

ALT=alanine aminotransferase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cr = creatinine; CRP = C-reactive protein; [redacted]; eGFR = estimated glomerular filtration rate; HRR = homologous recombination repair; INR = international normalized ratio; LDH = lactate dehydrogenase; MDRD = Modification of Diet in Renal Disease; [redacted] PK = pharmacokinetics; PSMA = prostate-specific membrane antigen; PT = prothrombin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell

[a] eGFR will be based on Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 1999):

- eGFR = 186 x (Serum Cr-1.154) x (age-0.203) x 1.212 (if subject is black) x 0.742 (if subject is female)
- use serum creatinine (Cr) in mg/dL for this formula

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Team

Dose Level Review Meetings (DLRM)

A Dose Level Review Meeting (DLRM) is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation (either to the next planned dose or to an intermediate dose), dose level de-escalation, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); modifying the [redacted] and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. Per DLRT recommendations additional prophylaxis may be implemented, including IV hydration (eg, 1 L normal saline), acetaminophen (eg, 975 mg PO single dose), and/or tocilizumab (4-8 mg/kg IV single dose) prior to or immediately after each AMG 160 doses in cycle 1. [redacted] The required Dose Level Review Team (DLRT) members are the medical monitor, Global Safety Officer (GSO), and Site Investigators. The DLRT will include all Site Investigators. The medical monitor, GSO, and Site Investigators are the only voting DLRT members. The following non-voting Amgen representatives may also be part of the DLRT: clinical study manager, biostatistician, or pharmacokinetics (PK) scientist.

The medical monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or Site Investigator(s). A Site Investigator may identify a delegate (eg, sub-Investigator) who is listed in the Delegation of Authority. If a Site Investigator does this, the Site Investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the medical monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must be present. A quorum is defined as more than 50% of the participating investigators or their qualified designee. The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed. Data to be reviewed will be cleaned/queried.

DLRM voting will occur as follows: there will be a total of 3 votes, 1 for the medical monitor, 1 for the GSO or delegate, and 1 for all of the Site Investigators or delegates combined. Regardless of how many Site Investigators there are, all of the Site Investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

DLRM recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 30 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate

signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the interactive response technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list

- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to non-small cell lung cancer (NSCLC) report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
    - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
    - Dates of onset and resolution (if resolved);
    - **Assessment of seriousness;**
    - Severity (or toxicity defined below);
    - assessment of relatedness to investigational product, other protocol-required therapies, and/or study-mandated procedure including ^{68}Gallium (^{68}Ga)- prostate-specific membrane antigen (PSMA)-11, and
    - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The **Common Terminology Criteria for Adverse Events**, version 5.0 which is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Cytokine release syndrome (CRS), which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 11.10.1) and tumor lysis syndrome (TLS), which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.10.2), and immune-effector cell associated neurologic syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al (2019) (see Section 11.10.3).

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and/or study-mandated procedure including ^{68}Ga-PSMA-11 and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is

very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.

- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's knowledge of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 11-1).
- **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator**

becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN
Study # 20180273
AMG 160

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship: Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP? AMG 160 No✓ Yes✓	Gs-PSMA No✓ Yes✓	<Device> No✓ Yes✓	<Device> No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 160	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Gs-PSMA	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*
Page 1 of 3

AMGEN Study # 20180273 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year) / Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20180273 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 4 months after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 4 months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)

- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 4 months after the last dose of AMG 160.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 4 months after the last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 4 months after discontinuing protocol-required therapies, the information will be

recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 4 months must practice sexual abstinence or use a condom through 4 months.
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 4 months after the last dose of AMG 160.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 226.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 4 months after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20180273_____

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID #_____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20180273_____

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ___(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood, [redacted], or pharmacokinetics (PK) samples collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the lung cancer, the dose response and/or prediction of response to AMG 160, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining sample types (eg, blood, [redacted]) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time > 5 x ULN but < 8x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic (PK) analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

11.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an FDA IND safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 11.4.

