Title Page

Protocol Title:		A Phase 1b Study Assessing Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 330 cIV in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Acute Myeloid Leukemia
Short Protocol Title:		A Phase 1b Study of AMG 330 in Combination With Pembrolizumab in Adult Subjects with Relapsed or Refractory Acute Myeloid Leukemia
Protocol Number:		20170646
Investigational Product:		AMG 330 + Pembrolizumab
Trade Name:		N/A
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		Not applicable
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Protocol Version Date:		**Document Version** **Date** **Original** 04 May 2020
Data Elements Standards Version:		6

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

NCT Number: NCT04478695
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1b Study Assessing Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 330 cIV in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Acute Myeloid Leukemia, dated 04 May 2020, 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 partner 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)

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1b Study Assessing Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 330 cIV in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Acute Myeloid Leukemia
Short Protocol Title: A Phase 1b Study of AMG 330 in Combination With Pembrolizumab in Adult Subjects with Relapsed or Refractory Acute Myeloid Leukemia

Study Phase: Phase 1b

Indication: Adult Subjects with Relapsed or Refractory Acute Myeloid Leukemia (AML)

Rationale

- AMG 330 is a canonical bispecific cluster of differentiation (CD)33/CD3 T-cell engager (BiTE®) molecule in development for myeloid malignancies.
- AMG 330 targets CD33 which is expressed on the cell surface of AML blasts from > 95% of AML cases.
- AMG 330 lead indication is relapsed or refractory AML (R/R AML), and this patient population is characterized by a poor prognosis, whose 5-year survival remains about 10%.
- CD33 represents a validated target in AML with development and approval of Mylotarg (gemtuzumab ozogamicin) that demonstrated clinical benefit in select AML patient populations.
- Preliminary efficacy has been demonstrated for AMG 330. During the ongoing phase 1a dose escalation study, 5 patients with R/R AML treated with [redacted], and [redacted] µg target doses achieved complete remission (CR)/incomplete recovery (CRi).
- AMG 330 dose levels from [redacted] to [redacted] µg have been assessed in the phase 1a monotherapy dose escalation study, considered safe and tolerable and will be tested in combination with pembrolizumab. Higher doses of AMG 330 have not been tested as monotherapy and will not be included in this study.
- Up-regulation of the programmed cell death 1 (PD-1) receptor and programmed cell death ligand 1 (PD-L1) immune checkpoint has been established in ex vivo cytotoxicity models as a key mediator of acquired resistance to AMG 330 therapy (Krupka et al, 2016). AMG 330-induced T-cell activation resulted in upregulation of PD-L1 on primary AML cells.
- Through blockade of the PD-1/PD-L1 interaction, AMG 330-mediated lysis, T-cell proliferation and interferon (IFN)-gamma secretion were significantly enhanced in vitro (Krupka et al, 2016).
- Preliminary assessment of T cells from patients treated with AMG 330 shows up-regulation of PD-1 expression.
- The hypothesis is that co-administration with a PD-1 immune checkpoint inhibitor will further augment AMG 330 activity, produce deeper and more durable remissions, and prevent and/or delay acquired resistance to AMG 330 therapy.
- Pembrolizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity and high affinity of binding to PD-1, thus blocking its interaction with PD-L1 and PD-L2. Pembrolizumab has an acceptable clinical safety profile, is indicated for the treatment of patients across a number of malignancies, and is in clinical development as an intravenous (IV) immunotherapy for additional advanced

tumors. For more details on specific indications for Keytruda® (pembrolizumab) refer to the Investigator's Brochure.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 330 administered in combination with pembrolizumab in subjects with relapsed or refractory acute myeloid leukemia (R/R AML)	• Dose-limiting toxicities (DLTs) • Treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• Evaluate the anti-leukemia activity of AMG 330 administered in combination with pembrolizumab in R/R AML patients	• Responses to treatment with AMG 330 administered in combination with pembrolizumab. Response is defined as any of the following: complete remission without mininum residual disease (CR_{MRD-}), complete remission (CR), CR with incomplete recovery (CRi), or morphological leukemia-free state (MLFS), or partial remission (all according to the 2017 European LeukemiaNet (ELN) criteria (Döhner et al, 2017). • Duration of response
• Evaluate the pharmacokinetics (PK) of AMG 330 when AMG 330 and pembrolizumab are administered in combination	• Descriptive statistics of AMG 330 concentrations and PK parameters.
• Evaluate the immunogenicity of AMG 330 when administered in combination with pembrolizumab	• Incidence of anti-AMG 330 antibody formation

Overall Design

This is a phase 1b study assessing safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 330 administered as continuous intravenous (cIV) infusion in combination with pembrolizumab in adult subjects with R/R AML.

The study is a non-randomized study and will consist of 2 sequential dosing cohorts. Both cohorts will include AMG 330 and pembrolizumab with the difference being the initiation date for pembrolizumab treatment.

This study will use a staggered enrollment approach. Subject enrollment will start with cohort 1. The first subject dosed in cohort 1 will serve as the sentinel subject. Subsequent subjects dosed in cohort 1 will start AMG 330 ([redacted] µg/day) administration once sentinel subject has cleared study day 21 (AMG 330 monotherapy at [redacted] µg/day). Per sponsor determination, if the sentinel subject does not experience a dose-limiting toxicity (DLT) during days 15 to 21 after pembrolizumab is administered, the other subjects in cohort 1 will be allowed to continue the planned treatment schedule. Investigators and sponsor will meet after all subjects in cohort 1 have completed study day 28 (ie, AMG 330 [redacted] µg/day dose level in combination with pembrolizumab) to assess the safety profile. If the safety data from cohort 1 is acceptable per the

pre-specified DLT criteria, subjects enrolled in cohort 2 may proceed with the treatment schedule. Similar to cohort 1, the first subject dosed in cohort 2 will serve as the sentinel subject. Per sponsor determination, if the sentinel subject does not experience a DLT during the first 7 days, the other subjects in cohort 2 will be allowed to continue the planned treatment schedule.

Safety data will be continuously monitored throughout the whole treatment period. Study team in consultation with investigators may reconvene to make appropriate safety measures and adjustments as needed.

Cohort 1 Design:

Cycle 1 is 77 days in duration and subsequent cycles are 57 days in duration. Treatment will start with AMG 330 on day 1. AMG 330 will be administered at a starting dose of [redacted] µg/day for 3 days, followed by [redacted] µg/day for 4 days, followed by [redacted] µg/day for 7 days. If the subject has not experienced a DLT by day 14, they will receive pembrolizumab on day 15. Pembrolizumab will be administered at a dose of 200 mg (Q3W) by a 30-minute IV infusion. The subject will remain at an AMG 330 dose level of [redacted] µg/day for an additional 7 days. Thereafter, AMG 330 dosing will continue as per Table 4-1, increasing dose levels up to [redacted] µg/day as tolerated by subjects. Pembrolizumab dosing will continue every 21 days starting from day 15.

Cohort 2 Design:

All cycles are 57 days in duration. Subjects in cohort 2 will receive both AMG 330 and pembrolizumab on day 1. Pembrolizumab will be administered at a dose of 200 mg (Q3W) by a 30-minute IV infusion. If the subject does not develop a ≥ grade 2 infusion reaction, or if the infusion reaction is reversible after a 1-hour observation period, the subject will start AMG 330 at a starting dose of [redacted] µg/day for 3 days, followed by [redacted] µg/day for 4 days, followed by [redacted] µg/day for 7 days, and continue dosing as per Table 4-3, increasing dose levels every 7 days up to [redacted] µg/day as tolerated by subjects. Pembrolizumab will be administered at 200 mg IV once every 3 weeks.

Cohorts 1 and 2:

Subjects in both cohort 1 and cohort 2 may continue with cycle 2 and beyond of AMG 330 and pembrolizumab up to 6 months if the combination regimen remains tolerable and is deriving clinical benefit in the opinion of the investigator. In both cohorts 1 and 2, subjects continuing with cycle 2 and beyond may be permitted to shorten the duration of AMG 330 step dose levels to 2 to 5 days based on individual clinical experience from cycle 1 and based on the clinical judgement of the investigator and in consultation and agreement with the sponsor. The duration of the combination treatment period for individual subjects may be extended up to 1 year if the subject is deriving clinical benefit in the opinion of the investigator and in consultation with the sponsor. If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression for a maximum of 35 cycles (approximately 2 years). If pembrolizumab is discontinued, AMG 330 may be continued as a monotherapy.

Number of Subjects

It is anticipated that approximately 20 subjects will be enrolled in this study, with at least 6 DLT evaluable subjects in each cohort. With 6 evaluable subjects in 1 cohort, there is an 82% chance of observing at least 1 DLT if the true DLT rate is 25%.

Summary of Subject Eligibility Criteria

This study will enroll adult subjects with relapsed/refractory AML.

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

Treatments

AMG 330 and the intravenous solution stabilizer (IVSS) will be manufactured and packaged by Amgen Inc. KEYTRUDA® (pembrolizumab) solution for infusion will be manufactured and packaged by Merck & Co Inc. Both products will be distributed using Amgen clinical study drug distribution procedures. AMG 330 is supplied as a sterile, single-use, powder for solution in a vial containing [redacted] mg of AMG 330. The drug product is formulated with potassium phosphate, captisol, sucrose, polysorbate 80, pH [redacted]. The final container is a 5 cc glass vial and contains 1 mL deliverable volume of AMG 330. The IVSS is supplied as a sterile solution in a 10 cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted], pH [redacted]). The IVSS is intended for pre-treatment of IV bags prior to dilution of AMG 330 drug product. KEYTRUDA® (pembrolizumab) will be supplied as two 100 mg/4 mL (25 mg/mL), single-dose vials.

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within the 14 days preceding administration of the first dose of (day 1), unless otherwise noted. Subjects will be seen in clinic where evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiogram (ECGs), PK, and [redacted] sample collections.

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 Table 1-1, Table 1-3, and Table 1-5.

Statistical Considerations

All subjects who are enrolled and receive at least 1 administration of the investigational product (AMG 330 and pembrolizumab) will be included in the analysis, unless otherwise specified.

The primary analysis will occur when all subjects complete end of study. Descriptive statistics will be provided for selected demographics, safety, efficacy, PK, [redacted], and [redacted] data overall and by cohort 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.

The number and percentage of subjects reporting any treatment-emergent adverse events (TEAEs) and treatment-related adverse events will be tabulated. The number of percentage of subjects reporting DLTs will be summarized for DLT evaluable subjects. Additional safety parameters including clinical laboratory test, ECG, and vital sign data may be summarized as data over time and/or changes from baseline over time.

The proportion of responding subjects (defined as any of the following: complete remission without mininum residual disease (CR_{MRD-}), CR, CRi, morphologic leukemia-free state (MLFS), or partial remission (PR) per 2017 European LeukemiaNet (ELN) response criteria will be tabulated. Duration of response will be presented per subject and Kaplan-Meier estimates may also be further presented if data allows. For a full description of statistical analysis methods, please refer to Section 9. Details of the statistical analysis will also be described in the statistical analysis plan.

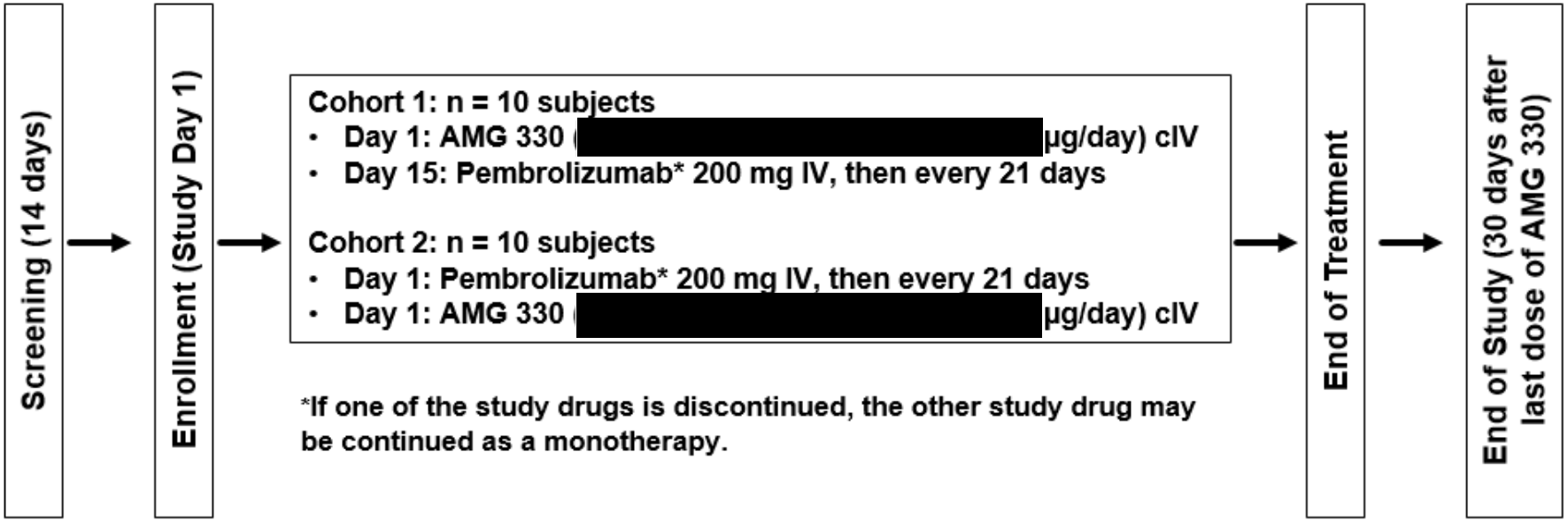
Statistical Hypotheses

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

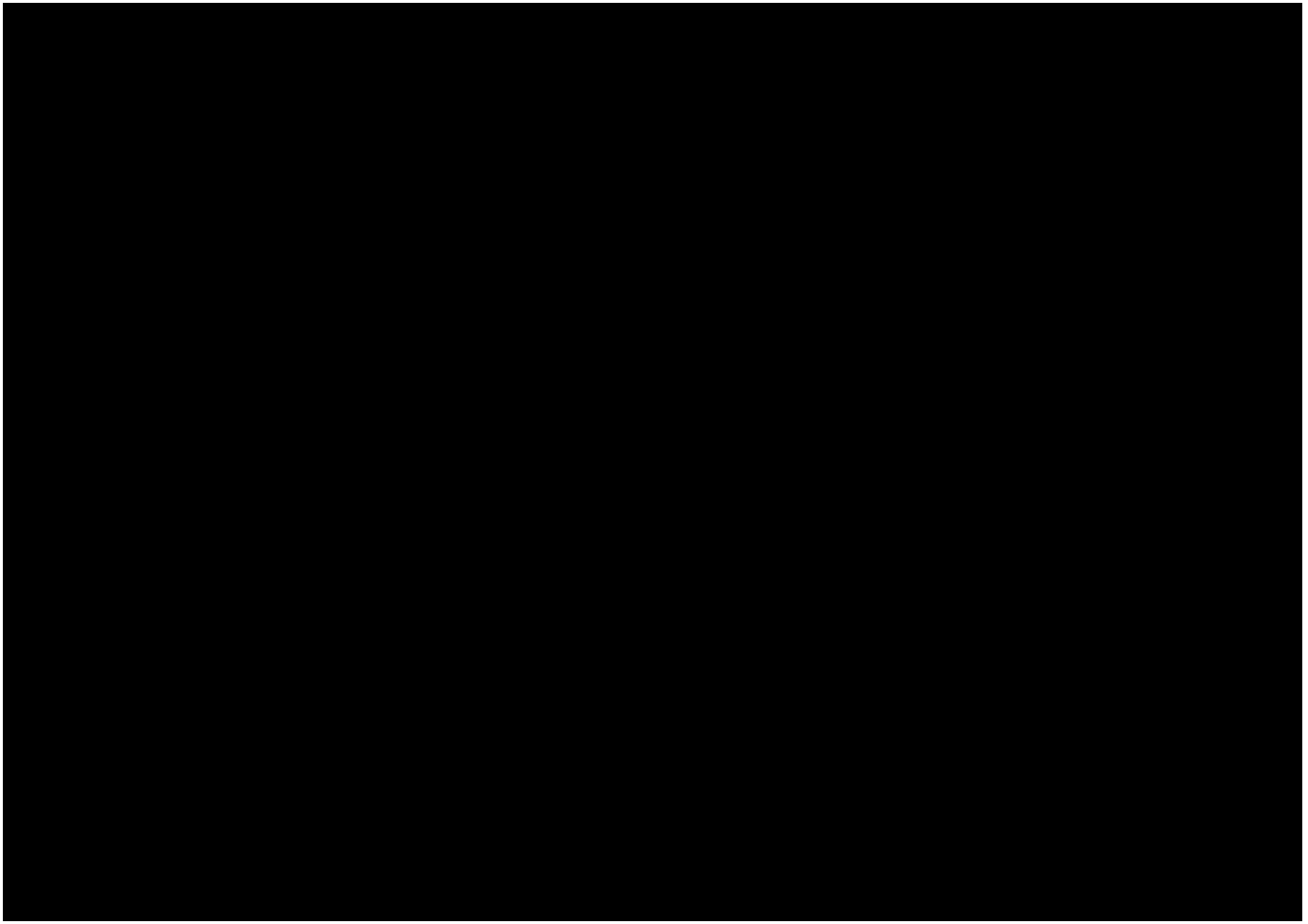
Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



clV = continuous intravenous; IV = intravenous



1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities for Cohort 1, Cycle 1

