Statistical Analysis Plan

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
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AML	Acute myeloid leukemia
[redacted]	
CI	Confidence interval
cIV	Continuous intravenous
CPMS	Clinical Pharmacology, Modeling and Simulation
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete count recovery
CR_{MRD-}	Complete remission without minimal residual disease
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose-limiting toxicity
DM	Data Management
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
ELN	European Leukemia Net
EOI	End of infusion
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSO	Global Safety Officer
HSCT	Hematopoietic stem cell transplantation
IP	Investigational Product
IPD	Important Protocol Deviation
IV	Intravenous
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
mg	Milligram
[redacted]	

Abbreviation or Term	Definition/Explanation
PK	Pharmacokinetic
PR	Partial remission
Q3W	Every 3 weeks
QTcB	Bazett-corrected QT Interval (QTcB)
QTcF	Fridericia-corrected QT Interval (QTcF)
R/R AML	Relapsed or refractory AML
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SFU	Safety follow-up
Study Day 1	Defined as the first day that investigational product(s) is administered to the subject
TEAE	Treatment-emergent adverse events
TLS	Tumor Lysis Syndrome
TRAE	Treatment-related adverse event
WHO	World Health Organization
µg	Microgram

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20170646, AMG 330 + Pembrolizumab dated 04 May 2020. The scope of this plan includes the final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. Pembrolizumab PK/ADA will be analyzed by Merck if required. [redacted]

2. Objectives, Endpoints and Hypotheses

2.1 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 minimal residual disease (CRMRD-), complete remission (CR), CR with incomplete recovery (CRi), or morphological leukemia-free state (MLFS), or partial remission (PR) (all according to the 2017 European Leukemia Net (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	• AMG 330 concentrations and PK parameters (eg: half-life, steady state concentration, volume of distribution, and clearance)
• Evaluate the immunogenicity of AMG 330 when administered in combination with pembrolizumab	• Anti-AMG 330 antibody formation

Objectives	Endpoints
Exploratory	
• Evaluate the pharmacokinetics (PK) of pembrolizumab when AMG 330 and pembrolizumab are administered in combination	• Pembrolizumab (serum samples) concentrations.
• Evaluate the immunogenicity of pembrolizumab when AMG 330 and pembrolizumab are administered in combination	• Anti-pembrolizumab antibody formation
[redacted]	
• Evaluate the relationship between AMG 330 and pembrolizumab exposure and response to treatment	• Serum levels AMG 330 and pembrolizumab, changes in tumor burden (exposure/efficacy) and adverse events (exposure/safety)

2.2 Hypotheses and/or Estimations

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

3. Study Overview

3.1 Study Design

This is a phase 1b study assessing safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), 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 (Section 3.1.1). 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 3.1.2) 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.

3.1.1 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 3-1, 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 50 to 56, 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.

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 3-2). 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 3-2.

Table 3-1. 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

Table 3-2. 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	
(infusion-free period)	D57-64	D57

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

3.1.2 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 3-3, 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 3-3. 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 of the protocol. The endpoints are defined in Section 2.1.

3.2 Sample Size

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.

3.3 Adaptive Design

Early stopping for safety rule is specified in Section 7.1.

4. Covariates and Subgroups

4.1 Planned Covariates

This phase 1 study has no prespecified covariates.

[redacted]

4.2 Subgroups

This phase 1 study has no prespecified subgroups.

5. Definitions

5.1 General Definitions

Age at Enrollment

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

Investigational Product (IP)

The term 'investigational product' is used in reference to AMG 330 in combination with pembrolizumab.

Amgen IP: refers to AMG 330 and Non-Amgen IP: refers to Pembrolizumab.

Cumulative Dose of AMG 330, Pembrolizumab

AMG 330: The cumulative dose in microgram (µg) is defined as the following with summation over infusions:

$\sum$ (duration of infusion (days) for each dose received × dose received [µg/day])

Pembrolizumab: The cumulative dose in milligram (mg) is defined as the following with summation over infusions:

$\sum$ (number of infusion for each dose received × dose received [mg])

Cumulative dose will be calculated within a cycle and across all cycles.

Bazett-corrected QT Interval (QTcB)

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

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcF=QT/ (RR/1000)^{1/3}$

5.2 Study Points of Reference

Baseline

For any variable, unless otherwise specified the baseline is the last assessment taken prior to the first administration of any IP. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of any IP, the baseline value is the value from the screening period measured closest to the day of first administration of any IP.

Baseline and Post-baseline ECG Values in Triplicate

The baseline ECG is defined as the mean of all pre-dose on cycle 1 day 1 assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

For post dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessments of a triplicate will be included in the average for a time point. When an ECG is missing within a triplicate, all available data will be averaged for that time point.