Anticipated Serious Adverse Events for Study 20180273

Preferred Term[a]
Brain metastases
Cancer pain bone pain
Fatigue
Hemoptysis
Hypercalcemia
Leukopenia
Pathologic fracture
Shortness of breath
Spinal cord compression

[a] MedDRA Version 22

11.9 Appendix 9. Modified Toxicity Probability Interval Design (mTPI)

Trial monitoring rules are based on a modified toxicity probability interval design (mTPI). Prespecified monitoring rules are based on mTPI to determine the maximum tolerated dose (MTD) with target dose-limiting toxicity (DLT) rate of 28% (Table 11-3). The mTPI 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 Dose Decision Outcomes with a 28% 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 three toxicity probability intervals (TPI).

- Under-dosing TPI: DLT rate from 0 to < 23%
- Target TPI: DLT rate from 23% to 33%, inclusive
- Over-dosing: DLT rate > 33%

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, MTD is the dose level with a DLT toxicity rate closest to 28%.

All subjects who are enrolled and receive at least 1 dose of AMG 160 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 step dose and target doses, support the determination of the recommended phase 2 dose (RP2D), and support the evaluation of benefit/risk profile of AMG 160.

Table 11-3. mTPI Trial Monitoring Table

Number of Subjects at current dose

# of DLTs	2	3	4	5	6	7	8	9	10
0	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	E	E	E	E
2	DU	D	S	S	S	S	S	S	S
3		DU	DU	D	D	S	S	S	S
4			DU	DU	DU	DU	D	S	S
5				DU	DU	DU	DU	DU	D
6					DU	DU	DU	DU	DU
7						DU	DU	DU	DU
8							DU	DU	DU
9								DU	DU
10									DU

E: Escalate to the next higher dose, if feasible; Otherwise, stay at the same dose;
S: Stay at the same dose; D: De-escalate to the previous lower dose;
DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial

11.10 Appendix 10. Specific Guidance for Cytokine Release Syndrome, Tumor Lysis Syndrome, and Immune-effector Cell-associated Neurologic Syndrome

11.10.1 Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome (CRS) is clinically defined and may have various manifestations. There are no established diagnostic criteria. Signs and symptoms of CRS may include:

- constitutional: fever, rigors, fatigue, malaise
- neurologic: headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure
- respiratory: dyspnea, tachypnea, hypoxemia
- cardiovascular: tachycardia, hypotension
- gastrointestinal (GI): nausea, vomiting, transaminitis, hyperbilirubinemia
- hematology: bleeding, hypofibrinogenemia, elevated D-dimer
- skin: rash

Subjects may be at an increased risk for CRS during the first few days following administration of protocol-required therapies. CRS may be life threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with protocol-required therapies, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Refer to the main protocol body for the more information on the following:

- grading and management of CRS (based on the adopted grading system referenced in Lee et al, 2014) should be performed according to the guidelines provided
- general guidance for re-start of infusion after interruptions/delay/withholding and dose modifications.
- dose-limiting toxicity (DLT) considerations for grade 3 and 4 CRS

Fever reported outside the context of CRS will be graded per Common Toxicology Criteria for Adverse Events (CTCAE) version 5.0.

11.10.2 Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies tumor lysis syndrome (TLS) in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 5.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this trial, the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 11-4) and clinical TLS (see Table 11-5) including grading.

Based on the Cairo and Bishop system, laboratory TLS is defined as any 2 or more abnormal serum values present within 3 days before or 7 days after initiation of treatment in the setting of adequate hydration (with or without alkalinization) and use of a hypouricemic agent (Table 11-4).

Table 11-4. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change from Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory tumor lysis syndrome.

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 11-5). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 11-5.

Table 11-5. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Grade	Creatinine[a,b]	Cardiac Arrhythmia[a]	Seizure[a]
0	≤ 1.5 x ULN	None	None
1	1.5 x ULN	Intervention not indicated	--
2	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL
3	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention
4	> 6.0 x ULN	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)
5	Death	Death	Death

Note. Laboratory TLS and at least 1 clinical complication will constitute clinical TLS.
ADL = activities of daily living; CHF = congestive heart failure; TLS = tumor lysis syndrome; ULN = upper limit of normal
[a] Not directly or probably attributable to therapeutic agent.
[b] If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 μmol/L; ≥ 12 to < 16 years, both male and female, 88 μmol/L; ≥ 16 years, female 105.6 μmol/L, male 114.4 μmol/L.