	SCR	Treatment Period																								Infusion-free period[a]							Pembrolizumab monotherapy Cycles 2-35[b]	EOT	SFU[c]
Cycle 1 Day:		1										2	3	4	8	15	22	29	36	43	50	57	64	71	78					79	80-84			
Hours		Pre-dose	0.5	1	2	3	4	6	8	12	16	20													EOI	0.5	2	4	8					
GENERAL AND SAFETY ASSESSMENTS																																		
Informed consent	X																																	
Hospitalization[d]		X										X	X	X	X	X	X	X	X	X	X	X	X	X									
Concomitant Medications		←==========																							==========→									
Serious adverse events		←==========																							==========→									
Adverse events[e]			←==========																						==========→									
Clinical Evaluation[f]	X	X										X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X
Vital signs, pulse oximetry[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X		X	X	X
12-lead ECG[h]	X	X	X									X													X									X
LABORATORY ASSESSMENTS																																		
Highly sensitive pregnancy test[i]	X	X																																X
Coagulation[j]	X	X							X			X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X
Hematology, Chemistry[j]	X	X							X			X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X
Urinalysis	X	X											X		X	X	X	X	X	X	X	X	X	X	X								X	X
Hepatitis Serology[k]	X																																	
Thyroid Function Tests[l]		X																		X												X		
Anti-AMG 330-antibody[m]		X														X		X	X			X			X								X	X
Anti-Pembrolizumab-antibody[m]																X			X			X			X									
INVESTIGATIONAL PRODUCT DOSING																																		
AMG 330			X																															
Pembrolizumab																X			X			X			X							X[b]		
GENERAL AND SAFETY ASSESSMENTS																																		
[redacted]																																		
PK ASSESSMENTS																																		
AMG 330 PK Collection[n]		X						X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pembrolizumab PK Collection (predose)[o]																X			X			X			X									
Pembrolizumab PK Collection (post dose)[p]																X			X			X			X									
DISEASE ASSESSMENTS																																		
Bone marrow aspirate/biopsy	X																	X[r]		X			X[r]		X							X[q]		X[s]

CD = cluster of differentiation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; [redacted] PK = pharmacokinetic; SCR = screening; SFU = safety follow-up

[a] If the investigator determines that the subject has derived treatment benefit, they may proceed to cycle 2 (Table 1-3). If the subject does not proceed to receive additional treatment cycles, they will proceed to end of study assessment on day 107 (30 days after last dose of investigational product).

[b] If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression, administered every 21 days, for a maximum of 35 cycles (approximately 2 years).
[c] Two safety follow-up visits should be performed: 30 days (+ 7 days) after the last dose of AMG 330 and 30 days (+ 7 days) after the last dose of pembrolizumab. If the 2 safety follow-up periods overlap, the 2 safety follow-up visits can be combined into one.
[d] Hospitalization will be required at the start of study day 1 and for a minimum of 72 hours following initiation of AMG 330, after each AMG 330 dose level increase and after each pembrolizumab administration.
[e] Adverse events will be collected from start of AMG 330 infusion on study day 1.
[f] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.
[g] Vital signs will be obtained after start of AMG 330 infusion on study day 1 and after AMG 330 dose level increases. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[h] Measurements to be taken in triplicate.
[i] A highly sensitive (serum or urine) pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[j] Coagulation, hematology, and chemistry to be collected 8 hours after start of AMG 330 infusion on study day 1.
[k] Hepatitis serologies include hepatitis B surface antigen (HBsAg) or quantifiable hepatitis B virus (HBV) viral load, hepatitis C antibody or RNA.
[l] Thyroid function testing every 6 weeks while on treatment. Thyroid panel should include: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH).
[m] Anti-AMG 330 antibody and anti-pembrolizumab antibody samples will be collected at the indicated time points during the study, and on days when both AMG 330 and pembrolizumab are to be administered, anti-AMG 330 antibody and anti-pembrolizumab antibody samples will be collected before administration of pembrolizumab and before administration of AMG 330 step-dose on that day at the indicated time points throughout the treatment period.

[redacted]

[p] Pembrolizumab PK samples will be collected 30 minutes post infusion of pembrolizumab (on day 15, 36, 57, and 78).

[redacted]

Table 1-2. [redacted] Collection Schedule for Cohort 1, Cycle 1

AMG 330 dose level (cIV)	AMG 330 days administered	Pembrolizumab days administered (IV infusion)	[redacted]
[redacted] µg/day	D1-3		
[redacted] µg/day	D4-7		
[redacted] µg/day	D8-14, D15-21	D15	
[redacted] µg/day	D22-28		
[redacted] µg/day	D29-35; D36-42	D36	
[redacted] µg/day	D43-49		
[redacted] µg/day	D50-56; D57-63	D57	
[redacted] µg/day	D64-77		
[redacted] µg/day (infusion free period)	D78-85	D78	

cIV = continuous intravenous; CXDX = cycle X day X; D = day; EOI = end of infusion; HR = hour; IV = intravenous

[redacted]

Table 1-3. Schedule of Activities for Cohort 1, Cycles 2 and beyond

	Treatment Period																				1 week infusion free interval [a]							Pembrolizumab monotherapy Cycles 3-35[b]	EOT	SFU [c]
Cycle Day:	1										2	3	4	8	15	22	29	36	43	50	57					58	59-63			
	Pre-dose	0.5	1	2	3	4	6	8	12	16	20										EOI	0.5	2	4	8					
GENERAL AND SAFETY ASSESSMENTS																														
Hospitalization[d]	X																													
Concomitant Medications		←==========																												
Serious adverse events		←==========																												
Adverse events[e]		←==========																												
Clinical Evaluation[f]	X										X	X	X	X	X	X	X	X	X	X	X							X	X	X
Vital signs, pulse oximetry[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X		X	X	
12-lead ECG[h]	X	X									X										X									X
LABORATORY ASSESSMENTS																														
Highly sensitive pregnancy test[i]	X																													X
Coagulation[j]	X							X				X	X	X	X	X	X	X	X	X	X							X	X	X
Hematology, Chemistry[j]	X							X				X	X	X	X	X	X	X	X	X	X							X	X	X
Urinalysis	X											X		X	X	X	X	X	X	X	X							X	X	X
Thyroid Function Tests[k]	X																		X									X		
Anti-AMG 330-antibody[l]	X														X		X	X			X								X	X
INVESTIGATIONAL PRODUCT DOSING																														
AMG 330		X																												
Pembrolizumab															X			X			X							X[b]		
GENERAL AND SAFETY ASSESSMENTS																														
[redacted]																														
PK ASSESSMENTS																														
AMG 330 PK Collection[m]	X						X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
DISEASE ASSESSMENTS																														
Bone marrow aspirate/biopsy	X[o]																X				X							X[n]		X[p]

CD = cluster of differentiation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic; SFU = safety follow-up

[a] If the investigator determines that the subject has derived treatment benefit, they may proceed to the next cycle (Table 1-3). If the subject does not proceed to receive additional treatment cycles, they will proceed to end of study assessment on day 107 (30 days after last dose of investigational product).

[b] If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression, administered every 21 days, for a maximum of 35 cycles (approximately 2 years).

[c] Two safety follow-up visits should be performed: 30 days (+ 7 days) after the last dose of AMG 330 and 30 days (+ 7 days) after the last dose of pembrolizumab. If the 2 safety follow-up periods overlap, the 2 safety follow-up visits can be combined into one.

[d] Hospitalization will be required at the start of study day 1 and for a minimum of 72 hours following initiation of AMG 330, after each AMG 330 dose level increase.

[e] Adverse events will be collected from the start of AMG 330 infusion on study day 1.

[f] Clinical evaluations will include physical exam, ECOG, and weight.

[g] Vital signs will be obtained after start of AMG 330 infusion on study day 1 and after AMG 330 dose level increases. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[h] Measurements to be taken in triplicate.

[i] A highly sensitive (serum or urine) pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[j] Coagulation, hematology, and chemistry to be collected 8 hours after start of AMG 330 infusion on study day 1.
[k] Thyroid function testing every 6 weeks while on treatment. Thyroid panel should include: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH).
[l] Anti-AMG 330 antibody samples will be collected at the indicated time points during the study, and on days when both AMG 330 and pembrolizumab are to be administered, anti-AMG 330 antibody samples will be collected before administration of pembrolizumab and before administration of AMG 330 step-dose on that day at the indicated time points throughout the treatment period.

[redacted]

Table 1-4. [redacted] Collection Schedule for Cohort 1, Cycle 2 and beyond

AMG 330 dose level (cIV)	AMG 330 days administered	Pembrolizumab days administered (IV infusion)	[redacted]
[redacted] µg/day	D1-3		
[redacted] µg/day	D4-7		
[redacted] µg/day	D8-14		
[redacted] µg/day	D15-21	D15	
[redacted] µg/day	D22-28		
[redacted] µg/day	D29-35		
[redacted] µg/day	D36-42	D36	
[redacted] µg/day	D43-56		
[redacted] µg/day (infusion free period)	D57-64	D57	

cIV = continuous intravenous; CXDX = cycle X day X; D = day; HR = hour; IV = intravenous

[redacted]

Table 1-5. Schedule of Activities for Cohort 2 (all cycles)

	SCR (C1 only)		Treatment Period																			1 week infusion free interval[a]							Pembrolizumab monotherapy Cycles 2-35[b]	EOT	SFU[c]
Cycle Day:			1									2	3	4	8	15	22	29	36	43	50	57					58	59-63			
		Pre-dose	0.5	1	2	3	4	6	8	12	16	20										EOI	0.5	2	4	8					
GENERAL AND SAFETY ASSESSMENTS																															
Informed consent	X																														
Hospitalization[d]		X																													
Concomitant Medications		←==========→																													
Serious adverse events		←==========→																													
Adverse events[e]		←==========→																													
Clinical Evaluation[f]	X	X										X	X	X	X	X	X	X	X	X	X	X							X	X	X
Vital signs, pulse oximetry[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X	X	X
12-lead ECG[h]	X	X	X									X										X									
LABORATORY ASSESSMENTS																															
Highly sensitive pregnancy test[i]	X	X																													X
Coagulation[j]	X	X							X			X	X	X	X	X	X	X	X	X	X	X							X	X	X
Hematology, Chemistry[j]	X	X							X			X	X	X	X	X	X	X	X	X	X	X							X	X	X
Urinalysis	X	X											X		X	X	X	X	X	X	X	X							X	X	X
Hepatitis Serology[k]	X																														
Thyroid Function Tests[l]		X																		X									X		
Anti-AMG 330-antibody[m]		X														X		X		X		X								X	X
Anti-pembrolizumab-antibody (C1 only)[m]		X															X			X											
INVESTIGATIONAL PRODUCT DOSING																															
AMG 330		X																													
Pembrolizumab		X															X			X									X[q]		
GENERAL AND SAFETY ASSESSMENTS																															
[redacted]																															
PK ASSESSMENTS																															
AMG 330 PK Collection[n]		X						X					X	X	X	X	X	X	X	X	X		X	X	X	X	X	X			
Pembrolizumab PK Collection (predose) (C1 only)[o]		X															X			X											
Pembrolizumab PK Collection (post dose) (C1 only)[p]		X															X			X											

	SCR (C1 only)		Treatment Period																			1 week infusion free interval[a]							Pembrolizumab monotherapy Cycles 2-35[b]	EOT	SFU[c]
Cycle Day:			1										2	3	4	8	15	22	29	36	43	50	57					58	59-63			
		Pre-dose	0.5	1	2	3	4	6	8	12	16	20											EOI	0.5	2	4	8					
DISEASE ASSESSMENTS																																
Bone marrow aspirate/biopsy	X																		X				X							X[q]		X[r]

CD = cluster of differentiation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; [redacted] PK = pharmacokinetic; SCR = screening; SFU = safety follow-up

[a] If the investigator determines that the subject has derived treatment benefit, they may proceed to cycle 2 (Table 1-5). If the subject does not proceed to receive additional treatment cycles, they will proceed to end of study assessment on day 107 (30 days after last dose of investigtational product).

[b] If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression, administered every 21 days, for a maximum of 35 cycles (approximately 2 years).

[c] Two safety follow-up visits should be performed: 30 days (+ 7 days) after the last dose of AMG 330 and 30 days (+ 7 days) after the last dose of pembrolizumab. If the 2 safety follow-up periods overlap, the 2 safety follow-up visits can be combined into one.

[d] Hospitalization will be required at the start of study day 1 and for a minimum of 72 hours following initiation of AMG 330, after each AMG 330 dose level increase.

[e] Adverse events will be collected from start of AMG 330 infusion on study day 1.

[f] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical history, and height will also be obtained.

[g] Vital signs will be obtained at hour 1, 2, 3, 4, 6, 8, 12, 16, and 20 after start of AMG 330 infusion on study day 1 and after AMG 330 dose level increases. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[h] Measurements to be taken in triplicate.

[i] A highly sensitive (serum or urine) pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[j] Coagulation, hematology, and chemistry to be collected 8 hours after start of AMG 330 infusion on study day 1.

[k] Hepatitis serologies include hepatitis B surface antigen (HBsAg) or quantifiable hepatitis B virus (HBV) viral load, hepatitis C antibody or RNA.

[l] Thyroid function testing every 6 weeks while on treatment. Thyroid panel should include: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH).

[m] Anti-AMG 330 antibody and anti-pembrolizumab antibody samples will be collected at the indicated time points during the study, and on days when both AMG 330 and pembrolizumab are to be administered, anti-AMG 330 antibody and anti-pembrolizumab antibody samples will be collected before administration of pembrolizumab and before administration of AMG 330 step-dose on that day at the indicated time points throughout the treatment period. Anti-pembrolizumab antibody samples are only collected during cycle 1.

[redacted]

[o] Pembrolizumab PK samples will be collected pre-dose (within 24 hours) before each infusion of pembrolizumab on cycle 1 only.

[p] Pembrolizumab PK samples will be collected 30 minutes post infusion of pembrolizumab on cycle 1 only.

