STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy	
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantitation
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Corona Virus Disease 2019
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete count recovery
CRMRD-	complete remission without minimal residual disease
$CR_{MRD+/UNK}$	complete remission with positive or unknown minimal residual disease
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	duration of complete remission
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELN	European Leukemia Net
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	5-Level EuroQol 5 Dimensions
EQ VAS	EQ visual analogue scale
EOT	end of treatment
ET	early termination
GHS/QoL	Global Health Status/Quality of Life
HLT	high-level term
HLGT	high-level group term
HRQoL	health-related quality of life

IA	Interim analysis
ICH	International Conference on Harmonization
ID	identification
IPD	mportant protocol deviation
ITT	Intent-to-Treat
IWG	International Working Group
IRR	infusion related reaction
IRT	interactive response technology
LLT	lower-level term
LOQ	limit of quantitation
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MST	MedDRA Search Term
ORR	objective response rate
OS	overall survival
PBIR	probability of being in response
PP	per-protocol
PR	partial remission
PRO	patient-reported outcome
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PT	preferred term
Q1, Q3	first quartile, third quartile
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
StD	standard deviation
SE	standard error
SMQ	Standardised MedDRA Queries
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TTD	time to first deterioration
TTR	time to response

ULN	upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis specified in the study protocol for Study GS-US-590-6154.

This SAP is based on GS-US-590-6154 Protocol Amendment 7 dated 15 December 2023. The SAP will be finalized prior to data finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objective of this study is as follows:

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in patients with previously untreated AML who are ineligible for intensive chemotherapy as measured by overall survival (OS)

The secondary objectives of this study are as follows:

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of complete remission (CR) + complete remission with partial hematologic recovery (CRh) within 6 cycles of treatment

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of CR within 6 cycles of treatment

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by event-free survival (EFS)

- To evaluate the duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment

- To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 cycles of treatment

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRh without minimal residual disease (MRD-) within 6 cycles of treatment

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR without minimal residual disease (CRMRD-) within 6 cycles of treatment

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by conversion rate of transfusion dependence to transfusion independence

- To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by time to first deterioration (TTD) on the global health status/quality of life (GHS/QoL) and the physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

- To assess the safety and tolerability of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine

- To evaluate the pharmacokinetics (PK) and immunogenicity of magarolimab

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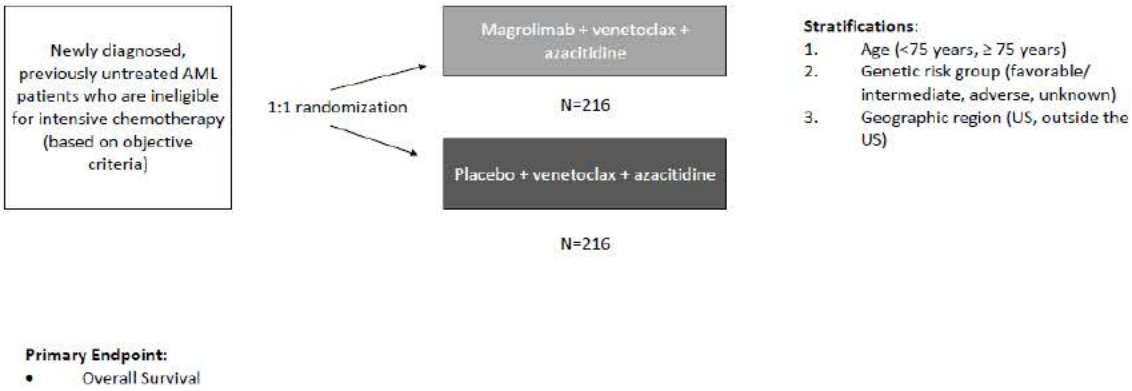
[redacted]

1.2. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of magrolimab versus placebo in combination with venetoclax and azacitidine in newly diagnosed, previously untreated patients with AML who are ineligible for intensive chemotherapy. Approximately 432 patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo + venetoclax + azacitidine (control arm). Randomization will be stratified by 3 factors:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown)
- geographic region (United States [US], outside the US)



The primary endpoint is OS. Two interim OS analyses will be conducted, the first one after 121 deaths (40% of the expected 303 deaths), and the second one after 227 deaths (75% of the expected 303 deaths) are observed among all patients; the primary OS analysis will be conducted after 303 deaths have occurred.Following completion of screening and admission assessments, eligible patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo + venetoclax + azacitidine (control arm).

The study treatments within each arm are described in Table 1-1:

Table 1-1. Dose Level and Schedule

Treatment Arm	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Experimental arm (magrolimab + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9
	Magrolimab Administration			
	Magrolimab 1 mg/kg IV (over 3 hours)	Days 1, 4		
	Magrolimab 15 mg/kg IV (over 3 hours)	Day 8		
	Magrolimab 30 mg/kg IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Magrolimab 30 mg/kg IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly 30 mg/kg dose		
Control arm (placebo + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1–5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1–7 or Days 1-5 and 8-9
	Placebo Administration			
	Placebo IV (over 3 hours)	Days 1, 4		
	Placebo IV (over 3 hours)	Day 8		
	Placebo IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Placebo IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly		

IV = intravenous; PO = orally; QW = every week; Q2W = every 2 weeks; SC = subcutaneous
a Azacitidine administered per region-specific labeling.

Cycle lengths are 28 days, and all patients will continue on study treatment until disease progression, relapse, loss of clinical benefit, unacceptable toxicities or other study treatment discontinuation criteria are met. Clinical benefit, as determined by the investigator, can include transfusion independence, adequate blood counts, symptomatic improvement, or other criteria as determined by the investigator.

Acute myeloid leukemia disease response assessment will be performed at the end of Cycle 1, Cycle 2, Cycle 4, Cycle 6, and every 3 cycles thereafter.

Patients will continue follow-up study visits unless they withdraw completely from the study.

All patients discontinue study treatment for reasons other than death or start of new anti-AML therapy (except maintenance and SCT) will participate in long-term follow-up for disease response unless the patient withdraws consent for such follow-up and withdraws completely from study.

In the event one or more components of the study treatment (magrolimab/placebo, azacitidine and/or venetoclax) are discontinued, the following combinations are permitted:

- Magrolimab/placebo + azacitidine
- Azacitidine (single agent)
- Venetoclax + azacitidine

The following combinations are not permitted:

- Magrolimab/placebo (single agent)
- Venetoclax (single agent)
- Magrolimab/placebo + venetoclax

If azacitidine is permanently discontinued, the patient must discontinue the remaining study treatment. Patients who discontinue study treatment but continue in a response or are achieving clinical benefit will continue to be followed on study for response assessments to ascertain relapse and for long-term survival.

All patients will be followed for survival until death, withdrawal of consent, loss to follow-up, completion of survival follow-up, or study termination by the sponsor, whichever occurs first. Duration of survival follow-up will be limited to 5 years from the end of treatment visit for each patient. For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

Following the independent data monitoring committee (DMC) meeting that occurred on 2 February 2024 for a planned futility analysis based on OS, Gilead has decided to terminate the study based on the determination of futility.

1.3. Sample Size and Power

The study will randomize approximately 432 patients in total into 2 treatment arms at a 1:1 ratio, determined by formal hypothesis testing performed on the primary efficacy endpoint: OS, with family-wise Type I error controlled at 1-sided significance level of 0.025.

It is assumed that administration of magrolimab + venetoclax + azacitidine to study patients will result in a median OS of approximately 21 months, improved from a median OS of 14.7 months in patients treated with placebo + venetoclax + azacitidine. This corresponds to an OS HR of 0.7. Assuming that the duration of OS is exponentially distributed in each of the 2 arms, with an HR equal to 1 under the null hypothesis of no difference between the 2 treatment arms, 303 events are needed to detect an HR of 0.7 with 86.4% power at a 1-sided significance level of 0.025 using a log-rank test, the first interim analysis with futility test when 40% of the information (121 deaths) is available, and the second interim analysis with superiority test together with a futility test when 75% of the information (227 deaths) is available, and one primary analysis. For the second OS interim analysis and the OS primary analysis, the Lan-DeMets alpha spending function with O'Brien-Fleming stopping boundary will be used. The futility boundaries for two interim analyses are obtained using a Gamma beta-spending function with parameter -5.