11.10.3 Specific Guidance for Immune-effector Cell-associated Neurologic Syndrome

For this trial, immune-effector cell associated neurologic syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al (2019). While the grading system has been developed in large part from chimeric antigen receptor T cells (CAR-T) therapies, symptoms of ICANS may be shared among immune effector-cell associated therapies such as bispecific T-cell engager (BiTE) molecules. Although there may be a wide range of symptoms associated with ICANS, subjects may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

ICANS grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause. Refer to the immune effector cellassociated encephalopathy (ICE) score below for grading of ICANS.

Immune Effector Cell-associated Encephalopathy (ICE) Assessment Tool

- Orientation: Orientation to year, month, city, hospital: 4 points
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
- Following commands: ability to follow simple commands (eg, “Show me two fingers” or “Close your eyes and stick out your tongue”): 1 point
- Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point
- Attention: ability to count backwards from 100 by 10: 1 point

ICE scoring

- 7-9, grade 1
- 3-6, grade 2
- 0-2, grade 3
- 0 due to subject unarousable and unable to perform ICE
- Assessment, grade 4

Table 11-6. ASBMT Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (subject is unarousable and unable and unable to perform ICE)
Depression level of consiousness[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASBMT = American Society for Blood and Marrow Transplantation; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune-effector cell associated neurologic syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable.

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading It may be graded according to CTCAE v5.0.

Source: Lee et al, 2019

Assessment and Supportive Care Recommendations (all grades)

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- MRI of the brain with and without contrast (or brain computed tomography (CT) if MRI is not feasible) for ≥ grade 2 neurotoxicity
- Neurology consultation at first sign of neurotoxicity

- Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity
- Aspiration precautions; IV hydration
- Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)

Table 11-7. Assessment and Supportive Care Recommendations

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
Grade 1	• Supportive care	In the setting of grade ≥ 3 CRS with hypotension, tocilizumab[e,f] 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)[d]
Grade 2[c]	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.	Anti-IL-6 therapy as per grade 1[d] Consider transferring subject to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[c]	• Supportive care • Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[a] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject had persistent grade ≥ 3 neurotoxicity.	Anti-IL-6 therapy as per grade 1[d]
Grade 4[c]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids [a,b] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject has persistent grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per grade 1[d]

CRS = cytokine release syndrome; CT = computed tomography; ICU = intensive care unit; IL-6 = interleukin-6; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetics.

[a] Antifungal prophylaxis should be strongly considered in subjects receiving steroids for the treatment of CRS and/or neurotoxicity.

[b] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

[c] Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.

[d] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

[e] If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of cytokine release syndrome, following the criteria outlined in the Management of Adverse Events table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 160. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

[f] A subgroup analysis for subjects treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

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11.11 Appendix 11. Performance Status According to Eastern Cooperative Oncology Group (ECOG)

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Source: Oken et al, 1982

11.12 Appendix 12. Response Evaluation Criteria in Solid Tumors Version 1.1 (modified RECIST 1.1)

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) are guidelines for assessing tumor burden changes in response to treatment (Eisenhauer et al, 2009). Additional patterns of response have been observed with immune-enhancing therapies, including delayed clinical response, leading to criteria modifications to capture treatment responses more accurately (Wolchok JD et al, 2009; Nishino M et al, 2013). This study utilizes modified RECIST 1.1 criteria which applies aspects of the immune-related response criteria (including requiring confirmation of disease progression) to RECIST 1.1 as outlined below.

Modified RECIST 1.1 tumor response assessment

- All measurable and non-measurable lesions should be assessed at screening, all defined tumor assessment time points (Schedule of Assessment), and any unscheduled imaging visits.

Measurable lesions:

- Non-nodal lesions with clear borders that can be measured accurately and serially in one dimension in the axial plane (longest diameter ≥ 10 mm measured by MRI/CT with scan slice thickness ≤ 5 mm).
- Nodal lesions with the longest diameter perpendicular to the long axis (short axis) ≥ 15 mm on MRI/CT.
- Must exclude simple cysts, pleural/pericardial effusions and ascites.

Non-measurable lesions:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) are considered non-measurable and characterized as non-**target** lesions.
- Other examples of non-measurable lesions include:
    - Lesions with prior local treatment:
        - Tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
    - Biopsied lesions
    - Categorically, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable. See Imaging Procedural Manual provided by the central imaging core laboratory for additional guidance.