[redacted]

Table 1-6. [redacted] Collection Schedule for Cohort 2, All Cycles

AMG 330 dose level (cIV)	AMG 330 days administered	Pembrolizumab days administered (IV infusion)	[redacted]	
			Cycle 1	Cycle 2-3
[redacted] µg/day	D1-3	D1	[redacted]	[redacted]
[redacted] µg/day	D4-7			
[redacted] µg/day	D8-14			
[redacted] µg/day	D15-21			
[redacted] µg/day	D22-28	D22		
[redacted] µg/day	D29-35			
[redacted] µg/day	D36-42			
[redacted] µg/day	D43-56	D43		
[redacted] µg/day (infusion free period)	D57-64			

cIV = continuous intravenous; CXDX = cycle X day X; D = day; EOI = end of infusion; HR = hour; IV = intravenous

[redacted]

Table 1-7. Schedule of Activities for Each AMG 330 Dose Step of a Repeat Cycle (Any Cohort)

Day (relative to dose step)	1										2[e]	3[e]	4[e]
Hours	prior to step	relative to start of dose step											
		0.5	1	2	4	6	8	12	16	20	24	48	72
GENERAL AND SAFETY ASSESSMENTS													
Hospitalization	X[b]												
Clinical evaluation[a]	X										X	X	X
Vital signs, pulse oximetry[c]	X		X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X										X		
LABORATORY ASSESSMENTS													
Coagulation	X						X				X	X	X
Hematology, chemistry	X						X				X	X	X
Urinalysis	X											X	
[redacted]													
PK ASSESSMENTS													
AMG 330 PK collection[d]	X[e]		X	X		X	X				X	X	
Pembrolizumab PK collection (C1 only)	X	X											

C = cycle; CD = cluster of differentiation; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic
[a] Clinical evaluations will include physical exam, ECOG, and weight.
[b] Hospitalization after dose step will be for a minimum of 72 hours.
[c] Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.
[redacted]

2. Introduction

2.1 Study Rationale

Cluster of differentiation (CD)33 is a promising cell surface target for treatment of acute myeloid leukemia (AML), as it is expressed on the cell surface of more than 90% of leukemia isolates from patients with AML with a very high average antigen density (Krupka et al, 2014). CD33 was also found cell surface of virtually all AML patient samples (Krupka et al, 2014) and CD33 expression is restricted to the hematopoietic system (La Russa et al, 1992; Andrews et al, 1989; Andrews et al, 1986). AMG 330 is a bispecific T-cell engager (BiTE®) construct that binds both CD33 and CD3, and redirects T cells toward $CD33^+$ cells. With the induced proximity, AMG 330 mediates T-cell cytotoxicity against AML blasts. Anti-AML activity of AMG 330 and other CD33/CD3 BiTE molecules has been previously reported (Westervelt et al, 2018; Ravandi et al, 2018). Recent assessment of preliminary efficacy demonstrated that 5 (10%) out 50 treated patients experienced complete remission (CR)/CR with incomplete recovery (CRi), while approximately 50% of treated patients experienced only a transient decrease in the number of AML blasts in bone marrow. This finding is in line with the current view that in AML, tumor-reactive T cell responses can be strongly impeded by various immune resistance including up-regulation of inhibitory checkpoints such as programmed cell death 1 (PD-1) receptor (Alfayez and Borthakur, 2018; Hobo et al, 2018). Indeed, pre-clinical findings demonstrate that the response to AMG 330 monotherapy may be suboptimal due to engagement of resistance mechanisms including up-regulation of PD-1 on T cells (Krupka et al, 2016). Current experience with AMG 330 shows upregulation of PD-1 expression in treated subjects with relapsed or refractory (R/R) AML (Amgen, data on file) providing a rationale for combining AMG 330 with PD-1 blockers to overcome the resistance. PD-1 expression on CD4+ and CD8+ lymphocytes appears to be AMG 330 dose-dependent and trends higher in non-responders (Amgen, data on file). Pembrolizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity and potency of binding the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2) and is indicated for the treatment of patients across a number of indications. However, PD-1 inhibition demonstrated limited single agent efficacy in paients with R/R AML suggesting a need for rationally designed combinations of PD-1 inhibitors with other immuno-oncology therapies aiming to improve T cell mediated cytotoxicity and surveillance (Boddu et al, 2017).

This study is will assess the safety and tolerability of the combination of AMG 330 with pembrolizumab and whether the inhibition of the PD-1/PD-L1 pathway by pembrolizumab will enhance the anti-AML activity of AMG 330. In cohort 1, subjects will be treated first with AMG 330 and then pembrolizumab will be subsequently administered to block PD-1 that became up-regulated in response to AMG 330. In cohort 2, pembrolizumab will be administered immediately prior to AMG 330 administration to block PD-1 that is expressed at baseline and any PD-1 up-regulated in response to AMG 330.

2.2 Background

2.2.1 Disease

AML is the most common form of acute leukemia in adults in the United States (US), with a rising incidence possibly due to an aging population, increased environmental exposure, and an increase in the population of cancer survivors previously exposed to chemotherapy and therapeutic radiation. In 2014, an estimated 18 860 new cases of AML were expected in the US with approximately 10 460 deaths from this disease (American Cancer Society, 2014).

Outcomes for most patients with AML remain poor (Burnett et al, 2011). In particular, relapsed disease is associated with unsatisfactory outcomes in the majority of patients (Ravandi, 2013). Although the majority of patients with AML initially achieve CR, over 60% will eventually relapse after a variable period of remission. Using the traditional cytotoxic chemotherapy regimens, the likelihood of achieving a second CR is low especially if the first CR was short in duration, particularly if less than 1 year (Estey et al, 1996).

Cluster of differentiation 33 (CD33) provides a useful target antigen for the treatment of patients with AML, as it is expressed on the cell surface of more than 90% of leukemia isolates from patients with AML with a very high average antigen density (Krupka et al, 2014; Tanimoto et al, 1989; Scheinberg et al, 1989). It is not expressed on tissues other than the hematopoietic system.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to

negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al, 2005; Okazaki et al, 2001). Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010; Weber, 2010; Hirano et al, 2005; Blank et al, 2004; Strome et al, 2003). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, AML and colorectal carcinoma (Curran et al, 2010; Pilon-Thomas et al, 2010; Zhang et al, 2009; Nomi et al, 2007; Strome et al, 2003). In such studies, tumor infiltration by CD8+ T cells and increased interferon (IFN)-gamma, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran et al, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Investigator's Brochure).

2.2.2 Amgen Investigational Product Background: AMG 330

BiTEs® have been designed to direct T effector memory cells towards target cells. The proximity induced by the BITE® triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation.

AMG 330, targeting the surface antigen CD33, is a novel BiTE® which is being developed with the intent to treat patients with AML. Other CD33 expressing myeloid diseases, myelodysplastic syndrome and chronic myeloid leukemia, may be evaluated later in clinical development.

AMG 330 is currently being evaluated in the ongoing phase 1 dose escalation study in subjects with R/R AML (NCT02520427). One of the most frequent adverse events observed during the dose escalation study is cytokine release syndrome (CRS). An onset of grade 3 CRS during dose escalation led to an introduction of dose steps resulting in ameliorating frequency and severity of CRS. Subsequently, maximum tolerated dose (MTD) in the ongoing first-in-human phase 1a dose escalation study has not been reached. A detailed description of the chemistry, pharmacology, safety and efficacy of AMG 330 is provided in the Investigator's Brochure.

2.2.2.1 Nonclinical Pharmacology: AMG 330

In vitro Pharmacology:

AMG 330 is a highly potent molecule selectively mediating redirected lysis of $CD33^+$ cells, while viability of target-negative cells remains unaltered. The cytotoxic effect of AMG 330 is time- and dose-dependent, with mean concentrations inducing half-maximal target cell lysis ranging from 24 to 200 pg/mL (0.4 to 3.7 pM) with human effector cells.

In the presence of target cells, AMG 330 induced a polyclonal activation of T cells, which resulted in an up-regulation of the T cell activation markers CD25 and CD69, induction of granzyme B and perforin synthesis, T cell proliferation and release of cytokines like interferon-γ, tumor necrosis factor (TNF), interleukin (IL)-2, IL-10 and IL-6.

In primary AML samples AMG 330 induced an expansion of residual autologous memory T cells and an efficient elimination of AML blasts even at low effector cell: target cell ratios.

CD33 can be shed from the cell surface and was found in bone marrow plasma of AML patients at concentrations ranging from 0.4 to 29.6 ng/mL. A recombinantly produced extracellular domain of CD33 at concentrations of up to 100 ng/mL barely affected AMG 330-mediated redirected lysis of target cells and concomitant upregulation of CD25.

In vivo Pharmacology

Antitumor activity of AMG 330 was evaluated in AML xenograft models.

Intravenous treatment of non-obese diabetic/severe combined immunodeficiency disease (NOD/SCID) mice bearing subcutaneous EOL-1 tumors with AMG 330 (1, 10, and 100 µg/kg/day) resulted in a statistically significant and dose-dependent tumor growth delay.

In an orthotopic AML model NOD/SCID mice were intravenously injected with MOLM-13 tumor cells. Administration of AMG 330 (2, 20, and 200 µg/kg/day) resulted in a significant prolonged survival even at a dose of 2 µg/kg/day AMG 330. In animals which survived until study termination on day 111, no CD33-positive target cells were detectable in blood, spleen and bone marrow.

2.2.2.2 Nonclinical Pharmacokinetics: AMG 330

After single intravenous (IV) administration, AMG 330 clearance (CL) was higher in mouse (53.5 mL/hour/kg) than in monkey (32 mL/hour/kg). The mean terminal half-life

($T_{1/2,z}$) of AMG 330 after a single IV bolus in mouse and 7 or 28 days of subcutaneous dosing in monkey was similar between these 2 species (4 to 8 hours); after 28 days of continuous intravenous (cIV) dosing $t_{1/2,z}$ of AMG 330 was 1.6 to 2.7 hours. The bioavailability of AMG 330 after subcutaneous dosing was 22% and ~40% in mouse and monkey, respectively. Dose proportionality was observed for exposure in both species after a single IV bolus injection in mouse and 7 days of cIV dosing in monkey; loss of exposure was observed after 28 days of cIV dosing due to the formation of anti-drug antibodies.

2.2.2.3 Nonclinical Toxicology: AMG 330

The potential toxicity of AMG 330 was evaluated in a Good Laboratory Practice (GLP)-compliant 28-day cynomolgus monkey toxicology study. AMG 330 was administered daily by cIV at 0, 3, 10, or 30 µg/kg or subcutaneously (SC) at 25 µg/kg. Two 30 µg/kg-cIV females were euthanized on days 10 and 11 due to infections along the catheter port tract and/or at the skin contact points of the infusion jacket. The infections were considered secondary to AMG 330-related decreases in mature myeloid cells in the bone marrow and in circulating leukocytes. Other AMG 330-related findings were consistent with its expected pharmacology and included decreased leukocytes, which correlated with decreased T-lymphocytes, along with expected increased activated T-lymphocytes, and increased cytokine levels in all dose groups. Some animals at 30 µg/kg cIV and 25 µg/kg SC had clinical signs associated with inflammation/infection at the dose administration site that resolved after topical antimicrobial application and were able to complete the intended 28-day dose administration. In animals that survived to scheduled termination, there were no AMG 330-related macroscopic, organ weight or light microscopic changes. The changes observed in this study were consistent with the expected pharmacology of AMG 330. The highest non-severely toxic dose (HNSTD) was considered to be 10 µg/kg/day cIV and 25 µg/kg/day SC.

No combination toxicology studies have been conducted with AMG 330 and pembrolizumab.

2.2.3 Non-Amgen Investigational Product Background: Pembrolizumab

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in

clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure/approved labeling for detailed background information on pembrolizumab.

Therapeutic studies of pembrolizumab in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010; Weber, 2010; Hirano et al, 2005; Blank et al, 2004; Strome et al, 2003). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, AML and colorectal carcinoma (Curran et al, 2010; Pilon-Thomas et al, 2010; Nomi et al, 2007; Zhang et al, 2004; Strome et al, 2003). In such studies, tumor infiltration by CD8+ T-cells and increased IFN-gamma, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran et al, 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the pembrolizumab Investigator's Brochure).

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis et al, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Hunder et al, 2008; Dudley et al, 2005).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune

responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and cytotoxic CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al, 2005; Okazaki et al, 2001). The structure of murine PD-1 has been resolved (Zhang et al, 2004).

PD-1 and its family members are type I transmembrane glycoproteins containing an Ig variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ) and zeta-chain-associated protein kinase (ZAP)70, which are involved in the CD3 T cell signaling cascade (Riley, 2009; Chemnitz et al, 2004; Sheppard et al, 2004; Okazaki, et al, 2001). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins (Francisco et al, 2010; Parry et al, 2005). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.

2.3 Benefit/Risk Assessment

As of 17 June 2019, 49 patients have received AMG 330 in the ongoing first in human study. Based on the mode of action targeting CD33 which is expressed on myeloid cells, myelosuppression and particularly neutropenia is expected. In addition, infections may be observed based on the myelosuppressive effect. Neutropenia and infections are conditions that are not unexpected in the setting of AML given the nature of this bone marrow disease.

Cytokine release syndrome (CRS) is an identified risk for AMG 330 and respective signs and symptoms were observed in 67% of subjects treated in the study so far.

Checkpoint inhibition may potentially increase the risk for increased frequency and severity of CRS. This risk is mitigated by the requirement for the administration of dexamethasone prior to each step dose of AMG 330. In addition, in cycle 1 of cohort 1, pembrolizumab is introduced 7 days following the step dose of AMG 330 which may reduce the likelihood or severity of CRS. Lastly, treatment with both dexamethasone and tocilizumab will be available for the treatment of clinically significant CRS.

Pembrolizumab has an acceptable clinical safety profile, is indicated for the treatment of patients across a number of malignancies and is in clinical development as an IV immunotherapy for additional advanced tumors. In patients with a history of allogeneic hematopoietic stem cell transplantation (HSCT), acute Graft versus Host Disease (GVHD), including fatal GVHD, has been reported after treatment with pembrolizumab. Based on the benefit of pembrolizumab treatment vs the risk of GVHD assessment, subjects undergone allogenic HSCT within 5 years prior to the study will be excluded.

One of the most frequent adverse events observed during the phase 1a AMG 330 dose escalation study is CRS associated with a release of several potent cytokines including pro-inflammatory IL-6 (Amgen, data on file). Up-regulation of PD-1 expression is a natural pathway employed by immune system to control the inflammation (de la Fuente, 2012), and there is a risk that blocking PD-1 may potentially interfere with the endogenous protective mechanisms and further aggravate the inflammatory cascade leading to higher grades of CRS in subjects treated with the combination regimen. Thus, PD-1/PD-L1 axis may play a dual role: protect from inflammation and to enable the resistance mechanisms. To mitigate this risk associated with inflammation, the following strategy will be used: administration of dexamethasone prior to each step dose of AMG 330, small step doses to reduce T cell challenge and 7-day duration of each step dose to allow prompt mitigation of potential inflammatory reactions. The potential benefit is to disable the resistance mechanisms to allow improved efficacy.

There is limited potential for other overlapping toxicities because more adverse events associated with pembrolizumab occur later during the treatment whereas AMG 330 related toxicities are acute and observed shortly after dose increase.

The above benefit risk assessment supports the conduct of this clinical study. See the AMG 330 Investigator's Brochure for further data on AMG 330 and Prescribing Information and the pembrolizumab Investigator's Brochure for further data on pembrolizumab.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 330 administered in combination with pembrolizumab in subjects with relapsed or refractory acute myeloid leukemia (R/R AML)	• Dose-limiting toxicities (DLTs) • Treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• Evaluate the anti-leukemia activity of AMG 330 administered in combination with pembrolizumab in R/R AML patients	• Responses to treatment with AMG 330 administered in combination with pembrolizumab. Response is defined as any of the following: complete remission without mininum residual disease (CR_{MRD-}), complete remission (CR), CR with incomplete recovery (CRi), or morphological leukemia-free state (MLFS), or partial remission (all according to the 2017 European LeukemiaNet (ELN) criteria (Döhner et al, 2017). • Duration of response
• Evaluate the pharmacokinetics (PK) of AMG 330 when AMG 330 and pembrolizumab are administered in combination	• Descriptive statistics of AMG 330 concentrations and PK parameters.
• Evaluate the immunogenicity of AMG 330 when administered in combination with pembrolizumab	• Incidence of anti-AMG 330 antibody formation
Exploratory	
• Evaluate the pharmacokinetics (PK) of pembrolizumab when AMG 330 and pembrolizumab are administered in combination	• Descriptive statistics of pembrolizumab concentrations.
• Evaluate the immunogenicity of pembrolizumab when AMG 330 and pembrolizumab are administered in combination	• Incidence of anti-pembrolizumab antibody formation
[redacted]	

[redacted]

• Evaluate the relationship between AMG 330 and pembrolizumab exposure and response to treatment	• Correlate the serum levels AMG 330 and pembrolizumab with changes in tumor burden (exposure/efficacy) and with adverse event incidence (exposure/safety)

4. Study Design

4.1 Overall Design

This is a phase 1b study assessing safety, tolerability, PK, pharmacodynamics, and efficacy of AMG 330 administered as cIV infusion in combination with pembrolizumab in adult subjects with R/R AML.