With an accrual period of 19 months (with approximately 51% of the patients enrolled during the initial 12 months, and the remaining 49% of the patients enrolled during the last 7 months), 24 months of follow up, and an annual 1.43% dropout rate (5% dropout chance by 43 months with time to dropout assuming exponentially distributed time-to-dropout), a total sample size of 432 patients (216 patients per treatment group) is needed to observe the required 303 events.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study, perform interim reviews of safety data at regular intervals, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination (ET) of the study in the best interests of the patient, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

In addition, the DMC will review the results from the 2 interim analyses. Based on the pre-specified superiority and futility rules, the DMC may make recommendations to Gilead as to whether the study should be stopped early due to overwhelming efficacy, be terminated for futility, or continue as planned. Efficacy superiority and futility boundaries are specified in study protocol Section 8.2.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

Two OS interim analyses (IA) are planned.

2.1.1. First Interim Analyses

The first interim analysis will be performed when approximately 121 deaths (40% of the expected 303 deaths) have occurred, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. An administrative 1-sided alpha =0.0001 is allocated to this interim analysis. The nonbinding futility analysis with a futility boundary of HR = 1.1 will be performed. A Gamma beta-spending function with parameter -5 is used to obtain the futility boundaries for both interim analysis.

2.1.2. Second Interim Analyses

The second interim analyses for the study will not be conducted since the study was terminated after the planned futility analysis.

2.2. Primary Analysis

Not applicable.

2.3. Final Analysis

The final analysis will be performed after all patients have completed or discontinued the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

Following the independent data monitoring committee (DMC) meeting that occurred on 2 February 2024 for a planned futility analysis based on OS, Gilead has decided to terminate the study based on the determination of futility. By the time the sponsor makes the decision to end the study, 378 patients have been randomized, which is less than the planned sample size of 432 patients.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of patients in each category will be presented; for continuous variables, the number of patients (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all patients in the Intent-to-Treat (ITT) Analysis Set and sorted by treatment group, subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the patients to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of patients eligible for inclusion will be summarized by treatment group.

3.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set includes all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified. This is the primary analysis set for efficacy analysis.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received. This is the primary analysis set for safety analyses.

3.1.3. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all randomized patients who took at least one dose of magrolimab and have at least 1 measurable (non - below the limit of quantitation (BLQ) numeric values) post-treatment serum concentration of magrolimab. This is the primary analysis set for all PK analyses.

3.1.4. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all randomized patients who received at least one dose of magrolimab and had at least one evaluable anti-magrolimab antibody test result.

3.2. Subject Grouping

For analyses based on the ITT Analysis Set, patients will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, patients will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set and the Immunogenicity Analysis Set, patients will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Patients will be randomized in a 1:1 ratio to treatment arms using an interactive response technology (IRT) with a stratified randomization schedule. Stratification will be based on the following variables:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown)
- geographic region (United States [US], outside the US)

If there are discrepancies in stratification factor values between the IRT and the clinical database, the values recorded in the clinical database will be used for analyses.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses when applicable, as specified in Section 6. If there is an imbalance in presumed prognostic baseline characteristics between treatment groups, efficacy evaluations may be performed that include these baseline values in efficacy analysis models as covariates; these evaluations will be considered as sensitivity analyses.

3.4. Examination of Subject Subgroups

Subgrouping of patients based on randomization stratification factors may be explored for subgroup analyses. The primary and selected secondary efficacy endpoints (defined in Section 6) may be examined using the following subgroups:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown)
- geographic region (US, outside the US)

The analysis may also be conducted in the subgroups by

- TP53 mutation status (mutant, wild type)
- ECOG (0-1, 2-3)

If there is an imbalance between treatment groups in presumed prognostic baseline characteristics that are not stratification factors, subgroupings based on these imbalanced baseline characteristics may also be explored for analysis of the primary endpoint and key secondary efficacy endpoints.

3.5. Multiple Comparisons

The adjustment for multiple comparisons is not applicable since the study has been terminated. Nominal P-values will be provided if applicable.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete dates initial AML diagnosis is described in Section 5.5, for date of death is described in Section 6.1.1, for the start date of new anti-AML therapy in Section 6.2.1, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 5.10.1 and 5.10.2. Imputation rules adopted in the efficacy analyses are specified in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then “15” will be imputed as the day of birth
- If only year of birth is collected, then “01 July” will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at the randomization (in years) will be used for analyses and presented in listings. If age at randomization is not available for a subject, then age derived based on date of birth and the randomization date will be used instead. For screen failures or unrandomized patients, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of any study drug, which is the date of the first dose of magrolimab/placebo, venetoclax or azacitidine, whichever occurs first and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of any study drug administration. If the subject is randomized but not dosed, the randomization date will be study day 1.

3.8.2. Analysis Visit Windows

Patient visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis windows for laboratory are provided in Table 3-1 to Table 3-3.

Table 3-1. Analysis Visit Windows for Hemoglobin

Analysis Visit	Nominal Study Visit or Study Day	Visit Window Study Day[a]	
		Lower Limit	Upper Limit
Baseline			1[b]
Day 1 post-dose	Set 1 Day 1, post-dose Unscheduled[d], post-dose	1[c]	1
Day 2	2	2	2
Day 3	3	3	3
Day 4 pre-dose	Set 1 Day 4, pre-dose Unscheduled[e], pre-dose	4	4
Day 4 post-dose	Set 1 Day 4, post-dose Unscheduled[f], post-dose	NA	NA
Week 1	8	5	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	46
Week 7	50	47	53
Week 8	57	54	63
Week 10	71	64	77
Week xx (every other week from Week 10)	xx*7 + 1	xx*7-6	xx*7+7

a The 1st magrolimab/placebo infusion date is considered as Day1 in study day calculation if subjects are administered magrolimab/placebo.
b On or prior to first magrolimab/placebo date/time if the patient is infused with magrolimab/placebo, otherwise use first dose date/time of any study drug.
c Post first magrolimab date/time if the patient is infused with magrolimab, otherwise use first dose date/time of any study drug.
d Hemoglobin collected at unscheduled post-dose visit on the same day of or one day after Set 1 Day 1 visit is mapped to Day 1 post-dose.
e Hemoglobin collected at unscheduled pre-dose visit on the same day of Set 1 Day 4 visit is mapped to Day 4 pre-dose.
f Hemoglobin collected at unscheduled post-dose visit on the same day of or one day after Set 1 Day 4 visit is mapped to Day 4 post-dose.

Table 3-2. Analysis Visit Windows for Calcium/ Creatinine/ Phosphorus/ Potassium/Uric Acid

Analysis Visit	Nominal Study Visit or Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1[a]
Day 1 Post-Dose 6-8 Hour	Cycle 1 Day 1, 6-8 Hour Post-Dose Unscheduled[b], 6-8 Hour post-dose	NA	NA
Day 2 Pre-Dose	Cycle 1 Day 2	2	2
Day 2 Post-Dose 6-8 Hour	Cycle 1 Day 2, 6-8 Hour Post-Dose Unscheduled[c], 6-8 Hour post-dose	NA	NA
Day 3 Pre-Dose	Cycle 1 Day 3 Cycle 1 Day 4	3	3
Day 3 Post-Dose 6-8 Hour	Cycle 1 Day 3, 6-8 Hour Post-Dose Unscheduled[d], 6-8 Hour post-dose	NA	NA
Day 3 Post-Dose 24 Hour	Cycle 1 Day 3, 24 Hour Post-Dose Unscheduled[e], 24 Hour post-dose	NA	NA
Week 1	8	4	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	46
Week 7	50	47	53
Week 8	57	54	63
Week 10	71	64	77
Week xx (every other week from Week 10)	xx*7 + 1	xx*7-6	xx*7+7

a On or prior to first dose date of any study drug.
b Laboratory records collected at unscheduled 6-8 hour post-dose visit on the same day of or one day after Cycle 1 Day 1 visit is mapped to Day 1 post-dose 6-8 hour.
c Laboratory records collected at unscheduled 6-8 hour post-dose visit on the same day of or one day after Cycle 1 Day 2 visit is mapped to Day 2 post-dose 6-8 hour.
d Laboratory records collected at unscheduled 6-8 hour post-dose visit on the same day of or one day after Cycle 1 Day 3 visit is mapped to Day 3 post-dose 6-8 hour.
e Laboratory records collected at unscheduled 24 hour post-dose visit on the same day of or one day after Cycle 1 Day 3 visit is mapped to Day 3 post-dose 24 hour.