Target lesions and measurable tumor burden:

- **Target** lesions:
  - Measurable lesions (≤ 5 lesions per organ, ≤ 10 total) selected at baseline on the basis of
    - Size and suitability for accurate repeated measurements by imaging.
    - Representative of the subject's tumor burden, all organs involved and overall disease status

Non-target lesions:

- All measurable lesions not selected as **target** lesions and non-measurable lesions
- Non **target** lesions will be qualitatively evaluated
  - Values: 'Present', 'absent' or 'unequivocal progression'.
- Other definitions
  - Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
  - Not Available (NA): Scan not available
  - Not Done (ND): Radiologic imaging was not performed at this time point to evaluate the **target** lesions

Target lesion response:

- At baseline and all subsequent tumor assessments, measurable tumor burden is the sum of the longest diameters (SLD) of all **target** lesions
- Complete Response (CR) – disappearance of all measurable lesions
  - Pathologic lymph nodes must have reduction in short axis to < 10 mm
- Partial Response (PR) – decrease of 30% or greater in tumor burden compared with baseline
- Stable Disease (SD) - not meeting the criteria for CR, PR, or progressive disease
- Progressive Disease – increase of 20% or greater in tumor burden compared with nadir, or the appearance of one or more new lesions

Non-target lesion response:

- CR – disappearance of all non-**target** lesions
  - Pathologic lymph nodes must have reduction in short axis to < 10 mm
- SD – persistence of one or more non-**target** lesions, not meeting the criteria for CR or progressive disease
- Progressive disease – unequivocal progression of existing non-**target** lesions, or the appearance of one or more new lesions

Overall response:

- CR
  - Complete disappearance of all lesions
    - Pathologic lymph nodes must have reduction in short axis to < 10 mm
  - Confirmation scan required - repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
  - CR is dated at time of confirmation scan
- PR
  - Decrease in tumor burden ≥ 30% relative to baseline, or
  - Complete disappearance of all **target** lesions with presence of non-**target** lesions
  - Confirmation scan required - repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
  - PR is dated at time of confirmation scan
- SD
  - **Target** lesions not meeting criteria for CR, PR or progressive disease, or
  - In subjects with only non-**target** disease, persistence of one or more non-**target** lesions
- Progressive Disease
  - Radiologic detection of ≥ 20% increase in tumor burden relative to nadir and at least 5 mm absolute increase, or
  - Unequivocal progression of non-**target** lesions, or
  - The presence of new lesions
  - Confirmation scan required - repeat, consecutive assessment 4-6 weeks from the date of the first documented response
    - Radiographic progressive disease is confirmed at repeat imaging (progressive disease on two consecutive scans 4-6 weeks apart) if:
      - Tumor burden remains increased by ≥ 20% and at least 5 mm absolute increase relative to nadir, or
      - Unequivocal progression of non-**target** lesions is observed, or
      - New lesions are present
    - Subjects with a global deterioration of health status requiring discontinuation of treatment prior to radiologic confirmation of disease progression should have the reason for treatment discontinuation classified as ‘clinical disease progression’ not ‘radiographic progressive disease’. Every effort should be made to radiologically confirm progression even after discontinuation of treatment.

Summary of Measurement and Tumor Response Assessment Based on Modified RECIST 1.1	
Measurable lesions	• Non-nodal lesions: ≥ 10 mm (unidimensional measurement) • Pathologic lymph nodes: longest diameter short axis ≥ 15 mm
Measurement of each lesion	• Non-nodal lesions: The longest diameter (mm) in the axial plane • Pathologic lymph nodes: short axis (mm)
Tumor burden	• Sum of the longest diameters (SLD) of all **target** lesions • Up to 5 lesions per organ, up to 10 total
Response assessment: **target** lesions (calculated from % change in tumor burden)	• CR: Disappearance of all lesions • Pathologic lymph nodes short axis < 10 mm • PR: ≥ 30% decrease from baseline • SD: Does not meet criteria for CR, PR or progressive disease. • Progressive disease: ≥ 20% increase (and ≥ 5 mm absolute increase) from nadir
Response assessment: non-**target** lesions	• CR: Disappearance of all lesions • Pathologic lymph nodes short axis < 10 mm • SD: Persistence of one or more non-**target** lesion(s) • Progressive disease: Unequivocal progression of existing non-**target** lesions
New Lesions	The presence of new lesion(s) defines progression
Confirmation	Confirmation by subsequent assessment after ≥4 weeks required for CR, PR and progressive disease.