Change from Baseline

Change from baseline is the arithmetic difference between post-dose assessment and baseline.

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

Percent Change from Baseline

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

5.3 Study Dates

Informed Consent Date

The date on which the subject signs the informed consent form.

End of Study (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, additional antibody testing), as applicable.

End of Investigational Product (IP) Administration Date

End of IP Administration for each subject is defined as the date of decision was made to end IP reported on the End of IP Administration CRF page.

Enrollment Date

A subject's enrollment date is defined as the date the investigator has determined he or she has met all eligibility criteria, as defined by the "Date of Enrollment" field on the Subject Enrollment form on the CRF.

Last Dose Date of AMG 330 / Pembrolizumab

This is the stop date of the last infusion of AMG 330/pembrolizumab administration reported on the Investigational Product Administration CRF.

Death Date

For subjects who die during the study, the death date will be recorded on the end of study, event and survival status CRF. The earliest date will be used if the dates are inconsistent among these CRF pages.

Study Day 1

Study Day 1 is defined as the first day that investigational product is administered to the subject.

Study Day:

Study Day is defined as:

Pre study day 1: study day = (date – date of study day 1)

Post study day 1: study day = (date - date of study day 1) + 1

5.4 Endpoints

Treatment-emergent Adverse Event (TEAE)

Treatment emergent adverse event refers to an adverse event that starts on or after first dose of any IP (as indicated by the flag whether an event starts before first dose of any IP is “No” or missing on the Events CRF page) and up to and including end of study date. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

Treatment-related Adverse Event (TRAE)

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by the investigational product (either AMG 330 or pembrolizumab or in combination of AMG 330 and pembrolizumab).

Dose Limiting toxicity (DLT)

Investigators will determine whether an adverse event qualifies as a DLT per protocol Section 6.2.1.

Duration of Response (DOR)

Duration of response is calculated for subjects who have achieved overall response (CR_{MRD-}, CR, CRi, PR or MLFS). It is defined as time from the first observation indicating an objective response to the subsequent date of disease progression or death, whichever is earlier.

DOR time in days: (date of disease progression or death - date of the first observation of objective response +1)

DOR time in months: (date of disease progression or death - date of the first observation of objective response +1)/30.4

Subjects without disease progression or death until the analysis data cut-off date will be censored at the last adequate disease assessment date.

5.5 Treatment Response

Treatment response is defined in Appendix D. The data will be recorded on Disease Response CRF page.

6. Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined in Section 6.1

6.1 Safety Analysis Set

Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 330 or pembrolizumab.

6.2 Dose Limiting Toxicity (DLT) Evaluable Analysis Set

Dose limiting toxicity evaluable Analysis Set is defined as DLT-evaluable subjects in the Safety Analysis Set (see definition of DLT-evaluable in Section 6.2.1. of the protocol). The analysis of DLT will be conducted on the DLT evaluable Analysis Set.

6.3 Pharmacokinetic Analyses Set(s)

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.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. The dose level review meeting (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.

7.2 Primary Analysis

The primary analysis will occur when all subjects have ended study.

7.3 Final Analysis

The primary analysis will also be the final analysis.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required:

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations. The clinical study team will identify and document the criteria for important protocol deviations following Amgen SOP.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

PK concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard CPMS practices. All excluded observations will be detailed by CPMS along with reasons for exclusion, in accordance with standard CPMS practices.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, 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).

9.2 Subject Accountability

The number (and percent) of subjects who were enrolled, received AMG 330 and pembrolizumab and ended the study will be summarized. The number (and percent) of subjects who discontinue each treatment and the study along with the reasons for discontinuation will be summarized. Also, the date that the first subject and last subject was enrolled will be presented based on the enrolled subjects.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and

descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

The baseline characteristics to be summarized include:

- Sex: Male, Female
- Age: < 65, ≥ 65 to < 75, ≥ 75
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix C)
- Prior HSCT: Yes, No
- Response to prior therapies : Yes, No
- ELN Classification of AML (at initial diagnosis and at study entry)
- Type of AML (at initial diagnosis and at study entry)
- White blood cell count
- Absolute Neutrophil count
- Height
- Weight
- Platelet count
- Percentage of bone marrow blast

9.5 Efficacy Analyses

Analysis of efficacy endpoints will be based on the Safety Analysis Set unless otherwise specified.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The percentage of subjects with a response (CR_{MRD-}, CR, CRi, MLFS, or PR) to treatment using the European Leukemia Net (ELN) Response Criteria in Acute Myeloid Leukemia (AML) (2017) will be summarized with an exact 80% confidence interval (CI) overall and by cohort. It will be presented using an exact method proposed by Clopper and Pearson (1934). Subjects missing post baseline disease assessments will be considered not to have achieved response.