Table 3-3. Analysis Visit Windows for Remaining Lab

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1[a]
Week 1	8	1[b]	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	46
Week 7	50	47	53
Week 8	57	54	63
Week 10	71	64	77
Week xx (every other week from Week 10)	xx*7 + 1	xx*7-6	xx*7+7

a On or prior to first dose date/time of any study drug
b Post first dose date/time of any study drug

Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of any study drug will be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of any study drug will be included in determining the maximum postbaseline toxicity grade and anti-magrolimab antibody status.
- Response assessments and patient-reported outcome (PRO) assessments performed at unscheduled visits after the date of randomization will be included in the analyses of the efficacy endpoints and the PRO related endpoints, respectively.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the arithmetic average of the

measurements for continuous data, or the measurement with the lowest severity for categorical data.

- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the arithmetic average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. PROTOCOL DEVIATIONS

Patients who did not meet the eligibility criteria for study entry, but enrolled in the study will be listed. A by-subject listing will be provided for those patients who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that patients did not meet and related comments, if collected.

Protocol deviations occurring after patients entered the study are documented during routine monitoring. The number and percentage of patients with important protocol deviations, with 1, 2, or 3 or more important protocol deviations, and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the ITT Analysis Set. A by-subject listing will be provided for those patients with important protocol deviation.

4.1. Assessment of COVID-19 Impact

The study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. The following by-subject listings will be provided:

- Study drug discontinuation Due to COVID-19
- Protocol deviations due to COVID-19
- Missed or virtual visits due to COVID-19
- Adverse events due to COVID-19

5. SUBJECT INFORMATION

5.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator and overall. The summary will present the number and percentage of patients enrolled. For each column, the denominator for the percentage calculation will be the total number of patients analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of patients in the stratum will be the total number of enrolled patients. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of patients with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group. This summary will present the number of patients screened, the number of patients screen failed, and the number of patients in each of the categories listed below by treatment group:

- ITT Analysis Set
- Safety Analysis Set
- Discontinued study treatment (magrolimab + venetoclax + azacitidine, placebo + venetoclax + azacitidine) with reasons for discontinuation
- Discontinued study with reasons for discontinuation

For the reasons of study drug discontinuation and study discontinuation, the number and percentage of patients in each category will be provided. The denominator for the percentage calculation will be the total number of patients in the ITT Analysis Set corresponding to that column.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for study drug discontinuation
- Reasons for study discontinuation

5.2. Extent of Study Drug Exposure and Relative Dose Intensity

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and relative dose intensity. Each variable will be calculated for magrolimab/placebo, venetoclax, and azacitidine separately. No formal statistical testing between treatment group is planned.

5.2.1. Duration of Exposure to Study Drug

Total duration of exposure to each study drug (magrolimab/placebo, venetoclax, and azacitidine) will be defined for a subject as last dosing date minus first dosing date plus 1 day, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

The total duration of exposure to each study drug will be summarized using descriptive statistics for continuous variables, as well as using the number (i.e., cumulative counts) and percentage of patients exposed for at least the following time periods: 1 day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks, etc.

The number of cycles patients exposed to venetoclax and azacitidine will be summarized using descriptive statistics, and the number and percentage of patients who received at least 1, 2 …, 6 cycles will be presented.

The number and percentage of patients who have dose reduction or delay for each drug and the reasons will be summarized.

By-subject listings of study drug administration will be provided.

5.2.2. Relative Dose Intensity

Relative dose intensity is the percentage of the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

For magrolimab/Placebo:

The relative dose intensity is the percentage of the total amount of study drug administered relative to the total amount of study drug expected to be administered.

$$\text{Relative dose intensity (\%)} = \left(\frac{\begin{array}{c}\text{Cumulative Dosage of Magrolimab/Placebo} \\ \text{Administered (in mg/kg)}\end{array}}{\begin{array}{c}\text{M grolimab/Placebo Dosage Expected to be Administere} \\ \text{on Treatment (in mg/kg)}\end{array}} \right) \text{x } 100$$

Cumulative dosage (mg/kg) administered for each subject is defined as the sum of dosages (mg/kg) of all infusions the subject received.

Magrolimab/placebo dosage expected to be administered on treatment (mg/kg) for each subject is defined as the total amount of magrolimab/placebo the subject was expected to receive during the subject's treatment period.

For venetoclax:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Total Amount of Venetoclax Administered (mg)}}{\text{Venetoclax Expected to be Administered on Treatment (mg)}}\right) \text{x } 100$$

For azacitidine:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Total Amount of Azacitidine Administered (mg/m\^2)}}{\text{Azacitidine Expected to be Administered on Treatment (mg/m\^2)}}\right) \text{x } 100$$

For each study drug, descriptive statistics for the relative dose intensity with the number and percentage of patients belonging to relative dose intensity categories (eg, < 75%, ≥ 75 to < 90%, ≥ 90%) will be provided by treatment group for the Safety Analysis Set.

For venetoclax, concomitatnt medications in Posaconazole/Other Strong CYP3A inhibitor/Moderate CYP3A inhibitor/P-gp inhibitor will be considered to reduce the amount of venetoclas expected to be administered.

A by-subject listing of each study drug administration will be provided by treatment group, subject ID number (in ascending order) and visit (in chronological order).

5.3. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, age group [< 75 years, ≥ 75 years], sex, race/ ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], Body Surface Area [BSA; in m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The summary of demographic data will be provided for the ITT Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by treatment group and subject ID number.

5.4. Other Baseline Characteristics

Other baseline characteristics include but are not limited to TP53 mutational status, Eastern Cooperative Oncology Group (ECOG) performance status, and World Health Organization (WHO) AML classification. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The summary of these baseline characteristics will be provided for the ITT Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided.

5.5. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Time since diagnosis (months) will be calculated by (date of randomization – date of diagnosis) / 30.4375. -In deriving the time since disease diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

A by-subject listing of general medical history will be provided by subject ID number in ascending order.

5.6. Prior Anti-Cancer Therapy

No summary or listing of prior anti-cancer therapy will be provided.

5.7. Prior and On Study Radiotherapy

No summary or listing of on study radiotherapy will be provided.

5.8. Surgeries and Procedures

No summary or listing of surgeries and procedures will be provided.

5.9. Prior Study Transfusion

No summary or listing of prior study transfusion will be provided.

5.10. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

5.10.1. Prior Medications

Prior medications are defined as any medications taken before a subject takes the first study drug.

Any medication with a start date prior to the first dosing date of study drug will be considered as prior medication regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included as prior medication, unless otherwise specified.

No summary of prior medications will be provided.

5.10.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug.

Any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on 70 days after the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or 70 days after the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug plus 70 days will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date plus 70 days will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

No summary of concomitant medications will be provided.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

5.11. Left Ventricular Ejection Fraction Results

No summary or listing of left ventricular ejection fraction results will be provided.

5.12. Post Treatment Anti-cancer Therapy

Post treatment anti-cancer therapy will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoints

6.1.1. Definition of Primary Efficacy Endpoint

The primary efficacy endpoint of this study is OS.

Overall Survival: The OS is measured from the date of randomization to the date of death from any cause. Patients whose deaths are not observed during the study will be censored at their last known alive date.

The date of the last known alive will be determined by selecting the last available date of the following study procedures for a subject: ADA sample collection, adverse event, anti-cancer therapy, bone marrow assessments, concomitant medication, consents, AML cancer diagnosis history, ECHO or MUGA scans, ECG performance date, study drug administration, cytogenetic assessment, healthcare encounters, enrollment, molecular markers, medical history, AML response assessment, biomarkers and PK sample collection, protocol deviation, radiotherapy, transfusion, performance status, PRO assessment, transfusion, clinical laboratory collection, SCT, surgeries and procedures, survival follow-up, and site transfer.

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

- If day is missing but the month and year are available, then the imputed date will be the first day of the month or the last known alive date + 1, whichever is later.
- If day and month are missing but year is available, then the imputed date will be 01Jan of that year or the last known alive date + 1, whichever is later.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

The primary efficacy hypothesis to be tested is that there is no difference between magrolimab + venetoclax + azacitidine (experimental arm) and placebo + venetoclax + azacitidine (control arm) in OS for patients. Using $S_{exp}(t)$ and $S_{ctrl}(t)$ to denote the OS distribution functions of the experimental arm and control arm, respectively, the statistical hypotheses to be tested in this study will be:

H_0: $S_{exp}(t) = S_{ctrl}(t)$

H_1: $S_{exp}(t) > S_{ctrl}(t)$ (experimental arm is superior to control arm in terms of OS)

6.1.3. Analysis of the Primary Efficacy Endpoint

The primary analysis of OS will compare the OS distributions of two treatment groups using the stratified log-rank test, stratified by the stratification factors at randomization for the ITT Analysis Set. Medians, Q1, Q3 of the OS distributions, and the proportion of patients who are alive at 6, 12 and 18 months from randomization will be estimated along with corresponding 95% CIs using the Kaplan-Meier method. Kaplan-Meier curves will be provided by treatment group.

