STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients with Myeloid Malignancies
Name of Test Drug:	Magrolimab
Study Number:	GS-US-546-5920
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ADA	anti-drug antibody
AE	adverse event
AEI	adverse events of interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
BICR	blinded independent central review
BLQ	below the limit of quantitation
BMI	body mass index
CBC	complete blood count
CC-486	Onureg
cCR	cytogenetic complete remission
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
COVID-19	Coronavirus disease 2019
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 positive or unknown minimal residual disease
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
FAS	Full Analysis Set
Hb	hemoglobin
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IV	intravenous
ITT	intent to treat

LTT	lower-level term
LOQ	limit of quantitation
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEC	mitoxantrone, etoposide, and cytarabine
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MST	MedDRA Search Term
ORR	overall response rate
OS	overall survival
PK	pharmacokinetic
PR	partial remission
PRO	Patient reported outcome
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RDI	relative dose intensity
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SCT	stem cell transplantation
SI (units)	international system of units
SMQ	Standardised MedDRA Queries
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
TF	treatment failure
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where “Dose” is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and defines key elements including variable definitions for analysis of data of Study GS-US-546-5920 in support of the clinical study report (CSR). This SAP is based on the study protocol amendment 6 dated 02 November 2023. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives and Endpoints

Objectives and endpoints are presented by cohort in Sections 1.1.1, 1.1.2, and 1.1.3.

1.1.1. Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza)

Primary, secondary, CCI [redacted] objectives and endpoints for patients with newly diagnosed, previously untreated acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy are as follows:

Primary Objective(s)	Primary Endpoint(s)
Efficacy	
• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine as determined by the complete remission (CR) rate (Phase 2 Cohort 1)	• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 1)
Safety	
• To evaluate the safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine (Safety Run-in Cohort 1)	• Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (AEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Safety Run-in Cohort 1)

Secondary Objective(s)	Secondary Endpoint(s)
Efficacy/Safety/PK delineate objectives and endpoints as appropriate.	
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine (Phase 2 Cohort 1) • To evaluate the pharmacokinetics (PK) of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine	• Overall response rate (ORR), including CR, complete remission with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), partial remission (PR), and morphologic leukemia-free state (MLFS) • CR/CRi rate • Complete remission without minimal residual disease (CR_{MRD-}) rate • Complete remission or complete remission with partial hematologic recovery (CR/CRh) rate • Cytogenetic complete remission (cCR) • Duration of responses (DOR) • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • Event-free survival (EFS) • Overall survival (OS) • Red blood cell (RBC) transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 1) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies
CCI [redacted]	[redacted]
[redacted]	[redacted]

1.1.2. Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)

Primary, secondary, CCI [redacted] objectives and endpoints for patients with relapsed or refractory (R/R) AML are as follows:

Primary Objective(s)	Primary Endpoint(s)
Efficacy	
• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy mitoxantrone, etoposide, and cytarabine (MEC) as determined by the CR rate (Phase 2 Cohort 2)	• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 2)
Safety	
• To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy MEC (Safety Run-in Cohort 2)	• Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 2)
Secondary Objective(s)	**Secondary Endpoint(s)**
Efficacy/Safety/PK delineate objectives and endpoints as appropriate.	
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy MEC • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy MEC (Phase 2 Cohort 2) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy MEC • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy MEC	• ORR, including CR, CRi, CRh, PR, and MLFS • CR/CRi rate • CR_{MRD-} rate • CR/CRh rate • cCR • DOR • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • EFS • OS • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 2) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

1.1.3. Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-Chemo Maint Mag+CC-486 [Onureg])

Primary, secondary, CCI objectives and endpoints for patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy are as follows:

Primary Objective(s)	Primary Endpoint(s)
Efficacy	
• To evaluate the efficacy of magrolimab in combination with anti-leukemia therapy CC-486 (Onureg) as determined by the MRD negative CR rate (Phase 2 Cohort 3)	• MRD negative CR rate, defined as the proportion of patients who maintain CR as determined by the investigator based on prespecified criteria and reach MRD negative disease status as determined using multiparameter flow cytometry with a sensitivity of < 0.1% (Phase 2 Cohort 3)
Safety	
• To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy CC-486 (Safety Run-in Cohort 3)	• Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 3)