The study is a non-randomized study and will consist of 2 sequential dosing cohorts. Both cohorts will include AMG 330 and pembrolizumab with the difference being the initiation date for pembrolizumab treatment.

This study will use a staggered enrollment approach. Subject enrollment will start with cohort 1 (Section 4.1.1). The first subject dosed in cohort 1 will serve as the sentinel subject. Subsequent subjects dosed in cohort 1 will start AMG 330 ([redacted] µg/day) administration once sentinel subject has cleared the study day 21 dose (AMG 330 monotherapy at [redacted] µg/day). Per sponsor determination, if the sentinel subject does not experience a dose-limiting toxicity (DLT) on days 15 to 21 after pembrolizumab is administered, the other subjects in cohort 1 will be allowed to continue the planned treatment schedule. If the sentinel subject experiences a DLT during days 15 to 21, the dose level review team (DLRT) will discuss the case and the decision will be made by the sponsor based on clinical assessments of the adverse event and potential decisions by the sponsor may include stopping AMG 330 and/or pembrolizumab, dose de-escalation of AMG 330, or continuing therapy at full dose. Investigators and sponsor will meet after all subjects in cohort 1 have completed study day 28 (ie, AMG 330 [redacted] µg/day dose level in combination with pembrolizumab) to assess the safety profile. If pre-specified safety criteria are met (≤ 3 out of 10 treated subjects in cohort 1 experienced DLT by day 28), subjects enrolled in cohort 2 (Section 4.1.2) may proceed with the treatment schedule. Similar to cohort 1, the first subject dosed in cohort 2 will serve as the sentinel subject. Per sponsor determination, if the sentinel subject does not

experience a DLT during the first 7 days, the other subjects in cohort 2 will be allowed to continue the planned treatment schedule.

Safety data will be continuously monitored throughout the whole treatment period. Sponsor in consultation with investigators may reconvene to make appropriate safety measures and adjustments as needed.

Subjects in both cohort 1 and cohort 2 may continue with cycle 2 and beyond of AMG 330 and pembrolizumab up to 6 months if the combination regimen remains tolerable and is deriving clinical benefit in the opinion of the investigator. In both cohorts 1 and 2, subjects continuing with cycle 2 and beyond may be permitted to shorten the duration of AMG 330 step dose levels to 2 to 5 days based on individual clinical experience from cycle 1 and based on the clinical judgement of the investigator and in consultation and agreement with the sponsor. The duration of the combination treatment period for individual subjects may be extended up to 1 year if the subject is deriving clinical benefit in the opinion of the investigator and in consultation with the sponsor. If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression for a maximum of 35 cycles (approximately 2 years). If pembrolizumab is discontinued, AMG 330 may be continued as a monotherapy.

4.1.1 Cohort 1 Design

Cycle 1 is 77 days in duration and subsequent cycles are 57 days. Treatment will start with AMG 330 on day 1. Dexamethasone 8 mg will be given to subjects 1 hour prior to each step dose of AMG 330. AMG 330 will be administered at a starting dose of [redacted] µg/day for 3 days, followed by [redacted] µg/day for 4 days, followed by [redacted] µg/day for 7 days. If the subject experiences DLT during these first 7 days of treatment with AMG 330 at [redacted] µg/day, this subject will be replaced. If the subject has not experienced a DLT by day 14, they will receive pembrolizumab on day 15. Pembrolizumab will be administered at a dose of 200 mg (Q3W) by a 30-minute IV infusion. The subject will remain at an AMG 330 dose level of [redacted] µg/day for additional 7 days.

Thereafter, AMG 330 dosing will continue as per Table 4-1, increasing dose levels to [redacted] µg/day for 7 days followed by [redacted] µg/day for 7 days. If the subject has not experienced a DLT at the [redacted] µg/day dose level of AMG 330 between days 29 to 35, they will receive pembrolizumab on day 36 and remain on the AMG 330 [redacted] µg/day dose for an additional 7 days. AMG 330 dosing will further increase to [redacted] µg/day for 7 days followed by [redacted] µg/day for 7 days. If the subject has not experienced a DLT at

the [redacted] µg/day dose level of AMG 330 between days [redacted] to [redacted], they will receive pembrolizumab on day 57 and remain on the [redacted] µg/day dose for additional 7 days. To complete cycle 1, a final dose level increase to [redacted] µg/day AMG 330 for an additional 14 days will be administered.

Cycle 1 will be followed by a 1-week interval without AMG 330 administration and administration of pembrolizumab will continue non-interrupted on the Q3W schedule. The AMG 330-infusion free interval may be extended up to 4 weeks (depending on safety, treatment response, and in case of prolonged marrow aplasia and cytopenia in aleukemic subjects) after consultation with the sponsor.

Table 4-1. Dosing for Cohort 1 (Cycle 1)

AMG 330 Dose Level (µg/day, cIV)	AMG 330 Days Administered	Pembrolizumab Days Administered (IV infusion)
[redacted]	D1-3	
	D4-7	
	D8-14, D15-21	D15
	D22-28	
	D29-35; D36-42	D36
	D43-49	
	D50-56; D57-63	D57
	D64-77	
(infusion-free period)	D78-85	D78

cIV = continuous intravenous; D = day; IV = intravenous

Cycle 2 will start with the initiation of AMG 330 administration and include the same step dose levels and duration as in cycle 1 with the exception of the [redacted] and [redacted] µg/day dose levels, which will be shortened from 14 days to 7 days (Table 4-2). The duration of AMG 330 step dose levels in cycle 2 and beyond can be shortened to 2 to 5 days if a subject tolerated the investigational product in cycle 1 and based on the discussion and agreement between the investigator and the sponsor. All subsequent cycles will be conducted similarly to cycle 2.

On days when pembrolizumab administration and an AMG 330 dose level increase will occur, the subject will receive dexamethasone 8 mg at the conclusion of the pembrolizumab infusion. Dexamethasone will be given 1 hour prior to increasing the AMG 330 dose. If the subject does not develop a ≥ grade 2 infusion reaction, or if the

infusion reaction is reversible after the 1-hour observation period, AMG 330 may be increased to the next dose level, as shown in Table 4-2.

Table 4-2. Dosing for Cohort 1 (Cycle 2 and Beyond)

AMG 330 Dose Level (µg/day, cIV)	AMG 330 Days Administered	Pembrolizumab Days Administered (IV infusion)
[redacted]	D1-3	
	D4-7	
	D8-14	
	D15-21	D15
	D22-28	
	D29-35	
	D36-42	D36
	D43-56	
(infusio period)	D57-64	D57

cIV = continuous intravenous; D = day; IV = intravenous

4.1.2 Cohort 2 Design

Subjects in cohort 2 will receive both AMG 330 and pembrolizumab on day 1. All cycles are 57 days in duration. Pembrolizumab will be administered at a dose of 200 mg (Q3W) by a 30-minute IV infusion. The subject will then receive dexamethasone 8 mg. Dexamethasone will be given 1 hour prior to each step dose of AMG 330. If the subject does not develop a ≥ grade 2 infusion reaction, or if the infusion reaction is reversible after the 1-hour observation period, the subject will start AMG 330 at a starting dose of [redacted] µg/day for 3 days, followed by [redacted] µg/day for 4 days, followed by [redacted] µg/day for 7 days, and continue dosing as per Table 4-3, increasing dose levels every 7 days up to [redacted] µg/day as tolerated by subjects. Pembrolizumab will be administered at 200 mg IV once every 3 weeks. Subjects will continue [redacted] µg/day of AMG 330 and pembrolizumab for 14 days. Cycle 1 will be followed by a 1-week interval without AMG 330 administration, and administration of pembrolizumab will continue non-interrupted on Q3W schedule. The AMG 330-infusion free interval may be extended up to 4 weeks (depending on safety, treatment response, and in case of prolonged marrow aplasia and cytopenia in aleukemic subjects) after consultation with the sponsor. Cycle 2 and all subsequent cycles will start with the initiation of AMG 330 administration and include the same step dose levels and duration as in cycle 1. The duration of AMG 330 step dose levels in cycle 2 and beyond can be shortened to 2 to 5 days if a subject tolerated the

investigational product in cycle 1 and based on the discussion and agreement between the investigator and the sponsor.

Table 4-3. Dosing for Cohort 2 (All Cycles)

AMG 330 Dose Level (µg/day, cIV)	AMG 330 Days Administered	Pembrolizumab Days Administered (IV infusion)
[redacted]	D1-3	D1
	D4-7	
	D8-14	
	D15-21	
	D22-28	D22
	D29-35	
	D36-42	
	D43-56	D43
(infusion-free period)	D57-64	

cIV = continuous intravenous; D = day; IV = intravenous

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

It is anticipated that approximately 20 subjects will be enrolled in the study, with at least 6 DLT evaluable subjects in each cohort. With 6 evaluable subjects in 1 cohort, there is an 82% chance of observing at least 1 DLT if the true DLT rate is 25%. For cohort 1, at least 10 subjects will be dosed through study day 28.

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

Ineligible subjects (ie, subjects who were exposed to AMG 330 or pembrolizumab, but post hoc were found to be ineligible) may be replaced. Subjects who do not meet the DLT evaluable criteria (see Section 6.2.1) may be replaced until at least 6 subjects become DLT evaluable in each cohort or at least 10 subjects in cohort 1 have been dosed through study day 28. If a sentinel subject in cohort 1 experiences a DLT at [redacted] µg/day, [redacted] µg/day or [redacted] µg/day of AMG 330 during the first 14 days of monotherapy treatment in cycle 1, this subject will be defined as DLT evaluable and will not proceed

with the combination regimen. The sentinel role will be re-assigned to the next available subject.

4.2.2 Number of Sites

Approximately 5 investigative sites in the United States will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

Justification for AMG 330 Dose

The planned dosing schedule for AMG 330 will evaluate doses that have been tested in the ongoing first-in-human study (Amgen Study 20120252) in subjects with R/R AML. Planned dose levels for step dose escalation will be as follows: [redacted] and [redacted] µg/day. The rationale for selecting these dose levels for the combination study includes following findings generated during the phase 1 dose escalation study: each of the proposed doses has been tested as a monotherapy and deemed safe and tolerable, and proposed dose levels include efficacious doses (CR/CRi have been reported at [redacted] and [redacted] µg dose levels).

As of 17 June 2019, treatment-emergent adverse events (TEAEs) were reported for 47 (95.9%) of 49 subjects. Forty subjects (81.6%) had grade ≥ 3 adverse events, 33 subjects (67.3%) had serious adverse events, and 2 subjects (4.1%) had fatal adverse events. Six subjects (12.2%) had adverse events that led to discontinuation of AMG 330. Dose-limiting toxicities (DLTs) were reported for 6 subjects. The most frequently reported adverse event by preferred term was CRS (31 subjects, 63.3%). Adverse events considered by the investigator to be related to AMG 330 were reported for 43 subjects (87.8%), the most frequently reported treatment-related adverse events (subject incidence ≥ 20%) were CRS (63.3%), rash (30.6%), febrile neutropenia (22.4%), and nausea (20.4%).

CRS mitigation approach developed for AMG 330 and implemented into the ongoing first in human study allows resolution of CRS within 7 days. Thus, the duration of each step dose is defined as at least 7 days to allow monitoring the frequency, severity and resolution dynamics of CRS in subjects treated with the combination regimen. An exception is given for first 2 lower doses ([redacted] µg/day and [redacted] µg/day), duration for which will be 3 and 4 days respectively, since the occurrence of CRS is rare at these doses due to the current CRS mitigation approach (ie, premedication with dexamethasone 8 mg 1 hour prior to each step dose of AMG 330).

As of the 17 June 2019 data snapshot date, 5 of 39 evaluable subjects had a response. One subject (cohort 11 [µg/day]) achieved CR, 3 subjects (1 each in cohort 8 [µg/day], cohort 9 [µg/day], and cohort 12 [µg/day]) achieved CRi, and 1 subject (cohort 2 [µg/day]) achieved morphologic leukemia-free state (MLFS). The objective response rate based on subjects who achieved either a CR, CRi, CR with partial hematologic recovery (CRh), partial remission (PR), or MLFS was 12.8% (80% CI: 6.4%, 22.5%). Two additional subjects in cohort 15 (µg/day) achieved CR (1 subject) and CRi (1 subject) after the data snapshot date of 17 June 2019.

Refer to the AMG 330 Investigational Brochure for further information.

Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All of these studies demonstrated flat dose and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose and exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and

classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.1 Justification for Non-investigational Product Dose

Not applicable

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).

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

The expected study duration for subjects will be approximately 121 days, including up to 14 days for screening activities, 77 (cohort 1) or 56 (cohort 2) days for treatment with AMG 330 in combination with pembrolizumab, and 30 days for safety follow-up. Subjects in both cohort 1 and cohort 2 may continue to repeat cycles of AMG 330 and pembrolizumab up to 6 months if the dose of the combination regimen remains tolerable and the subject is deriving benefit in the opinion of the investigator. The duration of the combination treatment period for individual subjects may be extended up to 1 year if the subject is deriving benefit in the opinion of the investigator and after consultation with sponsor. If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression for a maximum of 35 cycles (approximately 2 years). If either study drug is discontinued, the other may be continued as a monotherapy.

4.5 Patient Input on Study Design

Not applicable

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 Age ≥ 18 years on day of signing informed consent.

103 AML as defined by the WHO Classification (Section 11.10) persisting or recurring following 1 or more treatment courses. Exception: promyelocytic leukemia (APML) is excluded from the study.

104 More than 5% blasts in bone marrow.

105 Eastern Cooperative Oncology Group (ECOG, Section 11.9) Performance Status of ≤ 1.

106 Have adequate organ function as defined in Table 5-1. Specimens must be collected within 14 days prior to study day 1.

Table 5-1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Renal	
Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥ 30 mL/min for participant with creatinine levels > 1.5 x institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 xULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤ 1.5 x ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.
[a] Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

107 A male participant must agree to use contraception during the treatment period and for at least 120 days after receiving the last dose of study drug (AMG 330 or pembrolizumab).

- Acceptable methods of highly effective birth control include sexual abstinence; vasectomy; or a condom with spermicide (men) in combination with hormonal birth control or intrauterine device (IUD) (women).
- Males will not be allowed to donate sperm during this period.

108 A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)
- A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 120 days after the last dose of study treatment (AMG 330 or pembrolizumab)
- Acceptable methods of highly effective birth control include sexual abstinence; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with hormonal birth control or IUD (women).

5.2 Exclusion Criteria

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

Disease Related

201 Active extramedullary AML in the central nervous system (CNS).

Other Medical Conditions

202 Prior malignancy (other than in situ cancer) unless treated with curative intent and without evidence of disease for > 2 years before screening.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

203 History or evidence of significant cardiovascular risk including any of the following: symptomatic congestive heart failure, unstable angina, clinically significant arrhythmias (eg, ventricular fibrillation, ventricular tachycardia etc.), recent coronary angioplasty, intra-cardiac defibrillators or any clinically relevant concurrent disorder that may pose a risk to subject safety or interfere with study evaluation, procedures, or completion.

204 History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 12 months.

205 Active infection requiring IV antibiotics within 1 week of study enrollment (day 1).

206 Known positive test for human immunodeficiency virus (HIV).

207 History of chronic or active hepatitis B (known to be positive for hepatitis B surface antigen [HBsAg] or quantifiable hepatitis B virus [HBV] viral load). Positive for hepatitis B, and/or history of hepatitis B infections, or known to be positive for HBsAg/HBV DNA.

208 History of chronic or active hepatitis C. Active hepatitis C is defined by a known positive hepatitis C antibody result and known quantitative hepatitis C virus RNA results greater than the lower limits of detection of the assay.