In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model stratified by the stratification factors.

6.1.4. Follow-up Time

The follow-up time for OS is defined as the interval from date of randomization to the death date for patients who died on or prior to the data cutoff, or from the date of randomization to the earlier of the loss to follow-up or the last known alive date for patients who are alive up to the data cutoff or lost to follow-up. The follow-up time will be summarized by treatment groups using descriptive statistics including median and range (minimum and maximum).

6.1.5. Sensitivity Analysis of the Primary Efficacy Endpoint

No sensitivity analysis of the primary efficacy endpoint is planned.

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6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Rate of CR + CRh Within 6 Cycles of Treatment: the CR + CRh rate is the proportion of patients who achieve a CR (including CR_{MRD-} and $CR_{MRD+/unk}$) or CRh as defined by CR with partial platelet and absolute neutrophil count recovery (Appendix 2) within 6 cycles of treatment while on study prior to initiation of any new anti-AML therapy or SCT.

When the date of initiation of a new anti-AML therapy other than the study treatment or the date of SCT is incomplete or missing, the following algorithm will be followed:

If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the day of last dose + 1 if the month and year of new anti-AML therapy/SCT and the month and year of last dose are the same.

If day and month are missing but year is available, then the imputed day and month will be 01Jan or the date of last dose + 1 if the year of new anti-AML therapy/SCT and the year of last dose are the same.

Rate of CR Within 6 Cycles of Treatment: the CR rate is the proportion of patients who achieve a CR, including CR_{MRD-} and CR with positive or unknown minimal residual disease ($CR_{MRD+/unk}$) within 6 cycles of treatment, as determined by investigators based on the ELN 2017 for AML with modifications (Appendix 2) while on study prior to initiation of any new anti-AML therapy or SCT.

Event-Free Survival: The EFS is defined as time from the date of randomization to the earliest date of the documented relapse from CR, treatment failure (defined as failure to achieve CR within 6 cycles of treatment), or death from any cause. Response assessments or death post SCT or new anti-AML therapies will be included in the analysis. The date of randomization will be assigned as the event date for patients with treatment failure.

Patients who are not observed to have one of the specified events on or prior to data cutoff date (the date on which subsequently collected data will not be considered as part of the analysis) will be censored at the date of their last response assessment with clear documentation of no relapse on or prior to the data cutoff date. Patients will be censored at the date of randomization if no response assessment performed after randomization and the patients didn't die.

Table 6-1 summarizes the details of the EFS derivation algorithm

Table 6-1. Censoring Rules for EFS

Situation		Event/Censored	Event/Censored Date
Achieved CR* within 6 cycles from the randomization date	Had relapse or death	Event (Relapse/death)	Relapse date or death date whichever comes first
	No relapse or death	Censored	Last assessment date
Within 6 cycles, had at least one post-baseline response assessment, but didn't achieve CR	Had progression, death or new anti-AML therapies within 6 cycles	Event (Treatment Failure)	Randomization Date
	No progression, death or new anti-AML therapies within 6 cycles, and have been on study beyond 6 cycles	Event (Treatment Failure)	Randomization Date
	No progression, death or new anti-AML therapies within 6 cycles, and haven't been on study beyond 6 cycles	Censored	Randomization Date
Within 6 cycles, had no post-baseline response assessment	Had death or new anti-AML therapies within 6 cycles	Event (Treatment Failure)	Randomization Date
	No death or new anti-AML therapies within 6 cycles	Censored	Randomization Date

* CRs achieved within 6 cycles of treatment and before SCT or new anti-AML therapies.

Duration of CR+CRh: The duration of CR + CRh is measured from the time the assessment criteria are first met for CR (including CR_{MRD-} and $CR_{MRD+/unk}$) or CRh within 6 cycles of treatment until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death while on study will be censored at the date of their last response assessment with no evidence of relapse on or prior to the data cutoff date. If patients start taking new anti-AML therapies (excluding post-SCT maintenance therapy) before relapse, duration of CR + CRh will be censored at the last response assessment before the initiation of the new anti-AML therapies.

Duration of CR: the DCR is measured from the time the assessment criteria are first met for CR (including CR_{MRD-} and $CR_{MRD+/unk}$) within 6 cycles of treatment until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death while on study will be censored at the date of their last response assessment with no evidence of relapse on or prior to the data cutoff date. If patients start taking new anti-AML therapies (excluding post-SCT maintenance therapy) before relapse, DCR will be censored at the last response assessment before the initiation of the new anti-AML therapies.

Rate of CR/CRh_{MRD-} Within 6 Cycles of Treatment: the CR/CRh_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} or CRh_{MRD-} within 6 cycles of treatment while on study prior to initiation of any new anti-AML therapy or SCT. The threshold for MRD negativity in this study is a frequency of less than 1×10^{-3} phenotypic leukemic cells per total white blood cell (WBC).

Rate of CR_{MRD-} Within 6 Cycles of Treatment: the CR_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} within 6 cycles of treatment, as determined by investigators based on the ELN 2017 for AML with modifications (Appendix 2), while on study prior to initiation of any new anti-AML therapy or SCT. The threshold for MRD negativity in this study is a frequency of less than 1×10^{-3} phenotypic leukemic cells per total WBCs.

Transfusion Independence Conversion Rate: The transfusion independence conversion rate includes both RBC transfusion independence rate and platelet transfusion independence rate.

RBC Transfusion Independence Conversion Rate: The RBC transfusion independence conversion rate is the proportion of patients who have a 56-day or longer period with no RBC nor whole blood transfusions at any time between the date of first dose of study treatment and discontinuation of study treatment among all patients who are RBC transfusion-dependent at the baseline. The RBC transfusion dependence at baseline is defined as having received an RBC or whole blood transfusion within the 28 days prior to the first dose of study treatment.

Platelet Transfusion Independence Conversion Rate: The platelet transfusion independence conversion rate is the proportion of patients who have a 56-day or longer period with no platelet transfusions at any time between the date of first dose of study treatment and discontinuation of study treatment among all patients who are platelet transfusion-dependent at baseline. Platelet transfusion dependence at baseline is defined as having received a platelet transfusion within the 28 days prior to the first dose of study treatment.

Time to First Deterioration on the EORTC QLQ-C30 GHS/QoL Scale: the TTD on the EORTC QLQ-C30 GHS/QoL scale is defined as time from the date of randomization to the time a patient experienced at least 1 threshold value deterioration from baseline or death, whichever is earlier. Patients whose score does not reach 1 threshold value deterioration from baseline and with no death will be censored at their last assessment date. Patients with no baseline values, or no post baseline values or the baseline value less than the threshold will be censored on randomization date. Patients with missing two or more consecutive visits will be censored at the last available assessment visit with non-missing value. In the analysis, 1 threshold value deterioration will be defined as the 10-point threshold from literature. {Osoba 1998}

Time to First Deterioration on the EORTC QLQ-C30 Physical Functioning Scale: the TTD on the EORTC QLQC30 physical functioning scale is defined as time from the date of randomization to the time a patient experienced at least 1 threshold value deterioration from baseline or death, whichever is earlier. Patients whose score does not reach 1 threshold value deterioration from baseline and with no death will be censored at their last assessment date. Patients with no baseline values, or no post baseline values or the baseline value less than the threshold will be censored on randomization date. Patients with missing two or more consecutive visits will be censored at the last available assessment visit with non-missing value. In the analysis, 1 threshold value deterioration will be defined as the 10-point threshold.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

Key secondary efficacy endpoints will be tested according to the order specified in Section 3.5, after the superiority for the primary efficacy endpoint is established.

6.2.2.1. Event-Free Survival

The distribution of EFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using the stratified log-rank test, stratified by the stratification factors at randomization for the ITT Analysis Set. Medians, Q1, Q3 of the EFS distributions, and the proportion of patients who are event-free at 6, 12 and 18 months from randomization will be estimated along with corresponding 95% CIs using the Kaplan-Meier method. Kaplan-Meier curves will be provided by treatment group. The hazard ratio between treatment arms will be estimated using the Cox proportional hazards regression model stratified by the stratification factors.

6.2.2.2. RBC and Platelet Transfusion Independence Conversion Rates

The point estimates of RBC and platelet transfusion independence conversion rates and the corresponding 2-sided exact 95% CIs based on Clopper-Pearson method will be provided by treatment arm respectively. Estimation will be based on a subset of all randomized patients who are RBC/platelet transfusion dependent at baseline. The transfusion independence conversion rate between treatment group will be compared using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors.