Duration of response will be presented per subject and Kaplan-Meier (KM) estimates may be presented.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Subject incidence of DLT will be summarized overall and by planned cohort. The DLT summary will be based on the DLT evaluable analysis set.

The statistical analysis methods for other safety endpoints are described in Section 9.6.2 to Section 9.6.6.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, treatment-related adverse event, serious adverse events, grade 3 and above adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events. Also subject incidence of adverse event may be summarized by dose step.

Subject incidence of all treatment-emergent adverse events, treatment-related (AMG 330 related, pembrolizumab related and in combination of AMG 330 with pembrolizumab related) adverse events, serious adverse events (SAEs), grade 3 and above adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in decreasing order of frequency. In addition, treatment-emergent adverse events and treatment-related adverse events will be summarized by system organ class, preferred term, and worst grade. Also SAEs and grade 3 and above will be summarized by preferred term only in descending order of frequency. The severity of each adverse event will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria 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.

Treatment-emergent events of interest (EOIs) will be summarized by EOI category and preferred term. Subject incidence by PT and the worst grade will be summarized for selected EOIs. CSR symptoms will also be summarized.

9.6.3 Laboratory Test Results

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject. Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters may be provided.

9.6.4 Vital Signs

Vital signs will be listed and reviewed for each subject in dose level review meeting (DLRM). The analyses of vital signs including summary statistics over time and/or changes from baseline over time may be provided. The number and percentage of subjects with abnormal changes (defined in Appendix B, Table 14-1) in systolic blood pressure, diastolic blood pressure, temperature and heart rate may be summarized.

9.6.5 Physical Measurements

Physical measurements will be reviewed for each subject in DLRM. Summary statistics over time may be provided.

9.6.6 Electrocardiogram

All on-study electrocardiogram (ECG) data parameter (QRS, QT, QTc, RR, and PR intervals) will be listed and during the analysis one or all of these parameters will be plotted.

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.

Summaries over time and/or changes from baseline over time will be provided for all 12-lead ECG parameters. The analysis of Fridericia's (QTcF) QT correction and Bazett's (QTcB) QT correction will be performed using the derived results as specified in Section 5.2 .

Subjects will be categorized into the following groups per their maximum change from baseline in QTcF and QTcB. Unscheduled assessments will be included in the determination of the maximum change.

- ≤ 30 msec
- > 30 – 60 msec
- > 60 msec

The number and percentage of subjects in each group will be summarized. A listing of the subjects with > 60 msec change from baseline in QTcF and QTcB will be provided.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF and QTcB. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- ≤ 450 msec
- > 450 – 480 msec
- > 480 – 500 msec
- > 500 msec

The number of subjects in each group will be summarized for each dosing group. A listing of the subjects with > 500 msec post baseline in QTcF and QTcB will be provided.

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 330 antibodies (binding and if positive, neutralizing) and anti-pembrolizumab antibodies at any time will be tabulated overall and by cohort.

9.6.8 Exposure to Investigational Product

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

Descriptive statistics will be produced to describe the exposure to AMG 330 and pembrolizumab. The number of cycles initiated, completed, discontinued, and re-started will be summarized. In addition, the duration of therapy and the cumulative dose may be summarized by cycle and overall. The number and percentage of subjects with dose modifications (eg, dose changes, dose interruptions) and reasons for modification will be summarized.

9.6.9 Exposure to Other Protocol-required Therapy

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

9.6.10 Exposure to Concomitant Medication

The number and percent of subjects receiving concomitant medications from study day 1 through AMG 330 or pembrolizumab safety follow-up (SFU), whichever is later, will be summarized by preferred term or category or indication for each cohort as coded by the World Health Organization Drug (WHODRUG) dictionary.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic Endpoints

9.7.1.1 Pharmacokinetic Analysis of AMG 330

AMG 330 PK parameters (eg,: half-life, steady state concentration, volume of distribution, and clearance) will be determined as appropriate from the time-concentration profile using standard non-compartmental methods and will be listed for individual subjects. Serum concentrations below the lower limit of quantifications will be set to zero for the estimation of the pharmacokinetic parameters for each subject and for the calculation of the summary statistic for each time point. Analyses will be performed based on Pharmacokinetic Analysis Set.