209 Unresolved toxicities from prior antitumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 grade 1 or to levels dictated in the eligibility criteria. Exception: myelosuppression (eg, neutropenia, anemia, thrombocytopenia), alopecia or toxicities from prior antitumor therapy that are considered irreversible (defined as having been present and stable for > 2 months) which may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and Sponsor. Participants with ≤ grade 2 neuropathy may be eligible.

210 Current or recent (within 3 months of study drug administration) gastrointestinal disease such as chronic or intermittent diarrhea, or uncontrolled disorders that increase risk of diarrhea, such as inflammatory bowel disease.

Exception: non-chronic conditions (eg, infectious diarrhea) that are completely resolved for at least 2 weeks prior to starting study treatment.

211 History of (non-infectious) pneumonitis that required steroids or current pneumonitis.

212 Uncontrolled endocrine disorder including thyroid disease.

213 Subjects with active, known or suspected autoimmune disease. Exceptions: vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid subjects with history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions expected to recur in the absence of an external trigger.

214 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Sponsor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Prior/Concomitant Therapy

215 Autologous HSCT within 6 weeks prior to start of treatment.

216 Allogeneic HSCT within 5 years prior to start of treatment or active GVHD requiring systemic treatment.

217 Has had an allogenic tissue/solid organ transplant.

218 Prior treatment of AML with anti-CD33 chimeric antigen receptor (CAR) T cells.

219 Prior therapy with anti-PD-1 agent that was discontinued due to a grade ≥ 3 immune-related adverse event.

220 Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent) within 14 days or 5 half-lives (whichever is shorter) of day 1. Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed until start of investigational product treatment.

221 Treatment with systemic immune modulators including, but not limited to, non-topical systemic corticosteroids, cyclosporine, and tacrolimus within 2 weeks before enrollment (day 1). Exceptions: physiologic replacement steroids or hydrocortisone for treatment of transfusion reactions.

222 Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

223 Major surgery within 28 days of study day 1 with the exception of biopsy and long line insertion. Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

Prior/Concurrent Clinical Study Experience

224 Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 14 days prior to the first dose of study treatment.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 14 days after the last dose of the previous investigational agent.

Other Exclusions

225 White blood cells (WBC) > 15 x 10^9 cells/L at screening.

226 Known hypersensitivity to immunoglobulins or to any other component of AMG 330 formulation.

227 Has severe hypersensitivity (≥ grade 3) to pembrolizumab and/or any of its excipients.

228 Women with a positive pregnancy test.

229 Women who are lactating/breastfeeding or who plan to breastfeed while on study through 120 days after receiving the last dose of study drug.

230 Men and women of reproductive potential who are unwilling to practice a highly effective method(s) of birth control while on study and for at least 120 days after receiving the last dose of study drug. Acceptable methods of highly effective birth control include sexual abstinence (men, women); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with hormonal birth control or IUD (women).

231 Subjects likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

232 Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

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 (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's 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. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (up to 14 days prior to study day 1) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. 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, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study within the 14-day screening period (screen failure) may be rescreened up to 3 times at the discretion of the investigator. Refer to Section 8.1.1 for rescreening procedures.

5.5 Washout Period/Run-in Period/Invasive Procedure(s)

Not applicable

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).

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 330	Non-Amgen Investigational Product:[b] Pembrolizumab
Dosage Formulation	Powder for solution for infusion in a vial containing [redacted] mg of AMG 330 AMG 330 is formulated with potassium phosphate, captisol, sucrose, polysorbate 80, pH [redacted]. IVSS is supplied as a sterile solution in a 10-cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted], pH [redacted]). The IVSS is intended for pre-treatment of IV bags prior to dilution of AMG 330 drug product.	Solution for infusion
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Various dosage level(s) (see Table 4-1, Table 4-2, and Table 4-3).	100 mg/4 mL (25 mg/mL) single-dose vials Dosage level(s) 200 mg Q3W
Route of Administration	Continuous IV infusion	Intermittent IV infusion
Accountability	The amount dispensed, date dispensed, and lot number of investigational product is to be recorded on each subject's CRF.	The amount dispensed, date dispensed, and lot number of investigational product is to be recorded on each subject's CRF.
Dosing Instructions	Each vial will be reconstituted with 1.2 mL of sterile water for injection for a final concentration of 0.5 mg/mL AMG 330. The dose, start date/time, stop date/time, lot number of investigational product is to be recorded on each subject's CRF.	The dose, start date/time, stop date/time, lot number of investigational product is to be recorded on each subject's CRF.

CRF = case report form; IV = intravenous; Q3W = every 3 weeks (21 days)
[a] AMG 330 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.
[b] Pembrolizumab will be manufactured and packaged by Merck & Co Inc and distributed using Amgen clinical study drug distribution procedures.

6.1.1.1 AMG 330 Dosage, Administration, and Schedule

AMG 330 is administered as a cIV infusion. The infusion bags will be changed by site nursing personnel trained on the protocol and on the proper administration of AMG 330.

The first cycle of AMG 330 treatment is 56-77 days in duration. Please refer to the study schema (Figure 1-1). The first cycle is followed by a 7-day AMG 330 treatment-free interval. The dosing and schedule will be as outlined in Table 4-1 and Table 4-2.

The drug administration should not be interrupted, 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. Every interruption longer than 1 hour should be documented. Administration of dexamethasone premedication will occur as described in Section 6.7.

The start time of infusion should be chosen carefully so as to avoid any interference or inconvenience with time points of safety assessments, PK/pharmacodynamic measurements and changes of infusion bags. The site should record any unscheduled interruption of an infusion on the eCRF, and provide the start and stop date/time of the infusion and the bag change.

AMG 330 should be administered through a central venous access at a constant flow rate. The drug should not be administered as a bolus and flushing residual drug at the time of bag change is prohibited. In the event that administration through a central venous access is not possible, AMG 330 may be administered temporarily through a peripheral venous line if the subject is hospitalized. The final solution for infusion should be administered through a sterile 0.2 µm in-line filter.

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products but at least every 4 days. In the US, infusion bags should be changed at least every other day and in no case should AMG 330 be administered for more than 48 hours at ambient temperature.

The dose, start and stop date/time, and lot number of protocol-specified therapy is to be recorded on each subject's CRF. The date and time of infusion bag changes, all infusion start and stop times, and any dose modifications should also be recorded accurately.

6.1.1.1.1 Infusion-Free Interval for AMG 330

The planned length of an AMG 330 infusion-free interval between cycles is 1 week (+3 days if needed for logistical reasons). The duration can be extended up to 4 weeks after consultation with the sponsor for subjects who achieved a response (CR, CRh, CRi, or MLFS) with no detectable blasts in bone marrow at the end of infusion. Weekly hematology assessments should be performed to confirm recovery of peripheral blood counts. Once peripheral blood counts have returned to baseline levels, the next treatment cycle can be initiated.

In subjects who achieved a response with no detectable blasts in bone marrow at end of infusion, the infusion-free interval may also be extended up to a maximum of 6 weeks in case of insufficient recovery of peripheral blood counts (neutrophils < 500/µL, platelets < 20 000/µL without transfusion) and after consultation with the sponsor. In case the infusion-free interval is extended to 4-6 weeks, a bone marrow assessment is recommended 4 weeks after the end of the infusion cycle. In case this assessment shows detectable leukemic infiltration of the bone marrow, treatment should be resumed immediately even if peripheral blood counts have not yet recovered at this time point.

6.1.1.1.2 Overdose

A dose of up to 10% higher than the intended AMG 330 dose (per day) may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stabilized and no clinically relevant safety findings due to AMG 330 are observed, resumption of AMG 330 at a correct dose can be considered after consultation with the Amgen medical monitor.

For AMG 330, a dose of greater than 10% higher than the intended 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. If the overdose results in additional adverse event/s, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 11.4 of the protocol.

6.1.1.2 AMG 330 Inpatient Dosing

Subjects are required to be monitored in a hospital for a minimum of 72 hours following initiation of therapy and for a minimum of 72 hours after each dose level increase. Close monitoring is indicated because of the potential adverse events associated with T cell redistribution and potential cytokine release effects triggered by the administration of

AMG 330. Nurses/physicians familiar with such conditions should be available for immediate intervention in case of complications.

Also, if AMG 330 is interrupted for longer than 4 hours, re-start of the infusion should be performed in the hospital, under the supervision of the investigator or designee. The subject should be observed overnight for possible side effects after the re-start, either in the hospital or in the outpatient setting as applicable. Administration of dexamethasone premedication will occur as described in Section 6.7.

6.1.1.3 AMG 330 Outpatient Dosing

Apart from the situations where inpatient dosing is required per Section 6.1.1.1.2, and if deemed stable by the investigator, a subject may continue AMG 330 cIV infusion as an outpatient. Subjects will receive a patient card indicating that the subject is participating in a clinical study. The patient card will also provide site contact details to be used in case of questions on the study or an emergency. In the outpatient setting, the subject will either return to the study site for infusion bag changes or the subject will be visited by a well-trained home health care service provider at specific intervals to change the infusion bag, measure vital signs, monitor and document adverse events and/or serious adverse events, and document any issues with the cIV infusion or infusion pump. The subject and home health care service provider will be trained and will receive written instructions for storage of the IV bags, if applicable. The home health care service provider will complete the study delegation log and will be authorized by the investigator before any study-related tasks are started.

Refer to the home health care manual for detailed information on the storage, handling, and administration of AMG 330, mandatory procedures, and data collection requirements.

Following each visit or telephone contact by the home health care service provider, the information collected will be documented on the Home Health Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. If any adverse event occurs in the outpatient setting, the home health care service provider should directly contact the site for further management. The home health care service professionals provide 24 hour emergency on-call service for any pump related issues. In the event of an interruption of the AMG 330 cIV infusion of > 4 hours, restart of the infusion should be performed in the clinic/hospital under the supervision of the

investigator or designee and the subject should be hospitalized for a minimum of 48 hours (see Section 6.2.2.1).

6.1.1.4 Pembrolizumab Dosage, Administration, and Schedule

Trial treatment should begin as close as possible to the date on which the subject is allocated/assigned. The pembrolizumab treatment to be used in this study is outlined below in Table 6-2.

Schedule of pembrolizumab dosing and related assessments are specified in the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5). Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between - 5 minutes and + 10 minutes is permitted (ie, infusion time is 30 minutes - 5 minutes/+ 10 minutes). Following the completion of the pembrolizumab administration, the subject will be observed for 1 hour to monitor tolerability of the infusion.

For this study, an overdose of pembrolizumab will be defined as ≥ 1000 mg (≥ 5 times the indicated dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose of pembrolizumab, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Table 6-2. Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Maximum Length of Dosing	Route of Administration	Regimen[a]	Use
Pembrolizumab	200 mg	Every 21 days	Up to 35 cycles	Intravenous	Day 1 of each cycle. Starting at study day 15 (cohort 1), and study day 1 (cohort 2) (21-day cycles)	Experimental

[a] Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

When pembrolizumab administration falls on the same day as an AMG 330 dose level increase, pembrolizumab will be given first. After the pembrolizumab infusion is

complete, dexamethasone will be administered. The patient will then be observed for 1 hour. If the dose is well tolerated, the dose of AMG 330 may be increased to the next level. When pembrolizumab is administered as a monotherapy, dexamethasone will not be administered at the completion of the pembrolizumab infusion.

6.1.2 Non-investigational Products

There are no non-investigational products in this study.

6.1.3 Medical Devices

AMG 330 must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment in both the inpatient and outpatient setting. Investigational product infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines with a 0.2 µm in-line filter that are both compatible with the investigational product as described in the IPIM.

Additional details are provided in the IPIM.

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 dexamethasone and tocilizumab that are commercially available are not provided by Amgen. The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Dexamethasone:

Premedication with dexamethasone is required prior to each AMG 330 treatment cycle and prior to each dose step for the prevention of CRS. Dexamethasone should be administered as a single IV dose (8 mg) within 1 hour of start of AMG 330 infusion or dose step, respectively. Dexamethasone will not be given as a premedication prior to pembrolizumab administration.

In the case of re-start of AMG 330 infusion after an infusion interruption of > 24 hours, dexamethasone (8 mg IV) should be administered within 1 hour prior to re-start and within 1 hour prior to the dose step.

For administration of dexamethasone after occurrence of CRS or other immune related adverse events, follow guidance in Section 6.8 and Table 6-3.

Tocilizumab:

For administration of tocilizumab after occurrence of CRS, follow guidance in Section 6.8.

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. Supportive care may include premedication with anti-emetics to limit treatment-related nausea and vomiting. Subjects should receive medications for treatment-induced diarrhea as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Concomitant therapies are to be collected from the day of signing the informed consent, through the end of study. For all concomitant therapies collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.1.5 Other Treatment Procedures

Not applicable

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(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any investigational/non-investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen including AMG 330 and pembrolizumab.

Any product complaint(s) associated with an investigational product(s), non-investigational products(s), devices(s), or combination product(s) 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

Any antitumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, immunotherapy or any biological response modifiers, any other investigational agent, chronic systemic corticosteroid therapy, other immunosuppressive therapies, or HSCT is not allowed during screening and during the study treatment period until end of study. Exception: Hydroxyurea is allowed to control blasts as described in Section 6.7.2.

Radiotherapy is not permitted during screening and during the study treatment period until end of study except for palliation of symptoms and should be approved by Sponsor. Investigators should ensure that the need for radiation does not indicate progressive disease and that for subjects with measurable disease, radiation is not to the sole site of measurable disease.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

The following procedures should also not be undertaken within the timeframes specified prior to enrollment and during the study:

- Participation in an investigational study (drug or device) within 14 days of study day 1 and during the study
- Major surgery within 28 days of study day 1 (with the exception of biopsy or long line insertion)

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules, Dose-Limiting Toxicities (DLTs)

Step Dose Level Determination

A decision to proceed with the next step dose of AMG 330 for each subject in cohorts 1 and 2 will be based on investigator's assessment of safety and upon approval by Sponsor.

In cohort 1, a sentinel subject will be treated first. The minimal interval between treatment start for the sentinel subject and other subjects in the cohort is 21 days. If the sentinel subject has not experienced a DLT by day 14 at [redacted] µg/day AMG 330, he/she will proceed with 200 mg pembrolizumab on day 15 and remain at an AMG 330 dose level of [redacted] µg/day for 7 days (until day 21). If the sentinel subject experiences a DLT during the first 7 days of treatment with AMG 330 at [redacted] µg/day, this subject will be replaced, but the DLT will still be counted towards the study stopping rules. If the sentinel subject does not experience a DLT before or on day 21, the next subjects in the cohort may initiate dosing. If a sentinel subject experiences a DLT, the sponsor will issue a decision based on the evaluation of clinical significance of the adverse event by the DLRT and potential decisions by the sponsor may include stopping AMG 330 and/or pembrolizumab, dose de-escalation of AMG 330, or continuing therapy at full dose.

Cohort 2 will be initiated only after all subjects in cohort 1 completed study day 28 (ie, AMG 330 [redacted] µg/day dose level in combination with pembrolizumab for 7 days), and if the rate of DLT is ≤ 3 out of 10 subjects. After receiving the DLRT recommendation, sponsor will render a final decision and will issue a written notification of the decision to investigators. Further information on dose level review meetings (DLRMs) is provided in Section 11.3.

Individual Stopping Rules

Dosing for an individual will be stopped for any occurrence of a DLT. The event will be reviewed by the investigator and Sponsor for evidence of relationship to treatment and

clinical or medical significance to decide whether dosing may be resumed for the individual and any modifications to the dosing, if appropriate.

Dose Limiting Toxicities

A DLT will be defined as any of the events described below occurring in a subject during the DLT window, unless clearly attributable to causes other than investigational product. The DLT window will start on day 1 and last for the duration of cycle 1. The CTCAE v5 will be used to assess toxicities/adverse events with the exception of CRS (see Table 6-5 for grading of CRS).