6.2.2.3. CR+CRh Rate, CR Rate, CR/CRh$_{MRD-}$ Rate, CR$_{MRD-}$ Rate within 6 Cycles and Durations of Response

The analysis of CR+CRh rate, CR rate, CR/CRh$_{MRD-}$ rate and CR$_{MRD-}$ rate within 6 cycles will compare each response rate of two treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors at randomization. Odds ratio comparing the 2 arms adjusted for the stratification factors will be presented along with 95% confidence interval (CI).

The point estimate of each response rate within 6 cycles and the corresponding 2-sided exact 95% CI based on the Clopper-Pearson method will be provided for each arm. Patients, who are randomized but have no on-study response assessment or receive any new anti-AML therapy or SCT prior to achieving the response, will be considered as non-responders.

For the time-to-event endpoints of DCR and duration of CR+CRh, analyses will be conducted based on the subsets on which the outcome measures are defined. Specifically, DCR will be based on patients who achieve CR, and duration of CR+CRh will be based on patients who achieve CR or CRh. Kaplan-Meier method will be used to estimate median duration with its 95% CI, and the Kaplan-Meier plots will be provided.

6.2.2.4. TTD on the EORTC QLQ-C30 GHS/QoL and Physical Functioning Scales

The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain) and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties). Patients rate items on a four-point scale, with 1 as "not at all" and 4 as "very much", except that the GHS/QoL have 7-point scale. A higher score for a functional scale (e.g., physical functioning) or the global health status/QOL scale represents a better level of functioning or health status, whereas a higher score for a symptom scale represents a worse level of symptomatology.

Raw scores of the GHS/QoL and physical functioning scales will be transformed to 0-100 before analysis according to the current EORTC QLQ-C30 Scoring Manual (3rd Edition). TTD on the GHS/QoL scale and TTD on the physical functioning scale will be respectively analyzed using the Kaplan-Meier method on the ITT Analysis Set. The log-rank test stratified by randomization stratification factors will be conducted for the TTD comparison between treatment arms, and the HR estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will be provided.

6.3. Estimands for Primary and Key Secondary Endpoints

Following the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials, a summary of the aforementioned primary and key secondary endpoints are presented in the estimand framework. Table 6-2 summarizes the attributes of estimands and estimators defined for main analyses and sensitivity analyses. The sensitivity analyses and supplementary analyses are not included in the hierarchical testing (Section 3.5).

For all the estimands of the primary objectives and secondary objectives listed in the tables except for RBC/platelet transfusion independence conversion, the target population attribute is all AML patients defined by the study inclusion and exclusion criteria. For RBC/platelet transfusion independence conversion rates, the target population attribute is the AML patients defined by the inclusion and exclusion criteria with transfusion dependence at baseline.

Table 6-2. Estimands and Estimators of Main Analyses and Sensitivity Analyses for the Primary and Key Secondary Efficacy Endpoints

Treatments	Variable (Endpoint)	Intercurrent Events & Strategies	Population Level Summary	Estimators
magrolimab + venetoclax + azacitidine (experimental arm) vs. placebo + venetoclax + azacitidine (control arm), and with SCT/new anti-AML therapy as needed	OS	• Discontinuation of treatment: treatment policy • SCT: treatment policy • New anti-AML therapy: treatment policy • Loss to follow-up: hypothetical	Difference in OS distribution between the experimental arm and the control arm, regardless of whether patients discontinue study treatment or receive SCT or initiate new anti-AML therapy	**Main Estimator:** Test the difference by a stratified logrank test; Estimate hazard ratio from a stratified Cox regression model. **Sensitivity Estimator:** Test the difference by a unstratified logrank test; Estimate hazard ratio from a unstratified Cox regression model. Test the difference by a stratified longrak test in PP analysis set; Estimate the hazard ratio from a stratified Cox regression model in PP analysis set.
magrolimab + venetoclax + azacitidine (experimental arm) vs. placebo + venetoclax + azacytidine (control arm)	CR+CRh rate/ CR rate/ CR/ CRh_{MRD-} rate/ CR_{MRD-} rate	• Discontinuation of treatment:treatment policy • SCT: while-on-treatment • New anti-AML therapy: while-on-treatment • Loss to follow-up: while-on-treatment	Difference in CR+CRh rate / CR rate / CR/CRh_{MRD-} rate / CR_{MRD-} rate between the experimental arm and the control arm within 6 cycles of treatment, regardless of whether patients discontinue study treatment, prior to initiation of SCT or new anti-AML therapy	**Main Estimator:** Test the difference in terms of odds ratio by a stratified Cochran-Mantel-Haenszel test; Estimate rate and CIs based on the Clopper-Pearson method.

Treatments	Variable (Endpoint)	Intercurrent Events & Strategies	Population Level Summary	Estimators
magrolimab + venetoclax + azacitidine vs. placebo + venetoclax + azacitidine, and with SCT as needed	EFS	• Discontinuation of treatment: treatment policy • Death, Treatment failure: composite • SCT: treatment policy (after initial CR) and while-on-treatment (before initial CR) • New anti-AML therapy: treatment policy (after initial CR) and while-on-treatment (before initial CR) • Missing >=2 consecutive response assessments: treatment policy • Loss to follow-up: hypothetical	Difference in EFS distribution between the experimental arm and the control arm, regardless of whether patients discontinue study treatment or receive SCT or initiate new anti-AML therapy	**Main Estimator:** Test the difference by a stratified logrank test; Estimate hazard ratio from a stratified Cox regression model.
magrolimab + venetoclax + azacitidine vs. placebo + venetoclax + azacitidine	RBC/platelet transfusion independence conversion rate	• Discontinuation of treatment: while-on-treatment • Dose reduction or temporary delay: treatment policy • Loss to follow-up: while-on-treatment	Difference in RBC/platelet transfusion independence conversion rate between the experimental arm and the control arm, while patients receive study treatment	**Main Estimator:** Test the difference in terms of odds ratio by a stratified Cochran-Mantel-Haenszel test; Estimate rate and CIs based on the Clopper-Pearson method.
magrolimab + venetoclax + azacitidine vs. placebo + venetoclax + azacitidine	TTD on GHS/QoL scale / TTD on physical functioning scale	• Discontinuation of treatment: treatment policy • Death: composite • Loss to follow-up: hypothetical	Difference in TTD distribution between the experimental arm and the control arm while on study treatment	**Main Estimator:** Test the difference by a stratified logrank test; Estimate hazard ratio from a stratified Cox regression model.

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6.5. Patient-Reported Outcome

6.5.1. Definition of Patient-Reported Outcome Data

Four patient-reported outcome (PRO) instruments will be administered in this study: the EORTC QLQ-C30, the EQ-5D-5L, the PGIS, and the PGIC.

The EORTC QLQ-C30 measure is described in Section 6.2.2.4.

The EQ-5D-5L is an instrument for use as a measure of health outcome and consists of 2 sections: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The questionnaire is provided in the protocol Appendix 10.

The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical VAS, where the endpoints are labeled "the best health you can imagine" and "the worst health you can imagine." The EQ VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

The PGIS and PGIC assessments are both single-item assessments used to demonstrate sensitivity and meaningful change thresholds and bolster the validity of selected PRO assessments for health-related quality of life and the physical function. The questionnaires are provided in the protocol Appendix 11.

6.5.2. Analysis of Patient-Reported Outcome Data

For TTD on the EORTC QLQ-C30 GHS/QoL and Physical Functioning Scales, the analysis method is described in Section 6.2.2.4.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using MedDRA v26.0. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" for a drug on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and reported as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE that begins on or after the date of first dose of study treatment up to the date of last dose of study treatment plus 70 days or the day before initiation of new anti-AML therapy including SCT, whichever comes first. If the AE onset date is on or before the last dose date, the AE is considered as TEAE regardless of the start of new anti-AML therapy.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and

The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff date of TEAE period, which is defined as the date of the last dose of study treatment plus 70 days or the day before initiation of new anti-AML therapy including SCT, whichever comes first.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

If the day is missing but the month and year are available, then the imputed day will be the first dosing date if they have the same month and year, or the first day of the month otherwise.

If the day and month are missing but year is available, then the imputed day and month will be the first dosing date if they have the same year, or 01Jan otherwise.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number of percentage of patients who experienced at least 1 TEAE in the categories will be provided by treatment group. All deaths observed in the study will also be included in this summary.