9.7.1.2 Pharmacokinetic Analysis of Pembrolizumab

Pembrolizumab serum samples will be taken as listed in Schedule of Assessment of protocol. Summary statistics, including mean, standard deviation, CV%, median, range (Minimal, Maximal), geometric mean and CV% of geometric mean will be computed. Individual concentration-time data will be tabulated and presented in PK appendix. Analyses will be based on Pharmacokinetic Analysis Set.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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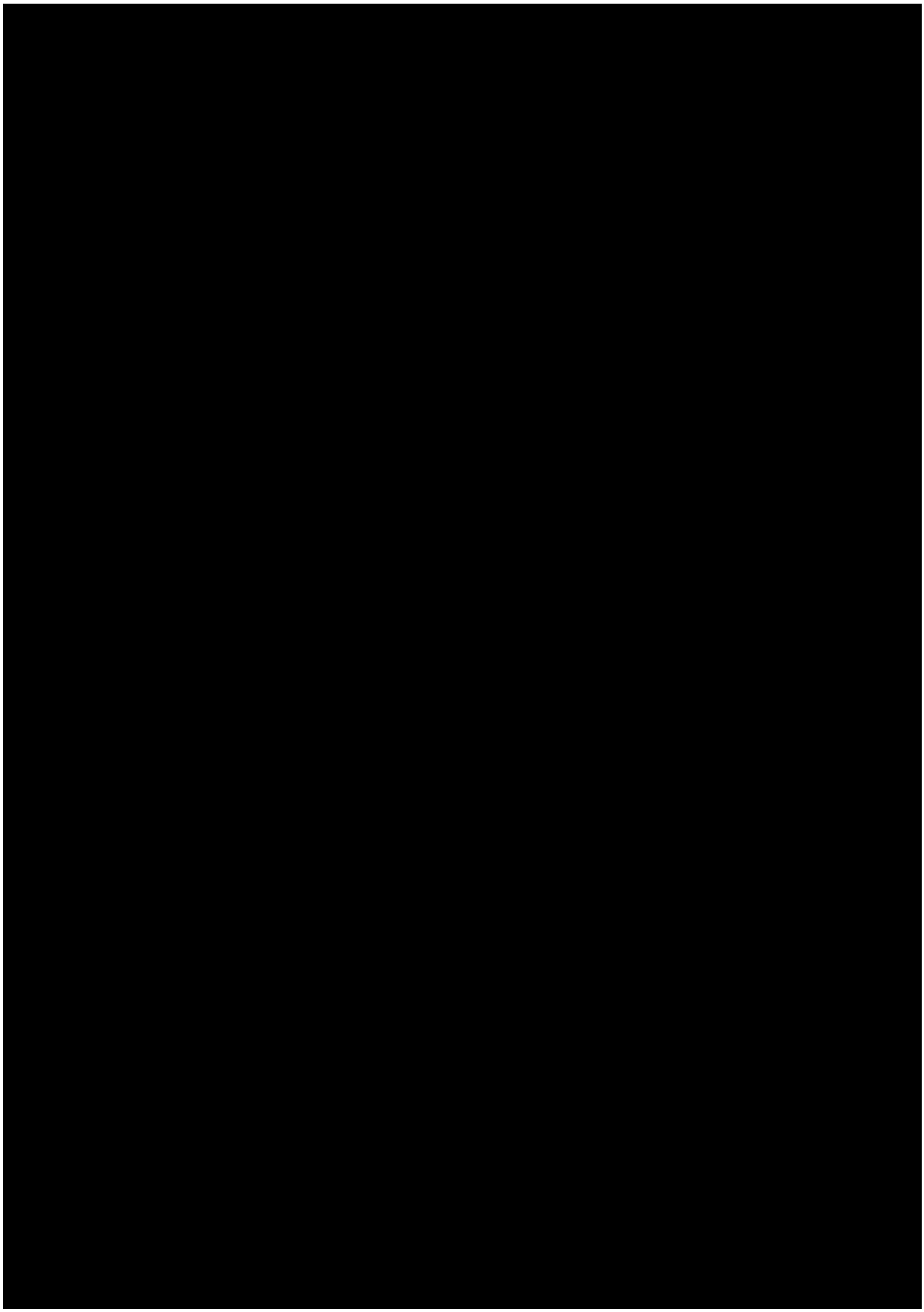
12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

None

14. Appendices



Appendix B. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used.

Refer to protocol Sections Table 6-3, Table 6-4 and Table 6-5.

Notable values for vital signs and physical measurements are defined in the following table.

Table 14-1. Notable Abnormalities of Vital Signs and Physical Measurement

Vital Signs or Physical Measurements		Notable Abnormalities
Heart rate (bpm)		> 120
		< 50
Blood pressure (mmHg)	Systolic	≥ 160
		≤ 90
	Diastolic	≥105
		≤ 50
Body temperature (°C)		> 39
Weight (kg)		Change from baseline ≥ 10% (in both directions)

Appendix C. 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

Appendix D. 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	

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Footnotes defined on next page of table

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)

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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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