DLT Evaluation

To be DLT evaluable, subjects must meet 1 of the following criteria during DLT evaluation period (cycle 1 day 1 to cycle 1 end of infusion):

- The subject experienced a DLT; OR
- The subject has received at least 70% of planned cumulative dose of AMG 330 and has not missed more than 1 dose of pembrolizumab; OR
- The subject did not experience a DLT and completed the DLT evaluation period

Events listed below are to be considered as DLTs and exceptions when occurring in a subject during the DLT window unless clearly attributable to causes other than AMG 330 and pembrolizumab treatment:

- Any treatment-related death.
- Grade 4 neutropenia lasting ≥ 4 weeks from last day of cycle in absence of evidence of active AML. Note: grade 4 neutropenia maybe assessed retrospectively and outside of the DLT window
- Grade 3−4 non-hematologic toxicity not clearly resulting from the underlying leukemia EXCEPT:
  - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
  - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
  - Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia
  - Grade 3 infusion reaction, unless attributed to pembrolizumab, if successfully managed and which resolves within 72 hours
  - Grade 3 rash or pruritus
  - Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage.

- Grade 3 or 4 isolated analyte abnormalities (ie, those occurring without clinical consequence) that resolve, with or without intervention, to < grade 2 levels in < 72 hours will not be considered DLT.
- Grade 3 or 4 asymptomatic enzyme elevations including aspartate aminotransferase (AST), alanine aminotransferase (ALT) (without bilirubin elevation), gamma glutamyl transferase that resolve, with or without intervention, to ≤ grade 2 within 7 days will not be considered a DLT, unless attributed to pembrolizumab.
- Isolated grade 3 elevation of amylase or lipase not associated with clinical or radiological evidence of pancreatitis
- Grade 3 endocrinopathy that is well controlled by hormone replacement

- CRS meeting any of the criteria listed below:
  - Grade 2 CRS that does not resolve, with or without intervention to grade 1 within 7 days will be considered a DLT
  - Grade 3 CRS that does not resolve, with or without intervention to ≤ grade 2 within 5 days, will be considered a DLT
  - Any grade 4 CRS
- Any grade 5 toxicity
- Receive less than 70% of the planned cumulative dose of AMG 330 or miss more than 1 dose of pembrolizumab during the first cycle due to investigational product(s) related toxicity that does not meet the DLT criteria listed above

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

6.2.2.1 Amgen Investigational Product: AMG 330

Subjects will be monitored continuously for adverse events while on study therapy. Subjects will be instructed to notify their physician immediately for any and all adverse events. The criteria presented in this section for dose modifications and delays for AMG 330 are meant as general guidelines.

Criteria for Dose Delay or Dose Reduction

Subjects will receive continuous AMG 330 therapy as long as they have not had disease progression or an adverse event requiring dose modification, as described below.

Subjects who experience a grade 4 non-hematologic adverse event will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Sponsor and investigators that it is in the best interest of the subject to receive additional therapy with AMG 330 (eg, if the subject has demonstrated a response to therapy).

Dose modifications, interruptions, or delays may occur in the setting of lower grade adverse events based on the clinical judgement of the investigator, and in consultation

with the sponsor. Dose reductions should be to the previous lower dose level, or to a dose level in between the previous dose level and the current dose level, after discussion between the investigator and the sponsor.

No more than 2 dose level reductions of AMG 330 will be allowed per subject. If a third dose reduction is required, the subject must discontinue AMG 330 (and pembrolizumab, if receiving combination therapy based on response to therapy). Dose re-escalation after a dose reduction may occur in limited circumstances (such as a change in attribution of adverse event, or if re-escalation is in the best interest of the subject) after discussion and agreement between the sponsor and the investigator.

For an adverse event requiring dose modification, AMG 330 (and pembrolizumab for subjects receiving combination therapy) should be interrupted to allow recovery from the adverse event. Re-initiation of study drug cannot occur until adverse event decreases to grade ≤ 1. In case of delayed recovery to grade ≤ 1 from treatment-related adverse events that results in a delay of treatment for > 21 days, the subject will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the sponsor and investigators that it is in the best interest of the subject to receive additional therapy with AMG 330 and pembrolizumab (eg, if subject demonstrated response to therapy).

Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests and previous experience with the agent) must be determined and documented by the investigator, prior to dose modification.

In case of grade 2 CRS, administration of AMG 330 can be continued on the currently tested dose level for 8 hours, and treatment provided to mitigate CRS symptoms. If symptoms do not improve to grade 1, the dose will be de-escalated by 50% for an additional 24 hours. If CRS grade 2 resolves to grade 1, the dose can be re-escalated back to the level being tested. If symptoms persist, AMG 330 infusion will be interrupted and pembrolizumab infusion will be delayed until symptoms improve to grade 1. If treatment is interrupted for < 24 hours, the interrupted AMG 330 dose can be resumed and re-escalated back to the tested dose level. If treatment is interrupted for > 24 hours, restart or repeat rules apply (see below).

In case of grade 3 CRS, AMG 330 treatment must be interrupted and pembrolizumab treatment postponed. Sponsor has to be consulted prior to a planned re-start. In case

of grade 4 CRS, treatment must be permanently discontinued. See Section 6.8 for specific instructions for the management of CRS.

If the same grade 3 non-hematologic adverse event recurs despite a dose reduction, a second dose reduction versus discontinuation of the subject from further protocol therapy should be discussed and agreed upon the sponsor and investigators.

If a DLT occurs in a subject with clinical benefit from treatment, a restart at a lower dose can be considered if the toxicity has resolved to grade ≤ 1 and after consultation with the sponsor. If AMG 330 is discontinued, pembrolizumab may be continued as a monotherapy until disease progression for a maximum of 35 cycles (approximately 2 years) after discussion and agreement between the sponsor and the investigator. If pembrolizumab is discontinued, AMG 330 may be continued as a monotherapy.

Dose delay: treatment should be interrupted until the adverse event is resolved to grade ≤ 1, and can then be resumed at the same dose unless the interruption lasted for more than 24 hours, please see below. (Note: if the event needs > 21 days to resolve, treatment has to be permanently discontinued, see also below).

Infusion Interruption

Significant events requiring a change in treatment will be managed by immediate infusion interruption:

- The subject experiences a DLT as defined in Section 6.2.1
- The subject experiences a clinically relevant grade 4 adverse event related to investigational product (see above) but does not meet the DLT criteria
- The subject meets criteria for discontinuation of investigational product as described in Section 6.2.2
- The subject experiences disease related adverse events and AMG 330 interruption is required for medical interventions
- Technical problem with the infusion pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

Restarting the Infusion

Treatment may resume if the interruption is ≤ 21 days and if:

- The interruption occurred due to other reasons than toxicity (disease-related events, technical or logistic reasons; eg, diagnostic measurements). The infusion can be restarted at the same dose and without additional measures.
- The toxicity has resolved to CTCAE v5 grade ≤ 1 (in case of dose reduction, infusion may be re-started without prior resolution of the toxicity to CTCAE v5 grade ≤ 1 if the adverse event is not clinically relevant and upon discussion and agreement between the investigator and the sponsor)

Please also refer to specific guidance on restart after CRS in Section 6.8. Restarting the infusion after a treatment interruption requires care. The re-start should be performed in the hospital, under supervision of the investigator or designee, if the reason for the interruption was other than a technical issue or the interruption exceeded 4 hours independent of reason. Assessments should be performed after infusion re-start depending on the length of the interruption. The subject should be hospitalized for at least 48 hours after re-start of the infusion.

In case of an AMG 330 infusion interruption of > 24 hours, regardless of the reason for interruption, re-start of the infusion (repeat cycle) should be performed using step doses, which will be defined upon consultation with the sponsor. Only 2 repeat cycles may be performed in cycle 1. For cycle 2 and beyond, additional repeat cycles can be permitted upon discussion and agreement between the investigator and sponsor.

Step doses will be performed within 1 – 2 weeks (± 1 day) to return to the interrupted AMG 330 dose level, and the number and duration of repeat step doses will depend on the level of interrupted AMG 330 dose. During this 1-2 weeks, Table 1-7 Schedule of Activities should be followed (eg, for AMG 330 doses interrupted at [redacted] µg/day and below, 2 step doses can be used: [redacted] µg/day for 3 days followed by [redacted] µg/day for 4 days; for doses interrupted above [redacted] µg/day, 3 step doses can be used: [redacted] µg/day for 1 day followed by [redacted] µg/day for 3 days followed by [redacted] µg/day for 3 days). In case of AMG 330 infusion interruption for < 24 hours, regardless of the reason for interruption, restart of infusion should be performed at the same dose level as the last dose level. Administration of pembrolizumab will remain on the Q3W schedule.

After 2 unsuccessful restarts, the subject may remain on the study and continue AMG 330 treatment with a previously tested target dose that has been well tolerated. The dose of pembrolizumab will remain unchanged.

Dexamethasone (8 mg IV) should be administered within 1 hour prior to re-start and within 1 hour prior to each AMG 330 dose step(s). Dexamethasone is not required prior to the pembrolizumab administration unless it co-occurs with the AMG 330 step dose. In cases when administration of pembrolizumab co-occurs with AMG 330 step, pembrolizumab is administered first followed by dexamethasone followed by AMG 330. The subject should be hospitalized starting from re-start of infusion until 72 hours after the dose step. After each dose level increase, vital signs will be obtained as per the Schedule of Activities (see Table 1-1, Table 1-3, Table 1-5).

The number of days of exposure to both investigational products before and after an interruption should sum up to at least 70% of planned cumulative dose of AMG 330. In this case, the subject would still be DLT-evaluable. However, if the cycle was interrupted for more than 24 hours but less than 21 days, a new repeat cycle should be started and the interrupted cycle would not be evaluable for DLT, unless the event that lead to the interruption was a DLT.

Note: The end of infusion bone marrow assessment should be performed once it is confirmed that the cycle will not be resumed to assess treatment response. [redacted].

Permanent Discontinuation

A subject will permanently discontinue treatment with investigational product in the event of:

- Dose-limiting or other unmanageable toxicity. Exception: If a DLT occurs in a subject with a clear clinical benefit from treatment a restart at a lower dose can be considered if the toxicity has resolved and after consultation with the sponsor. This includes:
  - Grade 4 CRS
  - Grade 3 CRS occurring at the initial step dose for a cycle (ie, at the 10 µg/day)
  - Grade 2 or 3 CRS meeting any of the criteria listed below:
    - Grade 2 or 3 CRS that does not improve to ≤ grade 1 within 7 days
    - Grade 3 CRS that does not improve to ≤ grade 2 within 5 days
- Re-occurrence of the same grade 4 adverse event
- 3 infusion interruptions > 24 hours in cycle 1
- Disease progression as defined by 2017 European LeukemiaNet (ELN) criteria (Döhner et al, 2017)
- Withdrawal of subject's consent to treatment
- Subject or investigator not compliant with the study protocol
- Occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study
- Hematological or extramedullary relapse subsequent to CR/CRh*/CRi/MLFS on protocol treatment. Exception: a blast count > 5% at the pre-dose assessment (after the infusion-free interval) would not lead to permanent treatment discontinuation even if the count had been < 5% directly after the previous treatment cycle.
- An infusion interruption of more than 21 days due to an adverse event not clearly related to the underlying disease.

- Occurrence of CNS-related adverse event considered related to AMG 330 by the investigator and meeting 1 or more of the following criteria:
  - More than 1 seizure
  - A CNS-related adverse event CTCAE grade 4
  - A CNS-related adverse event leading to treatment interruption that needed more than 1 week to resolve to CTCAE grade ≤ 1
- Non-manageable GVHD
- Investigator's decision that a change of therapy is in the subject's best interest
- Administration of relevant non-permitted concomitant medications

Women who become pregnant while on study through 1 week after receiving the last dose of study drug will not receive subsequent scheduled doses and will be followed for safety until the end of study visit.

Men with pregnant partners or whose partners become pregnant while the subject is on study will receive subsequent scheduled doses and must practice sexual abstinence or use a condom while on study through 120 days after receiving the last dose of study drug.

All reasons for treatment discontinuation should be clearly and concisely documented in the eCRF. If a subject has not continued to present for study visits, the investigator should determine the reason and circumstances as completely and accurately as possible.

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the end of treatment and safety follow-up visits. These data should be recorded, as they comprise an essential evaluation that should be performed prior to discharging any subject from the study and to allow for the evaluation of the study endpoints.

6.2.2.2 Non-Amgen Investigational Product(s): Pembrolizumab

6.2.2.2.1 Dose Modification of Pembrolizumab if AMG 330 has been Interrupted

If toxicities due to AMG 330 do not resolve to grade ≤ 1 within 7 days of treatment interruption and supportive care as outlined, pembrolizumab may be postponed until both may be resumed per protocol. If AMG 330 is discontinued, pembrolizumab treatment may be continued following discussion and agreement between the investigator and Sponsor.

6.2.2.2.2 Dose Modification for Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immune related response. These immune-related adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most immune-related adverse events ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab are provided in Table 6-3.

Table 6-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent grade 2, grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Participants with ≥ grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink
	Recurrent grade 3 or grade 4	Permanently discontinue		

				liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading	Grade 2	Withhold		

according to increased creatinine or acute kidney injury	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Persistent grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent grade 3 or grade 4	Permanently discontinue		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; ULN = upper limit of normal
[a] AST/ALT: > 3.0 - 5.0 x ULN if baseline normal; > 3.0 - 5.0 x baseline, if baseline abnormal; bilirubin: > 1.5 - 3.0 x ULN if baseline normal; > 1 .5 - 3.0 x baseline if baseline abnormal
[b] AST/ALT: > 5.0 to 20.0 x ULN, if baseline normal; > 5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:> 3.0 - 10.0 x ULN if baseline normal; > 3.0 - 10.0 x baseline if baseline abnormal
[c] AST/ALT: > 20.0 x ULN, if baseline normal; > 20.0 x baseline, if baseline abnormal; bilirubin: > 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal
[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ grade 2, pembrolizumab may be resumed.
[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion (Pembrolizumab Investigator's Brochure). Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6-4.

Table 6-4. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = non-steroidal anti-inflammatory drug

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury 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 products (AMG 330 and pembrolizumab) 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 330 in combination with pembrolizumab.

6.4.2 Blinding

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

6.5 Treatment Compliance

Not applicable

6.6 Treatment of Overdose

Treatment of Overdose with AMG 330

The effects of overdose of this product are not known. The daily AMG 330 dose may be up to 10% lower or higher in order to account for possible pump inaccuracies. A dose of up to 10% higher than the intended dose may not require specific intervention.

In case of overdose or medication error, the infusion should be immediately stopped. Consultation with the sponsor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the sponsor is also strongly recommended even if there are no adverse events, in order to discuss the minimal duration of dose interruption. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event(s) should be recorded/reported per Section 11.4. Resumption of AMG 330 is possible after consultation with the sponsor and should adhere to the guidelines in Section 6.2.2.1.

A dose of > 10% higher than the intended AMG 330 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.

Refer to the AMG 330 Investigational Brochure for further information.

Treatment of Overdose With Pembrolizumab:

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥ 5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from the time of initial diagnosis of AML through the signing of informed consent will be collected.

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.

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

Oxygen administration as supportive measure is permitted during study treatment.

Hydroxyurea for 7 days at a dose of 1 – 10 g/day is recommended prior to the first cycle of investigational product treatment for subjects with high WBC (> 15 000 cells/mcL). Administration of hydroxyurea after start of investigational product may be permitted after discussion with sponsor.

Premedication with dexamethasone is required prior to each AMG 330 treatment cycle and prior to each dose step for the prevention of CRS. Dexamethasone should be administered as a single IV dose (8 mg) within 1 hour of start of infusion or dose step, respectively.

In the case of re-start of infusion after an infusion interruption of > 24 hours, dexamethasone (8 mg IV) should be administered within 1 hour prior to re-start and within 1 hour prior to the dose step.

For administration of dexamethasone and tocilizumab after occurrence of CRS, follow guidance in Section 6.8.

6.8 Specific Recommendations for Cytokine Release Syndrome, Tumor Lysis Syndrome, and Infection Prophylaxis

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 – 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 the initial infusion of AMG 330. Cytokine release syndrome may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the infusion with AMG 330, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 6-5 (based on the adopted grading system referenced in Lee et al, 2014).