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs
- TEAEs with Grade 3 or higher
- TE treatment-related AEs for Magrolimab/Placebo
- TE SAEs
- TE treatment-related SAEs for each study drug
- TEAEs leading to discontinuation of each study drug
- TEAEs leading to dose reduction of each study drug
- TEAEs leading to drug interruption of each study drug
- TEAEs leading to death

The number and percentage of patients who experienced at least 1 TEAE will be provided and summarized by PT, severity and treatment group:

- TE treatment-related AEs for each study drug

The number and percentage of patients who experienced at least 1 TEAE will be provided and summarized by SOC, PT, maximum severity, and treatment group for the following categories:

- TEAEs with Grade 3 or higher

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, all TEAEs, TEAEs of Grade 3 or higher, TE SAEs and TE treatment-related AEs and TE treatment-related SAEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths

A summary (number and percentage of patients) of deaths will be provided by treatment group. Summary will include the following categories:

- All deaths
- Deaths within 30 days of the first dosing of study drug
- Deaths within 60 days of the first dosing of study drug
- Deaths within 30 days of the last dosing of study drug
- Deaths within 70 days of the last dosing of study drug
- Deaths beyond 30 days of the last dosing of study drug
- Deaths beyond 70 days of the last dosing of study drug

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Treatment-Emergent Adverse Events (TEAE) of Special Interest

Number and percentage of subjects with the following AEs of special interest will be summarized by PT:

- Anaemia (MedDRA Search Term (MST) - Anemia Extravascular Transient Hemolysis)
- Infusion Related Reaction (IRR) (Standardised MedDRA Queries (SMQ) - Hypersensitivity Narrow Terms) + within one day of latest infusion of any study drug
- Severe Neutropenia (PT - Neutrophil Count Decreased, Neutropenia and Febrile Neutropenia with Grade 3 or Higher)
- Serious Infections (SOC - Infections and infestations with Serious AE)
- Transfusion reactions due to magrolimab interference with RBC typing (Gilead's MST)
- Thromboembolic Events (SMQ - Embolic and Thrombotic Events Broad Terms)
- Pneumonitis (SMQ - Interstitial Lung Disease Broad Terms)

7.1.7.2. Other Important Safety Topics

Number and percentage of subjects with the following AEs of important safety topics will be summarized by PT:

- Immune-Mediated Events (SMQ - Immune-mediate and autoimmune disorder Narrow Terms)
- Hemorrhages (SMQ - Haemorrhages Broad Terms)

7.1.7.3. Regrouped AE Terms

For the regrouped AE terms described below, summaries will be provided by treatment group:

- Regrouped Anaemia and Haemoglobin Decreased
- Regrouped Neutropenia and Neutrophil Count Decreased
- Regrouped Thrombocytopenia and Platelet Count Decreased

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 70 days or the day before initiation of new anti-AML therapy including SCT, whichever comes first. If the laboratory data collection date is on or before the last dose date, the laboratory data is included regardless of the start of new anti-AML therapy. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by treatment group, subject ID and visit in chronological order for hematology, serum chemistry, and coagulation separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Postbaseline maximum value

- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of any study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values will be plotted using a line plot by treatment group and visit for the laboratory tests including but not limited to hemoglobin, platelet and absolute neutrophil counts.

In the case of multiple values associated with a visit, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 70 days or the day before initiation of new anti-AML therapy including SCT, whichever comes first, will be summarized by treatment group. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of patients in the study with the given response at baseline and each scheduled postbaseline time point.

The following summaries (number and percentage of patients) for treatment-emergent laboratory abnormalities will be provided by laboratory test and treatment group; patients will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Graded TE laboratory abnormalities

- TE Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of patients with nonmissing postbaseline values up to 70 days after the last dosing date or the day before initiation of new anti-AML therapy including SCT, whichever comes first.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the laboratory test of interest, with all applicable severity grades displayed.

7.2.3. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to the worst grade postbaseline for hematology, chemistry, and coagulation laboratory tests.

7.3. Body Weight and Vital Signs

No summary or listing of body weight and vital signs will be provided.

7.4. Electrocardiogram Results

No summary or listing of electrocardiogram results will be provided.

7.5. Other Safety Measures

A by-subject listing of pregnancy test report will be provided by subject ID number in ascending order.

7.6. Changes from Protocol-Specified Safety Analyses

The following changes are made from the protocol specified safety analyses:

In TEAE and TE laboratory abnormality definitions, new anticancer therapy is replaced by new anti-AML therapy to select qualified AE and laboratory data to summarize.

8. PHARMACOKINETIC (PK) AND IMMUNOGENECITY ANALYSES

8.1. PK Sample Collection

Blood samples for evaluating magrolimab serum concentrations will be collected as described in Protocol Appendix 3.

8.2. PK Analyses

The magrolimab PK concentration will be summarized for the PK Analysis Set. Individual subject's concentration data for magrolimab will be listed based on the sampling time point. Magrolimab PK data will be summarized per nominal time point using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for magrolimab serum concentration data at time point.

The sample size (number of patients) at each time point will be based on the number of patients with nonmissing concentration data at that time point. Missing concentration values will be reported as is in data listings. The number of patients with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0.

Sparse PK concentration values that are BLQ will be presented as "BLQ" in the concentration data listing.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the patients have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for postdose time points:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the patients have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the patients have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the patients have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all patients have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Due to the sparse nature of PK collection, PK parameters will not be calculated.

8.3. Immunogenicity Analysis

The rate and magnitude of magrolimab anti-drug antibody (ADA) prevalence, incidence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Neutralizing antibody occurrence rate will also be summarized.

ADA Prevalence: the proportion of subjects who had at least one positive ADA sample (baseline or post-baseline) based on the Immunogenicity Analysis Set.

Treatment-Induced ADA Rate: the proportion of subjects who had negative baseline ADA sample and at least one positive post-treatment ADA sample based on subjects who had both non-missing baseline and at least one post-treatment ADA result reported (i.e. ADA Incidence Analysis Set).

Treatment-Boosted ADA Rate: the proportion of subjects who had positive baseline ADA sample and at least one positive post-treatment ADA sample and the (max titer of the post-treatment ADA) / (titer of baseline ADA) >= 4 based on the ADA Incidence Analysis Set.

ADA Incidence (treatment-emergent ADA): the proportion of subjects who had treatment-induced or treatment-boosted ADA based on subjects who had non-missing baseline ADA sample and at least one post-treatment ADA result reported in Immunogenicity Analysis Set.

Persistent ADA is defined as:

a) Treatment-Induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive sample (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer.

or

b) Treatment-Induced ADA detected in the last sampling time point of the treatment study period.

ADA Persistence Rate: the proportion of subjects who had persistent ADA based on the ADA Incidence Analysis Set.

Transient ADA is defined as:

Treatment-Induced ADA that does not meet the definition of persistent ADA. The proportion of subjects who had transient ADA is based on the subjects evaluable for ADA incidence.

Neutralizing antibody (NAb) Incidence: the proportion of subjects who had at least one positive neutralizing antibody result reported based on the treatment-emergent ADA (treatment-induced or treatment-boosted ADA) among the subjects evaluable for ADA incidence.

Titer summaries may also be generated, if relevant. CCI [redacted]

9. PHARMACODYNAMIC ANALYSES

CCI [redacted] Additional details will be provided by the biomarker sciences group.

10. REFERENCES

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21 (24):4642-9.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129 (4):424-47.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139-144

11. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Schedule of Assessments

Appendix Table 1. Schedule of Assessments – Screening[a]

Assessment	Screening -30 to -1
Informed consent[a]	X
Demographics	X
Medical and cancer history, including date of most recent RBC and/or platelet transfusion(s)	X
Physical examination	X
Vital signs, height, and weight[b]	X
Pregnancy test[g]	X
CBC with differential, platelets, reticulocytes, blasts	X
Serum or plasma chemistry	X
PT, INR, and aPTT (or PTT)	X
Blood phenotyping or genotyping, type, and screen (ABO/Rh), DAT	X
Urinalysis	X
ECOG performance status	X
12 Lead ECG (single)	X
Adverse Events[c]	X
Concomitant medications[d]	X
Eligibility criteria	X
Randomization[a]	X
Peripheral blood smear (for blasts)[e]	X
Bone marrow aspirate for biomarker studies[f]	X
Bone marrow biopsy for biomarker studies[f]	X
Bone marrow aspirate for response assessment, cytogenetics, and MRD assessment[f]	X
Bone marrow aspirate ± biopsy slides or blocks for independent central review[f]	X

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MRD = minimal residual disease; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; Rh = Rhesus factor; SAE = serious adverse event; WBC = white blood cell

a Screening must be completed prior to randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 72 hours after Randomization.

b Vital signs will be assessed prior to administration of any study treatment. Height will be collected at screening only. Weight will be collected at screening and Day 1 of each cycle.

c All SAEs and any AEs related to protocol-mandated procedures should be collected at screening. Adverse events should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

d Prior and concomitant medications should be collected at screening. Concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

e Peripheral blood smear for blasts are to be collected along with bone marrow aspirate/biopsy.

f A trephine (biopsy) is to be collected if the aspirate sample is dry (not obtainable). If a bone marrow aspirate sample is un-evaluable, another aspirate sample must be performed within 7 days. At screening, this procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for response assessment (eg, blast evaluation), cytogenetics, MRD assessment, biomarker studies, and biobanking. When done on the same day, bone marrow aspirate samples are to be obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics are to be tested per institutional standards.

g A serum pregnancy test will be conducted at screening and urine pregnancy tests will be conducted from Cycle 1 Day 1 onward. A follicle-stimulating hormone test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration.