Summary of modified RECIST 1.1 Overall Response Assessment			
Target lesions (tumor burden)[a], %	Non-**target** lesions	New lesions	Overall Response using modified RECIST 1.1
↓ 100%	Absent	Absent	CR[b]
None[d]	Absent	Absent	CR[b]
↓ 100%	Present	Absent	PR[b]
↓ ≥30%	Absent/Present	Absent	PR[b]
↓ <30% to ↑ <20%	Absent/Present	Absent	SD
None[d]	Present	Absent	SD
↑ ≥20%	Any	Any	Progressive disease[c]
Any	Unequivocal progression	Any	Progressive disease[c]
Any	Any	Present	Progressive disease[c]
NA/ND/UE	Absent/Present	Absent	UE
None[d]	NA/ND/UE	Absent	UE

CR = complete response; NA = not available; ND = not done; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UE = unable to evaluate

[a] Decrease assessed relative to baseline. Increase assessed relative to nadir.

[b] Response: CR and PR require a confirmation assessment after ≥4 weeks, may also wait until the next scheduled imaging

[c] Progression: Progressive disease requires a confirmation assessment 4-6 weeks after initial radiographic progressive disease is observed

[d] Subjects with non-**target** lesions only

11.13 Appendix 13. COVID-19 Guidance

- Subjects who test positive for coronavirus disease 2019 (COVID-19) using a test consistent with the institutional standard of care or who are exhibiting symptoms consistent with COVID-19 should not be enrolled in the study until complete resolution of symptoms.
- If an enrolled subject is exhibiting symptoms consistent with COVID-19, contact the Amgen Medical Monitor within 1 business day to ensure appropriate documentation and management of study activities.
- If a subject is unable to travel to the site for protocol-specified study visits and procedures, he/she can remain in the trial, provided that safety monitoring can occur. Alternatives, such as telemedicine to conduct visits, should be considered.
- On-site monitoring visits may be replaced by remote monitoring visits during COVID-19. Additionally, remote source document verification may be utilized for critical data points.
- Additional COVID-19 guidance from Food and Drug Administration (FDA) and European Medicines Agency (EMA) should be followed in consultation with Amgen medical monitor.

Amendment 4

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Amgen Protocol Number (AMG 160) 20180273

NCT Number: NCT04822298

Amendment Date: 25 March 2022

Rationale:

This protocol is being amended due to a change in the key safety risks for AMG 160. [redacted]

Amendment 3

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Amgen Protocol Number AMG 160 20180273

EudraCT number: to be determined

NCT Number: NCT04822298

Amendment Date: 19 October 2021

Rationale:

This protocol is being amended to address site shortages of tocilizumab. Applicable sections of the protocol are being modified to clarify the use of siltuximab in place of tocilizumab for the treatment of potential cytokine release syndrome (CRS) during a treatment-related adverse event. [redacted]. Additional language was included to update/clarify other items in the protocol. The following changes were incorporated into the study:

- Electrocardiograms (ECGs) were removed from the primary endpoints.
- [redacted]
- Added language to Overall Design in Sections 1.1 and 4.1 to allow additional subjects to be enrolled at 1 or more monotherapy dose levels that have been shown to be safe and tolerable.

- Subject Enrollment in Section 5.3 was modified to incorporate designee or staff members as additional personnel responsible for the documentation of subject enrollment to study.
- Added language to Subject Enrollment in Section 5.3 to clarify that:
    - subject enrollment in study will need additional confirmation from sponsor
    - study treatment should begin following study enrollment but no later than 7 days after enrollment
- Treatment/Other Protocol-Required Therapies Section 6.1.5 was added to clarify that sites are required to have tocilizumab or siltuximab for potential treatment of CRS.
- Criteria for use of siltuximab in place of tocilizumab, justification for the proposed dose and schedule, and safety stopping rules were included as Section 6.2.1.4.
- Added language to Concomitant Treatments Section 6.7.2 to clarify site availability of tocilizumab or siltuximab for CRS treatment.
- Added language to Section 8.1.1 to clarify that the use of standard of care radiographic assessments can be used for the screening process prior to signing of informed consent.
- Vital Sign Time Points Table 8-1 was updated to incorporate vital sign measurements for short term infusions.
- Added footnotes to Tables 6-3 and 11-7 to clarify the alternative use of siltuximab when tocilizumab is unavailable, and to incorporate a subgroup analysis that evaluates CRS outcomes, safety, and pharmacokinetic (PK) data of siltuximab-treated subjects.
- Administrative, typographical, and formatting changes throughout the protocol.