Table 6-5. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention[c]	Instructions for Interruption of AMG 330
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	• Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever, fluids for hypotension). • Consider use of tocilizumab 4 mg/kg IV. Up to 3 additional doses can be given 8 hours apart, if needed. • 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
2	Symptoms require and respond to moderate intervention • Oxygen requirement < 40%, OR • Hypotension responsive to fluids or low dose of 1 vasopressor, OR • Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever; vasopressors for hypotension) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 100 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. • Consider use of tocilizumab 8 mg/kg IV. Up to 3 additional doses can be given 8 hours apart, if needed. 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.	Institute medical management. If hypotension persists 8 hours after adequate medical management, de-escalate AMG 330 to 50% of the current dose for 24 hours. If symptoms persist, interrupt AMG 330. Refer to Section 6.2.2 for dose interruption guidelines. If symptoms improve to ≤ grade 1, re-escalate to the dose at which the CRS event previously occurred. If symptoms progress to grade 3 criteria, see row below. Discontinue AMG 330 if there is no improvement to CRS ≤ grade 1 within 7 days. Do not administer pembrolizumab until symptoms improve to CRS grade ≤ 1

Page 1 of 2

Footnotes defined on next page of table

Table 6-5. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 330
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40%, OR • Hypotension requiring high dose[b] or multiple vasopressors, OR • Grade 3 organ toxicity or grade 4 transaminitis per CTCAE v5 criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer tocilizumab 8 mg/kg IV. Up to 3 additional doses of 8 mg/kg of tocilizumab can be given 8 hours apart, if needed. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise.	Immediately interrupt AMG 330 until event resolves to CRS grade ≤ 1. Discontinue AMG 330 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. Permanently discontinue AMG 330 if CRS grade 3 occurs at the initial step dose (ie, at MTD1). Do not administer pembrolizumab until symptoms improve to CRS grade ≤ 1 If recurrent grade 3 CRS, permanently discontinue pembrolizumab.
4	Life-threatening symptoms • 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 dexamethasone (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 should be administered at a dose of 8 mg/kg. Up to 3 additional doses can be given 8 hours apart, if needed.	Immediately stop the infusion and permanently discontinue AMG 330 therapy and pembrolizumab therapy.

Page 2 of 2

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; MTD = maximum tolerated dose

[a] Revised grading system for cytokine release syndrome (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] Investigators may also consider additional therapy, based on clinical judgment.

Re-start of Treatment after Infusion Interruption due to Cytokine Release Syndrome:

After interruption of AMG 330 infusion due to grade 3 CRS, the infusion may be re-started if all of the following criteria are met:

- Sponsor must be consulted prior to re-starting treatment
- The event has resolved to grade ≤ 1 prior to re-starting treatment

In case of an infusion interruption of > 24 hours, regardless of the reason for interruption, re-start of the infusion should be performed at the initial dose and dose steps should be performed prior to administering the interrupted dose. The dose level for each step and number of steps should be determined in consultation with the Sponsor prior to re-initiation of the infusion.

Tumor Lysis Syndrome

Subjects with AML and WBC < 10 000/µL are considered to be at low risk for tumor lysis syndrome. WBC > 10 000/µL and < 50 000/µL are considered to be at intermediate risk, and subjects with WBC > 50 000/µL are considered at high risk. This protocol requires that subjects have a maximum WBC count of 15 000/µL.

Additional high risk features include baseline uric acid > 450 µg/L (7.5 mg/dL), serum creatinine > 1.4 mg/dL, and lactate dehydrogenase (LDH) greater than the upper limit of normal (ULN).

Patients with intermediate risk WBC count and elevated baseline uric acid (> 450 µg/L), serum creatinine > 1.4 mg/dL, or LDH greater than ULN will be recommended to receive allopurinol prophylaxis. Typical dosing is 600-800 mg/day administered bid or qid and should begin 3 days before the first dose of study drug. Patients should be well hydrated and supplemented with IV fluid as clinically indicated.

For grade 3 and 4 tumor lysis syndrome, please see Section 6.2.1 for DLT considerations.

Infection Prophylaxis

Subjects who may experience neutropenia for 7 days or longer are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial (eg, fluoroquinolones), antifungal and antiviral medications. These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification.

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 and Section 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized 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 Table 1-1, Table 1-3, Table 1-5) 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 device-related 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
- Decision by investigator
- Ineligibility determined
- Protocol deviation

- Non-compliance
- Disease progression
- Requirement for alternative therapy
- Protocol-specified criteria
- Pregnancy
- Recurrent grade 2 pneumonitis
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose of pembrolizumab.

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 (Table 1-1, Table 1-3, Table 1-5) 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 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 (see Table 1-1, Table 1-3, Table 1-5).

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 or discontinuation of standard therapy for any disallowed therapy. The screening window is up to 14 days.

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 rescreening up to 3 times at the discretion of the investigator.

Once the subject is registered as rescreened, a new 14 day/week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 14 days after the original signing of the ICF, screening procedures, including informed consent, must be repeated. Hepatitis serology does not need to be repeated in case of rescreening if it was performed within 6 weeks prior to start of treatment with AMG 330. Bone marrow assessment does not need to be repeated in case it was performed within 3 weeks prior to start of treatment with AMG 330.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5). The date of the first dose of protocol-required therapies (AMG 330 and/or pembrolizumab) is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Cycle 1 on-study visits have a ± 1-day window from designated time point. All subsequent visits beginning in cycle 2 will have a ± 3-day window.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, 2 safety follow-up visits should be performed: 30 days (+ 7 days) after the last dose of AMG 330 and 30 days (+ 7 days) after the last dose of pembrolizumab. If the 2 safety follow-up periods overlap, the 2 safety follow-up visits can be combined into one.

If a subject starts a new anti-leukemia treatment within 30 (± 3) days of their last dose of protocol-assigned therapy, a safety follow-up visit must be conducted immediately prior to starting any new treatment.

8.1.4 Long-term Follow-up

Not applicable

8.1.5 End of Study

The end of study visit is defined as the date of the final study 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 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 [redacted] and pharmacokinetics of the protocol-required therapies.

8.2.1.3 Medical History

The Investigator or designee will collect a complete medical and surgical history that is not related to AML and started within 5 years prior to screening through the time of signing of the informed consent. Record all findings on the medical history CRF.

Relevant medical history, including previous chemotherapy or radiotherapy, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (resolved and ongoing) will be collected. AML history must date back to the initial diagnosis and any response duration must be recorded. The current toxicity grade will be collected for each condition that has not resolved. Exception: no toxicity grade should be recorded for ongoing AML history.

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 Physical Measurements

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

8.2.1.6 Performance Status

The Eastern Cooperating Oncology Group (ECOG) Performance status will be recorded at the time points noted in the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5).

8.2.2 Efficacy Assessments

8.2.2.1 Disease Response

Disease response assessments will be based upon review of cytogenetics, bone marrow aspirates/biopsies, and peripheral blood count. Refer to the 2017 ELN criteria in

Section 11.11 for additional detail. In addition, a presence of AML blasts in extramedullary compartment can be assessed using other approaches (eg, tissue biopsies, peripheral blood, etc.). Response must be established from a bone marrow sample supplemented with neutrophil and platelet counts.

8.2.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1, Table 1-3, Table 1-5).

8.2.4.1 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.

8.2.4.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before electrocardiogram (ECG) assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 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.

- 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) (total 9 ECGs)
- Triplicate ECGs at time points after dosing

Baseline is defined as pre-dose on cycle 1 day 1. The investigator or designated site physician will review all ECGs. ECGs will be transferred electronically to an ECG central reader for analysis 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 or designee. Standard ECG machines should be used for all study-related ECG requirements.

8.2.4.3 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.

8.2.4.4 Other Safety

Not applicable

8.2.5 Adverse Events and Serious Adverse Events

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

8.2.5.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE v5 and is described in Section 11.4.

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 investigational product(s)/study treatment/protocol-required therapies through the safety follow-up visit

or 30 days following cessation of study treatment, whichever is later, are reported using the Event CRF.

8.2.5.1.2 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 safety follow-up visit or 90 days following cessation of study treatment, (30 days following cessation of study treatment if the subject initiates new anticancer therapy), whichever is later, 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 v5 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.

8.2.5.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge 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.

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.

8.2.5.1.4 Pembrolizumab Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor. Refer to Section 8.2.5.1.2 and

8.2.5.1.3 for the required reporting period and the reporting requirements for non-serious and serious ECIs.

- an overdose of pembrolizumab, as defined in Section 6.1.1.4
- an elevated AST or ALT lab value that is greater than or equal to 3 x ULN and an elevated total bilirubin lab value that is greater than or equal to 2 x ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.2.5.1.5 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (subject incidence of DLTs, TEAEs, treatment-related adverse events [TRAEs], and changes in vital signs, ECGs, and clinical laboratory tests) 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).

8.2.5.2 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.

8.2.5.3 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 follow-up 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.

8.2.5.4 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 has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment 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.

8.2.5.5 Safety Monitoring Plan

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

8.2.5.6 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 120 days following cessation of study treatment or 30 days following cessation of study treatment if the subject initiates a new anti-cancer therapy.

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.

8.2.6 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5) 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 (Table 1-1, Table 1-3, Table 1-5).

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 24 hours of initiation of investigational product for females of childbearing potential (eg, after admission and prior to a first dose of investigational product).

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, Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

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

8.2.7 Pharmacokinetic Assessments

All subjects enrolled in the study will have pharmacokinetic samples assessed.

Blood samples of approximately 5 mL will be collected for measurement of serum concentrations of AMG 330 and pembrolizumab 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.

Blood must not be drawn from the port catheter. If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally. If the PK sample must be drawn through the central line, AMG 330 administration should be interrupted during sample withdrawal. PK samples for pembrolizumab will be collected and held for PK assessments.

8.2.8 Pharmacodynamic Assessments

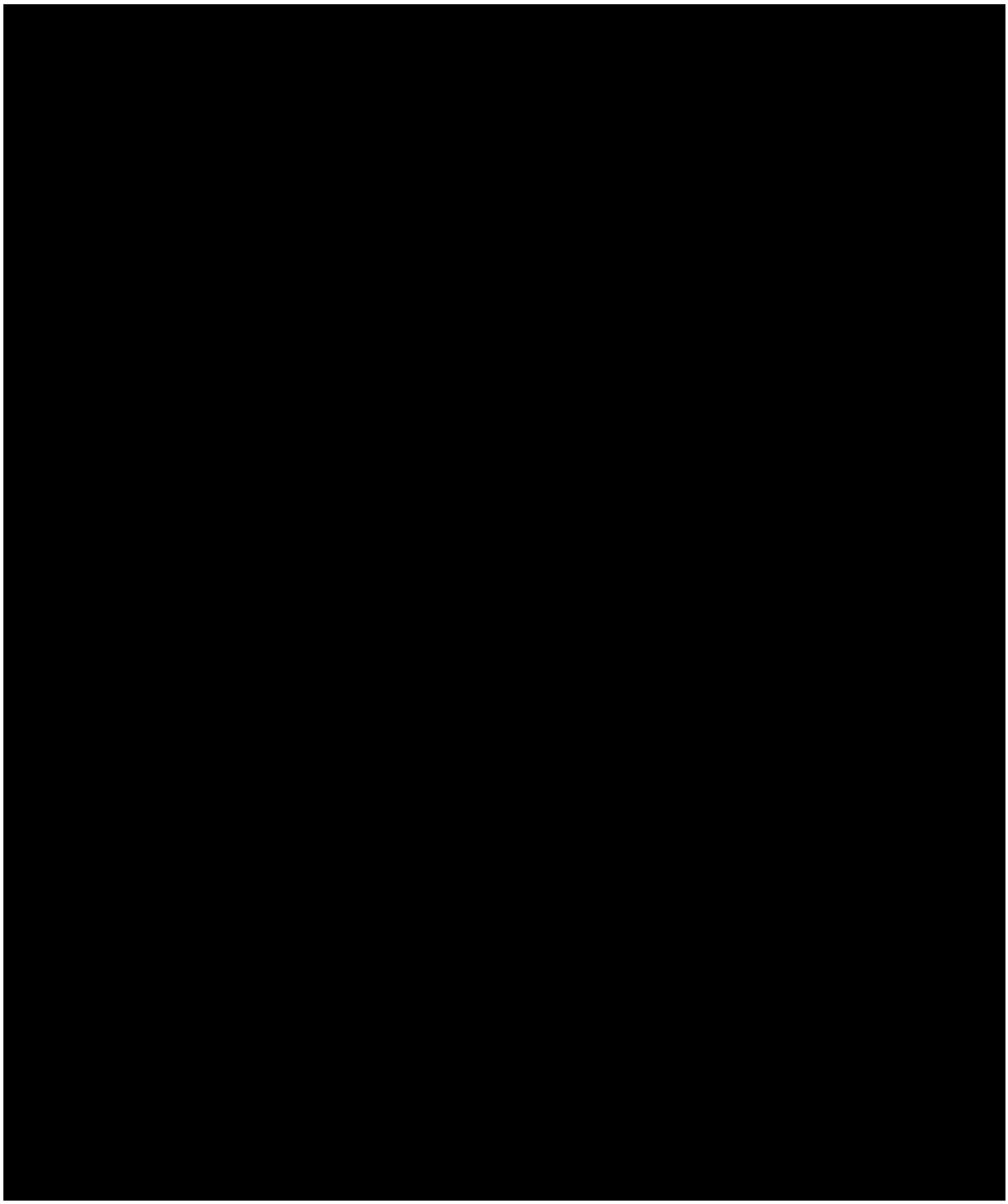
Venous blood samples of approximately 3 mL will be collected for measurement of [redacted] at timepoints listed in the Schedule of Activities.

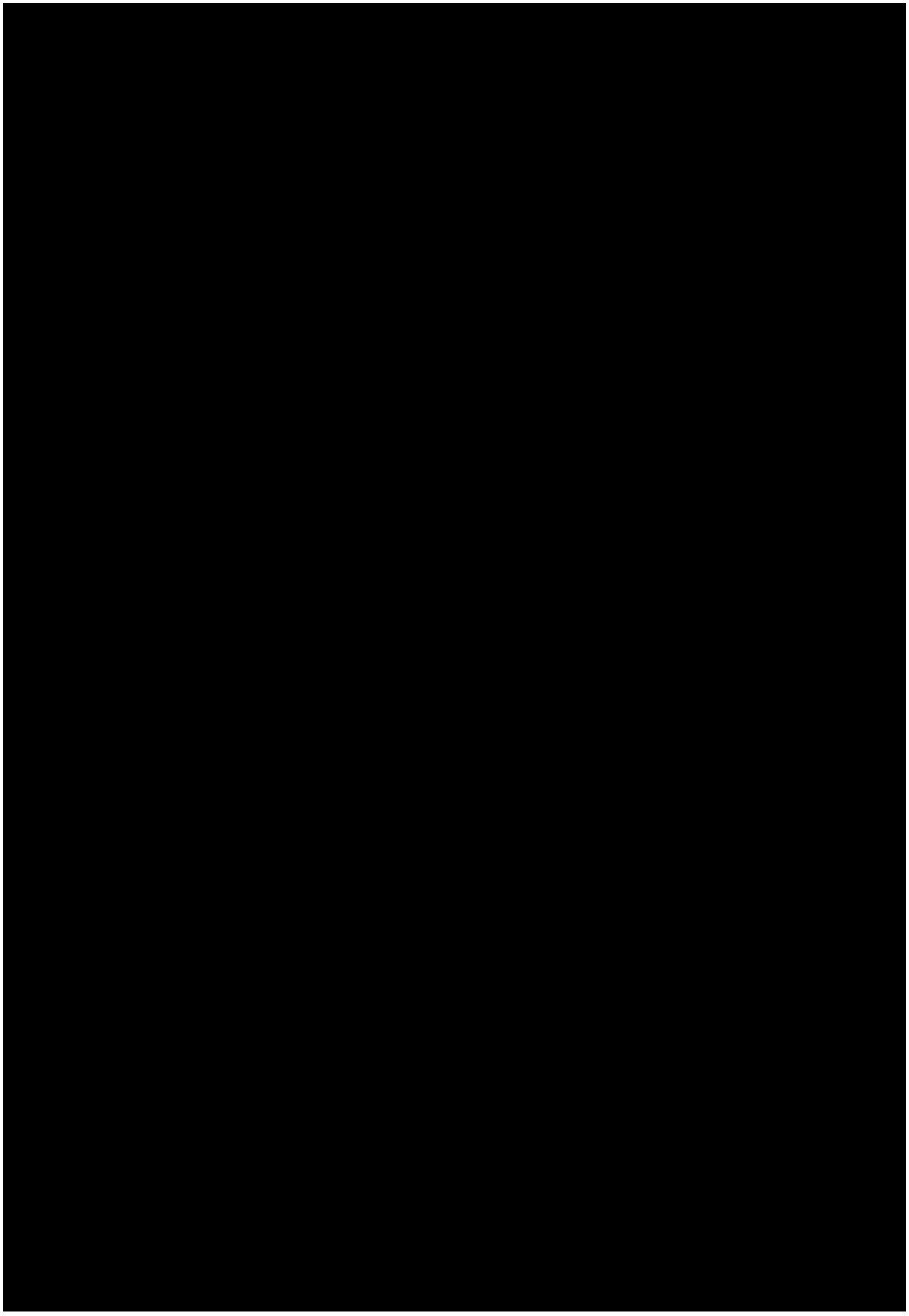
[redacted]

8.2.10 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5) for the measurement of anti-AMG 330 binding antibodies and anti-pembrolizumab antibody (as necessary). Subjects testing positive for binding antibodies may be further characterized. Subjects who test positive for anti-AMG 330 antibodies at the final scheduled antibody time point and have clinical sequelae that are considered potentially related to an anti-AMG 330 antibody response will also be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months from the last

antibody time point and continue until: (1) antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 330. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns. Refer to the Schedule of Activities (Table 1-1, Table 1-3, Table 1-5), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.