Appendix Table 2. Schedule of Assessments - Treatment Period for magrolimab + venetoclax + azacitidine and placebo + venetoclax + azacitidine Regimens

	Cycle (28-day Cycles)																			
	1[a]										2						3+			
Visit Window (Days)[b]	None		± 3								± 3						± 3			
Cycle Day	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[c]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[c]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[c]
Informed consent[d]																				
Demographics																				
Medical and cancer history, including date of most recent RBC and/or platelet transfusion(s)																				
Physical examination[e,f]	X				X		X				X						X			
Vital signs, height, and weight[f,g]	X	X	X	X	X	X	X	X			X	X	X	X			X			
Pregnancy test[f,h]	X										X						X			
CBC with differential, platelets, reticulocytes, blasts[f,i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[f]	X				X						X									
Serum or plasma chemistry[f]	X[j]	X[j]	X[j]	X[j]	X		X	X			X		X				X			
PT, INR, and aPTT (or PTT)																				

	Cycle (28-day Cycles)																			
	1[a]										2						3+			
Visit Window (Days)[b]	**None**		± 3								± 3						± 3			
Cycle Day	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**
Peripheral blood smear for general morphology[e,k]	X	X				X														
Blood phenotyping or genotyping, type, and screen (ABO/Rh), DAT																				
Urinalysis																				
ECOG performance status																				
12 Lead ECG (single)																				
Adverse events[l]																				
Concomitant medications[m]																				
Eligibility criteria																				
Randomization[c]																				
Efficacy/Biomarkers																				
PRO assessment[n]	X										X						X			
Peripheral blood smear (for blasts)[o]									X						X				C4D28, C6D28, then Q3C	

	Cycle (28-day Cycles)																			
	1[a]										2						3+			
Visit Window (Days)[b]	**None**		± 3								± 3						± 3			
Cycle Day	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**
Peripheral blood sample for biomarker studies[p]	X				X[q]				X		X[r]				X		X[r]		C3D28, C6D28	
Bone marrow aspirate for biomarker studies[s]									X						X				C4D28, C12D28	
Bone marrow biopsy for biomarker studies[s]									X										C12D28	
Bone marrow aspirate for response assessment, cytogenetics, and MRD assessment[s,t]									X						X				C4D28, C6D28, then Q3C	
Bone marrow aspirate ± biopsy slides or blocks for independent central review[s]									X						X				C4D28, C6D28, then Q3C	
Buccal swab[u]	X																			
PK/Immunogenicity																				
PK[v]	X				X						X						C3D1, C5D1, C7D1, C10D1, C13D1, and EOT			

	Cycle (28-day Cycles)																			
	1[a]										2						3+			
Visit Window (Days)[b]	**None**		± 3								± 3						± 3			
Cycle Day	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**	**1**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[c]**
Antidrug antibodies[v,w]	X										X						C3D1, C5D1, C7D1, C10D1, C13D1, and EOT			

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT= end of treatment; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PK = pharmacokinetic(s); PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; Q3C = every 3 cycles; RBC = red blood cell; Rh = Rhesus factor; RO = receptor occupancy; SAE = serious adverse event; WBC = white blood cell

a In cases of magrolimab/placebo repriming/re-escalation following a treatment delay (Protocol Section 5.5.2), follow the safety assessment schedule for Cycle 1, and then the assigned cycles. Efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number.

b Any other visit window specifications for individual assessments should be applied.

c If the patient is cytopenic at Day 28, CBC is to be monitored at least twice per week for 2 weeks or until optimal count recovery is reached (whichever comes first) The best CBC result within the ± 2-week window is to be used for the response assessment, with the date of response being the date of the bone marrow assessment. Complete blood count need not be repeated if the prior CBD (including prior Day 28 CBC) iis within 3 days of Day 1.

d Screening must be completed prior to randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 72 hours after randomization.

e Complete physical examination is to be performed at screening and symptom-directed physical examination is to be performed from Cycle 1 Day 1.

f Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to any study treatment administration.

g Vital signs will be assessed prior to administration of any study treatment. Details are provided in Protocol Section 6.6.4. Height will be collected at screening only. Weight will be collected at screening and Day 1 of each cycle.

h A serum pregnancy test will be conducted at screening and urine pregnancy tests will be conducted from Cycle 1 Day 1 onward. A follicle-stimulating hormone test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Additional guidance is provided in Protocol Section 6.6.1.

i Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ $20 \times 10^3/\mu L$ prior to each magrolimab/placebo dose during Cycle 1.

j To monitor the risk of tumor lysis syndrome during venetoclax ramp-up, blood chemistry is to be collected predose and 6 to 8 hours postdose of venetoclax administration on Cycle 1 Day 1, Cycle 1 Day 2, and Cycle 1 Day 3. Blood chemistry on Cycle 1 Day 4 is to be collected 24 hours after the dose of venetoclax given on Cycle 1 Day 3.

k Peripheral blood smears will be collected predose and assessed locally.

l All SAEs and any AEs related to protocol-mandated procedures should be collected at screening. Adverse events should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

m Prior and concomitant medications should be collected at screening. Concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

n Four PRO instruments will be administered in this study: the EORTC QLQ-C30 questionnaire, the EQ-5D-5L, the PGIS, and the PGIC. The patient should complete these questionnaires before any other study procedures at required visits. EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC. PGIC is not required at Cycle 1 Day 1.

o Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy.

p Samples will be collected predose within 12 hours prior to study treatment administration.

q Blood samples at Cycle 1 Day 8 to be collected both predose and 1 hour postdose.

r Starting at Cycle 2 Day 1, peripheral blood samples for biomarker studies on Cycle X Day 1 do not need to be repeated at Day 1 of the cycle if they have been collected within the past 7 days.

s A trephine (biopsy) is to be collected if the aspirate sample is dry (not obtainable). If a bone marrow aspirate sample is not evaluable, another aspirate sample must be performed within 7 days. At screening, this procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for response assessment (eg, blast evaluation), cytogenetics, MRD assessment, biomarker studies, and biobanking. When done on the same day, bone marrow aspirate samples are to be obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics are to be tested per institutional standards.

t Response assessments may be adjusted by ± 1 week for Day 28 of Cycles 1 and 2. After Cycle 2 Day 28, the window is ± 14 days. Bone marrow response information from Day 28 may be required to decide start of the next cycle per dosing modification guidelines in the protocol.

u Single sample will be collected on Day 1 or at any time during the study.

v Predose PK samples will be collected on the day of magrolimab/placebo dosing, prior to the dosing of azacitidine and magrolimab/placebo. On Cycle 3 Day 1, an additional sample for postdose PK sample will be collected at 1 hour (± 15 minutes) after the end of infusion of magrolimab/placebo.

w When collected on the day of study treatment dosing, the blood sample for ADA must be collected at the same time as the predose PK sample.