Amendment 2

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Amgen Protocol Number AMG 160 (acapatamab) 20180273

Amendment Date: 29 July 2021

Rationale:

The rationale for this protocol amendment is to include the following updates:

[redacted]

- Updated to include guidance relating to coronavirus disease 2019 (COVID-19):
  - Eligibility criteria was updated to exclude subjects that have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
  - Guidance for COVID-19 vaccinations was added (Sections 6.7.2 and 6.7.2.6)
  - Table 6-3 was updated to include management for subjects with asympotomatic and symptomatic SARS-COV-2 infection and COVID-19 disease

[redacted]

- Update to include minor clarifications regarding Statistical Considerations such as the modified toxicity probability interval (mTPI) (Section 9.2 and Table 11-3) and the futility analysis (Section 9.4.1.1)
- Several sections of the protocol have been updated to include required alignments with current Amgen protocol template (Sections 8.2.4, 8.2.4.1.3, 11.2, 11.3, 11.13).
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Superseded Amendment 1

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Amgen Protocol Number AMG 160 20180273

Amendment Date:	20 October 2020
Superseded Amendment Date:	25 January 2021

Rationale:

- Potential differences in prostate specific membrane antigen (PSMA) expression between castrate-resistant prostate cancer (CRPC) and non-small cell lung cancer (NSCLC) may lead to disease-related safety profile differences. Given the potential for a different safety profile in NSCLC, the starting dose has been adjusted to begin at 1 dose level below the RP2D identified in Study 20180101

- The dose limiting toxicity (DLT) definition has been modified to include additional life-threatening events, including Grade 4 anemia, Grade 4 non-hematologic laboratory abnormality of any duration and Grade 3 or higher thrombocytopenia with clinically significant bleeding regardless of duration of thrombocytopenia. Additionally, the DLT definition has been updated to include Grade 4 neutropenia lasting > 7 days, Grade 4 thrombocytopenia lasting > 7 days and Grade ≥ 3 transaminitis associated with CRS that resolves to grade ≤ 1 within 5 days. DLT criteria has also been updated to include AST/ALT/bilirubin elevations meeting Hy's law criteria as a DLT

- Updated inclusion criteria # 105 regarding prior adjuvant or neoadjuvant chemotherapy to specify platinum-based adjuvant or neoadjuvant chemotherapy and to adjusted inclusion criteria # 105 to allow subjects who progress on at least 1 prior anti-PD1/PDL1 therapy and deemed unsuitable for treatment with chemotherapy or actively refused treatment with chemotherapy to be eligible

On 25 January 2021, the protocol was superseded to correct minor typographical errors in the approved amendment.

Amendment 1

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 160 in Subjects with Non-Small Cell Lung Cancer

Amgen Protocol Number AMG 160 20180273

Amendment Date: 20 October 2020

Rationale:

[redacted]

- Potential differences in prostate specific membrane antigen (PSMA) expression between castrate-resistant prostate cancer (CRPC) and non-small cell lung cancer (NSCLC) may lead to disease-related safety profile differences. Given the potential for a different safety profile in NSCLC, the starting dose has been adjusted to begin at 1 dose level below the RP2D identified in Study 20180101

[redacted]

- The dose limiting toxicity (DLT) definition has been modified to include additional life-threatening events, including Grade 4 anemia, Grade 4 non-hematologic

laboratory abnormality of any duration and Grade 3 or higher thrombocytopenia with clinically significant bleeding regardless of duration of thrombocytopenia. Additionally, the DLT definition has been updated to include Grade 4 neutropenia lasting > 7 days, Grade 4 thrombocytopenia lasting > 7 days and Grade ≥ 3 transaminitis associated with CRS that resolves to grade ≤ 1 within 5 days. DLT criteria has also been updated to include AST/ALT/bilirubin elevations meeting Hy's law criteria as a DLT

[redacted]

- Updated inclusion criteria # 105 regarding prior adjuvant or neoadjuvant chemotherapy to specify platinum-based adjuvant or neoadjuvant chemotherapy and to adjusted inclusion criteria # 105 to allow subjects who progress on at least 1 prior anti-PD1/PDL1 therapy and deemed unsuitable for treatment with chemotherapy or actively refused treatment with chemotherapy to be eligible

[redacted]