9. Statistical Considerations

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

Approximately 20 subjects will be enrolled in this study with at least 6 DLT evaluable subjects in each cohort. With 6 evaluable subjects in 1 cohort, there is an 82% chance of observing at least 1 DLT if the true DLT rate is 25%. For cohort 1, at least 10 subjects will be dosed through study day 28.

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 330 or pembrolizumab.

The analysis of DLT will be restricted to DLT-evaluable subjects (see definition of DLT-evaluable in Section 6.2.1).

The PK Analysis Set will contain all subjects who have received at least 1 dose of the AMG 330 or pembrolizumab and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

9.3.2 Covariates

This phase 1 study has no prespecified covariates.

[redacted]

9.3.3 Subgroups

This phase 1 study has no prespecified subgroups.

9.3.4 Handling of Missing and Incomplete Data

Details on handling of missing and incomplete data are described in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Details of the statistical analysis will be described in the statistical analysis plan. 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. A DLRM will occur when at least 10 treated subjects in cohort 1 have been dosed through study day 28 to determine if the safety profile of initial steps in cohort 1 is acceptable to begin enrollment of cohort 2 or if the study should be stopped. If 3 or more of the 10 treated subjects in cohort 1 experience a DLT by day 28, the guidance to the DLRT is to recommend not to initiate cohort 2. The stopping rule is based on having at least a posterior probability of > 70% that the DLT rate is > 20% assuming a prior distribution of Beta (0.40, 1.60). If the true DLT rate is 10%, 20%, 30%, 40%, or 50%, then the probability of stopping the study at the interim analysis is 7%, 32%, 62%, 83%, 95%, respectively.

9.4.1.2 Primary Analysis

The primary analysis will occur when all subjects complete end of study.

9.4.1.3 Final Analysis

The primary analysis will also be the final analysis.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, [redacted] and [redacted] data overall and by cohort 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 and Pearson (1934).

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	The proportion of subjects with a response to treatment (CR_{MRD-}, CR, CRi, MLFS, or CRh*) and exact 80% CI will be tabulated overall by cohort. Duration of response will be presented per subject and Kaplan-Meier estimates may also be further presented if data allows.
Exploratory	Details will be provided in the statistical analysis plan

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 of safety endpoints will be done using subjects from the safety analysis set. Subject incidence of DLT will be tabulated overall and by planned cohort. The statistical analysis methods for other safety endpoints are described in Sections 9.4.2.3.2 through 9.4.2.3.6.

9.4.2.3.2 Adverse Events

Subject incidence of all TEAEs will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies will be provided.

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

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 330 antibodies at any time will be tabulated overall and by cohort.

9.4.2.3.8 Exposure to Investigational Product

Details of AMG 330 and pembrolizumab administration will be listed for every subject.

9.4.2.3.9 Exposure to Other Protocol-required Therapy

Details of dexamethasone and tocilizumab administration will be listed for every subject.

9.4.2.3.10 Exposure to Concomitant Medication

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

9.4.2.4 Other Analyses

Based on the review of the data, analyses to describe the relationship between AMG 330/pembrolizumab exposure and either [redacted] and/or clinical outcome may also be performed.

10. References

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APML	promyelocytic leukemia
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BiTE	bispecific T-cell engager
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
cIV	continuous intravenous
CL	clearance
CNS	central nervous system
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete count recovery
CR_{MRD-}	complete remission without mininum residual disease
CRS	cytokine release syndrome
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECI	Events of Clinical Interest
ECOG	Easter Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European LeukemiaNet
EOI	end of infusion
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
GSO	Global Safety Officer
GVHD	Graft versus Host Disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRT	hormonal replacement therapy
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IND	Investigational New Drug
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
IVSS	intravenous solution stabilizer
LDH	lactate dehydrogenase
[redacted]	[redacted]
MLFS	morphologic leukemia-free state
[redacted]	[redacted]
MTD	maximum tolerated dose
NCT	National Clinical Trials
NOD	non-obese diabetic
PCR	polymerase chain reaction
PD-1	programmed cell death receptor
PD-L1/PD-L2	programmed cell death ligand 1/2
PK	pharmacokinetic
PR	partial remission

R/R AML	relapsed or refractory AML
RBC	red blood cell
SAP	Statistical Analysis Plan
SC	subcutaneous
SCID	severe combined immunodeficiency
SFU	safety follow-up
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TEAE	treatment-emergent adverse events
TLS	tumor lysis syndrome
TRAE	treatment-related adverse event
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization
WOCBP	woman of childbearing potential
ZAP	zeta-chain-associated protein kinase

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory. 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. Analyte Listing

<table>
<tr><th colspan="5">Local Laboratory</th></tr>
<tr><th>Chemistry</th><th>Urinalysis</th><th colspan="2">Hematology</th><th>Coagulation</th></tr>
<tr><td>sodium
potassium
chloride
bicarbonate
total protein
albumin
calcium
magnesium
phosphorus
glucose
creatinine
uric acid
total bilirubin
ALP
LDH
AST (SGOT)
ALT (SGPT)
CRP
ferritin</td><td>specific gravity
pH
blood
protein
glucose
bilirubin
ketones
<u>Microscopic exam</u>
(performed at the discretion of the investigator):
WBC
RBC
epithelial cells
bacteria
casts
crystals</td><td>RBC
nucleated RBC
hemoglobin
hematocrit
MCV
reticulocytes
platelets</td><td>WBC
WBC differential:
• total neutrophils
• seg. neutrophils
• bands/stabs
• eosinophils
• basophils
• lymphocytes
• monocytes
• myeloblasts
• monoblasts
• megakaryoblasts
• promyelocytes
• myelocytes
• metamyelocytes
• atypical
• lymphocytes
• blasts
• immature granulocytes</td><td>PTT/APTT
PT/INR
fibrinogen
AT III
Thyroid Function Tests
T3 or FT3
FT4
TSH
Other Labs
HLA typing
hep B surface antigen
hep C antibody
HBV DNA
HCV RNA
HIV[a]
serum or urine pregnancy
[redacted]</td></tr>
<tr><th colspan="5">Central Laboratory</th></tr>
<tr><td colspan="2">anti-AMG 330 antibodies
anti-pembrolizumab antibodies[b]
AMG 330 PK samples
pembrolizumab PK samples[b]
[redacted]</td><td colspan="3">[redacted]</td></tr>
</table>

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; AT III = antithrombin III; CRP = c-reactive protein; FT3 = free triiodothyronine; FT4 = free thyroxine; HBV = hepatitis B virus; HCV = hepatitis C virus; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; [redacted]; MCV = mean corpuscular volume; [redacted]; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WBC = white blood cell count

[a] HIV assessment is recommended.

[b] Collect and hold; analysis to be triggered at the discretion of the sponsor.

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Meetings

In this study, a dose level review meeting (DLRM) will be conducted 1 time to review and interpret safety data for the purposes of making recommendations about opening cohort 2 and evaluating safety signals for purposes of applying dose cohort/individual stopping rules. The Dose Level Review Team (DLRT) will meet to confirm the decision rules when the following criterion is met:

- at least 10 treated subjects in cohort 1 have been dosed through the end of [redacted] µg/day Step Dose (study day 28).

The required DLRT members are the Early Development Lead, Medical Monitor, Global Safety Officer (GSO), and Site Investigators. The DLRT will also include the Early Development Medical Director (Merck) in an advisory role. The DLRT will include Site Investigators from activated sites. The Early Development Lead, 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, pharmacokinetics (PK) scientist.

The Early Development Lead and 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 Early Development Lead and 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 unqueried.

DLRM voting will occur as follows: there will be a total of 4 votes, 1 for Early Development Lead, 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 (cohort 2) 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, then this should be reflected in the DLRM Memo.

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 (ICF), 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 ICF 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. 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 ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written ICF 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 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 ICF.

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 ICF is to be signed and personally dated by the subject 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 6.8.

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

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject.

Subjects who are rescreened are required to sign a new ICF.

The 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 ICFs) 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 Techonology (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.

- Subject files containing completed CRFs, ICFs, 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)

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 (TEAEs) 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 acute myeloid leukemia (AML), 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);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product, other protocol-required therapies and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor 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

Assesment 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 (CTCAE)**, version 5.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

with the exception of cytokine release syndrome (CRS), which must be graded using the criteria referenced in the publication by Lee et al (2014), and tumor lysis syndrome (TLS), which must be graded using the Cairo-Bishop criteria.

The Amgen Standard Grading Scale as show below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product or protocol-required therapies 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 Event 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 the Serious Adverse Event Contingency Report Form (see Figure 11-1).

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

A Study # 20170646 AMG 330	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

US AMGEN SAFETY FAX # : +888 814 8653

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 death. 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 the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 330 No✓ / Yes✓ Pembrolizumab 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

		Prior to, or at time of Event						
		Date of Initial Dose	Date of Dose	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:		Day Month Year	Day Month Year					
Amgen IP/IMP: AMG 330	☑ Open Label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Non-Amgen IP/IMP: Pembrolizumab	☑ Open Label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

Page 1 of 3

Approved

A Study # 20170646 AMG 330	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

A Study # 20170646 AMG 330	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 subjects of childbearing potential are outlined in Sections 5.1 and 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 120 days 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 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 follicle stimulating hormone 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

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system
- 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 study and the preferred and usual lifestyle of the subject)

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 study and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 120 days after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, intrauterine hormonal-releasing system, 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 120 days after the last dose of study drug.
- 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 120 days 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 120 days 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).

- 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 120 days after the last dose of study drug.
- Information will be recorded on the Lactation Notification Form (Figure 11-2) 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 229.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and comlete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 120 days 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: 20170646

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
AMG 330				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: 20170646

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
AMG 330				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, bone marrow, or saliva sample 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 leukemia disease state, the dose response and/or prediction of response to AMG 330 in combination with pembrolizumab, 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] or other exploratory studies 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 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 [redacted] (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	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x 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 > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x 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/or other protocol-required therapies 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 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 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 20170646

System Organ Class (SOC)	Disease-related Events
Blood and lymphatic system disorders	Febrile neutropenia, anaemia, neutropenia, thrombocytopenia, leukopenia, leukocytosis, disseminated intravascular coagulation
Cardiac disorders	Palpitations, tachycardia
Ear and labyrinth disorders	Ear pain, tinnitus
Eye disorders	Blurred vision, photophobia
Gastrointestinal disorders	Abdominal distention, abdominal pain, constipation, diarrhoea, gingival pain, nausea
General disorders and administration site conditions	Fatigue, pyrexia, malaise, pain, chest pain
Infections and infestations	Infections[1], sepsis
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, white blood cell count decreased, haemoglobin decreased, platelet count decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatraemia, hypomagnesaemia, hypophosphataemia, hypocalcaemia, hyperuricaemia
Musculoskeletal and connective tissue disorders	Skeletal pain, muscular pain, arthralgia, generalized muscle weakness, neck pain
Nervous system disorders	Cranial nerve disorder, dizziness, headache, lethargy, meningismus, syncope
Respiratory, thoracic and mediastinal disorders	Cough, dyspnea, epistaxis, pleuritic pain
Other	Haemorrhage[2]

[1]Represents preferred terms under *Infections and infestations* SOC
[2]Represents haemorrhage HLGT preferred terms contained within multiple SOCs
Coded: MedDRA v17.0

11.9 Appendix 9. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
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

Source: Oken et al, 1982

11.10 Appendix 10. World Health Organization Classification for Acute Myeloid Leukemias

Definition acute myeloid leukemia (AML): ≥ 20% myeloblasts in blood or in bone marrow

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. **Patients with promyelocytic leukemia (APML) are not eligible for this study.**

First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized.

Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (Arber et al, 2016).

Table 11-3. 2016 WHO Classification for AML

Type of AML diagnosis
• Acute myeloid leukemia with recurrent genetic abnormalities • Acute myeloid leukemia with myelodysplasia-related changes • Therapy-related myeloid neoplasms • Acute myeloid leukemia not otherwise specified • Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma) • Myeloid proliferations related to Down syndrome • Blastic plasmacytoid dendritic cell neoplasm • Acute leukemias of ambiguous lineage • Other
Subtype of AML at diagnosis for acute myeloid leukemia with recurrent genetic abnormalities
• AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 • AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 • AML with PML-RARA • AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A • AML with t(6;9)(p23;q34.1); DEK-NUP214 • AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM • AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1 • Provisional entity: AML with BCR-ABL1 • AML with mutated NPM1 • AML with biallelic mutations of CEBPA • Provisional entity: AML with mutated RUNX1

Page 1 of 2

Table 11-3. 2016 WHO Classification for AML

Subtype of AML at diagnosis for acute myeloid leukemia, not otherwise specified
• Acute myeloid leukemia with minimal differentiation • Acute myeloid leukemia without maturation • Acute myeloid leukemia with maturation • Acute myelomonocytic leukemia • Acute monoblastic/monocytic leukemia • Pure erythroid leukemia • Acute megakaryoblastic leukemia • Acute basophilic leukemia • Acute panmyelosis with myelofibrosis
Subtype of AML at diagnosis for myeloid proliferations related to down syndrome
• Transient abnormal myelopoiesis • Myeloid leukemia associated with Down syndrome
Subtype of AML at diagnosis for acute leukemias of ambiguous lineage
• Acute undifferentiated leukemia • Mixed phenotype acute leukemia with t(9;22)(q34.1;q11.2); BCR-ABL1‖ • Mixed phenotype acute leukemia with t(v;11q23.3); KMT2A rearranged • Mixed phenotype acute leukemia, B/myeloid, NOS • Mixed phenotype acute leukemia, T/myeloid, NOS

Page 2 of 2

11.11 Appendix 11. European LeukemiaNet (ELN) Response Criteria in Acute Myeloid Leukemia (2017)

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT–qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L (1000/µL); platelet count ≥ 100 x 10^9/L (100 000/µL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/µL]) or thrombocytopenia (< 100 x 10^9/L [100 000/µL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1/2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Category	Definition	Comment
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 months
Progressive disease (PD)*¶	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/µL], and/or platelet count to > 50 x 10^9/L [50 000/µL] nontransfused); or • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (> 25 000/µL) (in the absence of differentiation syndrome)¶; or • New extramedullary disease	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CRi)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT–qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Page 2 of 2

ANC = absolute neutrophil count; CR = complete response; CR_{MRD-} = CR without minimal residual disease; IDH = isocitrate dehydrogenase; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = measurable residual disease (also known as minimal residual disease); PD = progressive disease; PR = partial remission; RT-qPCR = real-time quantitative polymerase chain reaction; WBC = white blood cell.

* The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

¶ Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

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