Appendix Table 3. Schedule of Assessments – Post Treatment

	End-of-Treatment Visit	Safety Follow-up Visit/Telephone Call[a]	Safety Follow-up Visit/Telephone Call[a]	Long-term Follow-up	Long-term Follow-up after SCT	Survival Follow-up
	Within 7 Days after Last Dose or EOT Decision, whichever occurs later	30 Days after Last Dose	70 Days after Last Dose	Until Disease Progression[b] or Start of a New Anti-AML Therapy	Until Disease Progression[b] or Start of a New Anti-AML Therapy	Every 2 Months (up to 5 years from EOT visit) Until Death or End of Study, whichever occurs first
Visit Window	± 7 Days	± 7 Days	± 7 Days	± 14 days	± 14 days	—
Symptom-directed physical examination	X					
Vital signs	X					
Urine pregnancy test[c]	Q4W	→	→	→	→	→
CBC with differential, platelets, reticulocytes, blasts	X			Q12W	Q12W	
Serum or plasma chemistry	X					
ECOG performance status	X					
Adverse events[d]	X	X	X			
Concomitant medications	X	X	X			
New anti-AML therapy reporting[e]	X	X	X	X	X	X
PRO assessment[f]	X					
Peripheral blood smear (for blasts)	X			Q12W	Q12W	
Peripheral blood sample for biomarker studies	X					
Bone marrow aspirate for biomarker studies	X					

	End-of-Treatment Visit	Safety Follow-up Visit/Telephone Call[a]	Safety Follow-up Visit/Telephone Call[a]	Long-term Follow-up	Long-term Follow-up after SCT	Survival Follow-up
	Within 7 Days after Last Dose or EOT Decision, whichever occurs later	30 Days after Last Dose	70 Days after Last Dose	Until Disease Progression[b] or Start of a New Anti-AML Therapy	Until Disease Progression[b] or Start of a New Anti-AML Therapy	Every 2 Months (up to 5 years from EOT visit) Until Death or End of Study, whichever occurs first
Visit Window	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 14 days**	**± 14 days**	**—**
Bone marrow aspirate for response assessment, and cytogenetics[g,h]	X			Q12W	Q12W	
Pharmacokinetics	X					
Antidrug antibodies	X					
Survival follow-up						X

AE = adverse event; CBC = complete blood count; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PGIS/PGIC = Patient Global Impression of Severity/Patient Global Impression of Change; Q4W = every 4 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SCT = stem cell transplantation

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site.
b Disease progression includes relapse after CR/CRi/CRh or disease progression after partial remission, stable disease, or MLFS.
c Pregnancy testing will be continued monthly up to 3 months after the end of treatment per the duration of contraception requirement as discussed in Protocol Appendix 5. Testing during survival follow-up may be done at home and the result self-reported by the patient.
d Report all AEs through the Safety Follow-up Visit/Call, and any treatment-related SAEs thereafter.
e Collect data for the first new anti-AML therapy following the last dose of study treatment or following SCT.
f EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC.
g Response assessment at EOT visit not required if performed within the last 30 days or documented disease progression/relapse or start of new anti-AML therapy, whichever occurs first. (SCT and maintenance therapy are not considered new anti-AML therapy.)
h Conventional cytogenetic testing (per institutional standards) is required for all patients.

Appendix 2. Disease Response Criteria Based on European LeukemiaNet (ELN) and International Working Group (IWG) Criteria

Assessment of leukemia response in AML patients will be conducted using the European LeukemiaNet (ELN) 2017 recommendations for AML with modifications {Dohner 2017} (Appendix Table 4). Response classifications include complete remission without minimal residual disease (CR_{MRD-}), complete remission with positive or unknown minimal residual disease ($CR_{MRD+/unk}$), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), and stable disease (SD).

In addition, CR with partial hematologic recovery (CRh) will be assessed for AML, as defined as patients who achieve a CR per AML ELN 2017 recommendations {Dohner 2017}, but with only partial recovery of peripheral blood counts (platelets > 50×10^9/L and absolute neutrophil count (ANC) > 0.5×10^9/L).

Cytogenetic CR (cCR) will be assessed by 2003 IWG criteria as CR with normal cytogenetics (Appendix Table 5) {Cheson 2003}.

Hematologic improvement will be assessed by 2006 IWG criteria {Cheson 2006} to compare with disease response assessed by 2017 ELN criteria (Appendix Table 6) {Dohner 2017}.

The date of the bone marrow assessment should be used as the date of response assessment. Complete blood count results used for the response assessment will be derived from the best accompanying laboratory CBC result within the ± 2-week window of the bone marrow assessment used to support the efficacy response assessment. All components (eg, platelets, absolute neutrophils) should come from the same test. If PD or relapse is assessed based on CBC assessments or new extramedullary disease, other than bone marrow blast assessments, then the date of the corresponding CBC or new extramedullary disease assessment date will be used as the date of response assessment

Appendix Table 4. Response Criteria in Acute Myeloid Leukemia (ELN 2017 Recommendations with Modifications)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Complete Remission Without Minimal Residual Disease (CR_{MRD-})	> 1.0×10^9/L	> 100×10^9/L	< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease. CR with MRD negative status as determined using multiparameter flow cytometry with a sensitivity of < 0.1%.
Complete Remission with MRD Positive /MRD Unknown ($CR_{MRD+/unk}$)	> 1.0×10^9/L	> 100×10^9/L	< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; MRD positive or unknown.
Complete Remission with Incomplete Hematologic Recovery (CRi)	Neutrophils > 1.0×10^9/L OR Platelets > 100×10^9/L		< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; MRD positive or unknown. (All CR criteria except residual neutropenia [< 1.0×10^9/L] or thrombocytopenia [< 100×10^9/L]).
Complete Remission with Partial Hematologic Recovery (CRh)[a]	> 0.5×10^9/L	> 50×10^9/L	< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
Morphologic Leukemia-Free State (MLFS)			< 5%	Absence of circulating blasts and 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)	> 1.0×10^9/L	> 100×10^9/L	Decrease of bone marrow blast percentage to 5% to 25% and decrease of pretreatment bone marrow blast percentage by at least 50%.	Blasts < 5% with Auer rods may also be considered a PR.

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Stable Disease (SD)	Absence of CR_{MRD-}, $CR_{MRD+/unk}$, CRi, CRh, PR, MLFS; and criteria for progressive disease not met			
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 > 0.5×10^9/L [500/µL], and/or platelet count to > 50×10^9/L [50,000/µL] nontransfused); or > 50% increase in peripheral blasts (WBC × % blasts) to > 25×10^9/L (> 25,000/µL) (in the absence of differentiation syndrome); or New extramedullary disease.			
Hematologic relapse (after CR_{MRD-}, $CR_{MRD+/unk}$, CRi, CRh)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease			

AML = acute myeloid leukemia; ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CR_{MRD-} = complete remission without minimal residual disease; $CR_{MRD+/unk}$ = complete remission with MRD Positive/MRD Unknown; ELN = European LeukemiaNet; MLFS = morphologic leukemia-free state MRD = minimal residual disease; PD = progressive disease; PR = partial remission; SD = stable disease; WBC = white blood cell count

a Not in the ELN 2017 guidelines. Modification for the purpose of this protocol. A response could be classified as both CRh and CRi if both criteria are met.

Source: {Dohner 2017}

Appendix Table 5. Additional Response Definitions Used in This Study (2003 IWG Criteria)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Cytogenetic CR (cCR)	> 1.0×10^9/L	> 100×10^9/L	< 5%	Cytogenetics normal and no evidence of extramedullary disease
Treatment Failure[a]	Failure to achieve CR within 6 cycles of treatment			

cCR = cytogenetic complete remission; CR = complete remission; IWG = International Working Group

a Treatment failure defined for this protocol.

Source: {Cheson 2003}

Appendix Table 6. Response Criteria for Hematologic Improvement

Hematologic Improvement (HI) Category[a]	Response Criteria
Erythroid Response (HI-E) (pretreatment < 110 g/L)	Pretransfusion increase in hemoglobin by 15 g/L or Compared to an 8-week pretreatment period, a reduction in transfusion requirements by 4 units in an 8-week posttreatment period
Platelet Response (HI-P) (pretreatment < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patient starting with a platelet count > 20×10^9/L pretreatment or Increase from < 20×10^9/L pretreatment to > 20×10^9/L post-treatment and by at least 100%
Neutrophil Response (HI-N) (pretreatment < 1.0×10^9/L)	At least 100% increase and an absolute increase of > 0.5×10^9/L
Progression/relapse after Hematological Improvement[b]	One or more of the following ≥ 50% decrement from maximum response in neutrophils or platelets Reduction in hemoglobin by ≥ 15 g/L Transfusion dependence

a Pretreatment counts should be an average of at least 2 measurements (not influenced by transfusions) performed ≥ 1 week apart.
b In the absence of another explanation. For example, including, but not restricted to, acute infection, gastrointestinal bleeding and hemolysis.
Source: {Cheson 2006}

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	10-May-2024 15:30:08
PPD	Global Development Lead (GDL) eSigned	10-May-2024 15:57:04