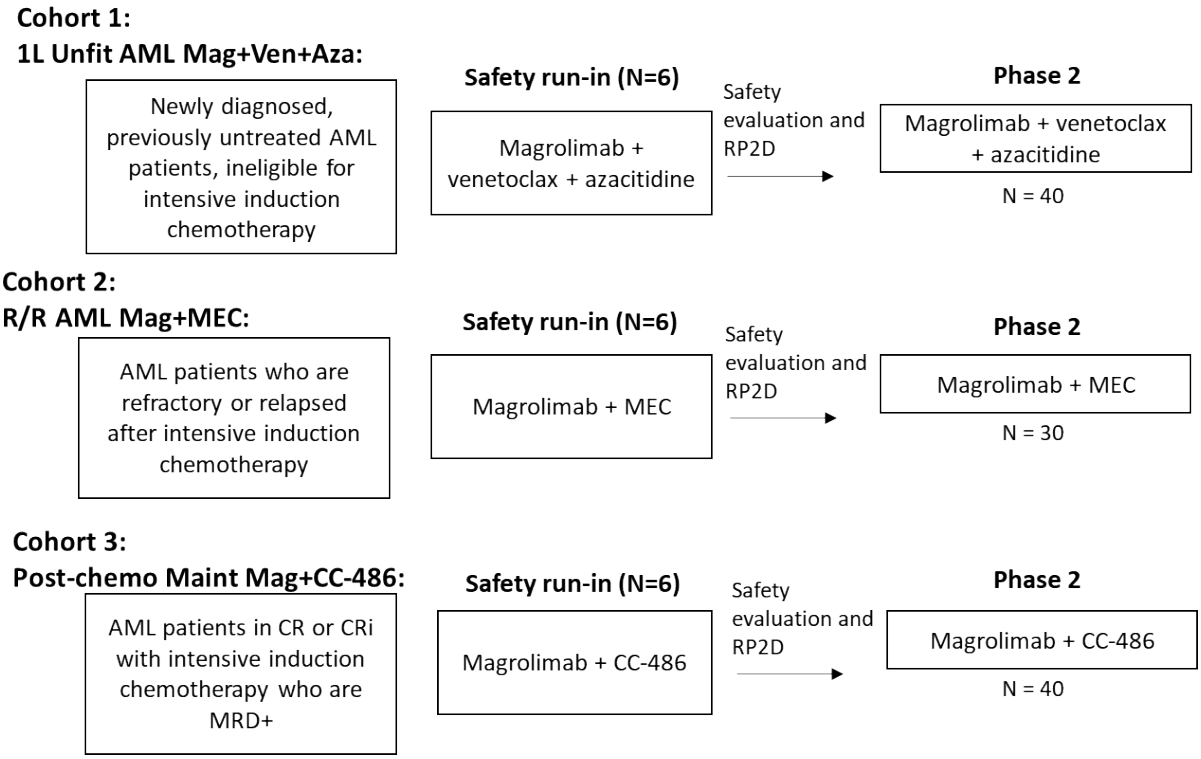
Secondary Objective(s)	Secondary Endpoint(s)
Efficacy/Safety/PK delineate objectives and endpoints as appropriate.	
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy CC-486 (Phase 2 Cohort 3) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy CC-486	• MRD negative CR/CRi rate • Relapse-free survival (RFS) • OS • Duration of MRD negative CR • Duration of MRD negative CR/CRi • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 3) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies
CCI [redacted]	[redacted]
[redacted]	[redacted]

1.2. Study Design

This is a Phase 2, open-label, multicenter, multi-arm study to evaluate magrolimab in combination with anti-leukemia therapies in patients with AML. This trial includes safety run-in cohorts and Phase 2 cohorts.

The study schematic is presented in Figure 1.

Figure 1. Study Schema



AML = acute myeloid leukemia; MEC = mitoxantrone, etoposide, and cytarabine; MRD = minimal residual disease; RP2D = recommended Phase 2 dose

Up to approximately 164 patients will be enrolled in the study, with up to 54 patients in the safety run-in cohorts and approximately 110 patients in the Phase 2 cohorts.

Initially, 6 patients will be enrolled into Safety Run-in Cohorts 1, 2, and 3, respectively. A DLT assessment period of 1 cycle (28 days) will occur.

Dose de-escalation decisions will be made as follows:

- If no more than 2 patients in a safety run-in cohort experience a DLT in Cycle 1, enrollment into the corresponding Phase 2 cohort will begin at this dose level.

- If 3 or more (> 33%) patients in a safety run-in cohort experience a DLT up to the end of Cycle 1, another 6 patients will be enrolled in that cohort at a lower dose and evaluated in the same manner to define the RP2D.

After completion of each safety run-in cohort and identification of the RP2D for that cohort, the corresponding Phase 2 cohort may be enrolled, with 40 patients in Phase 2 Cohorts 1 and 3 each and 30 patients in Cohort 2.

Study treatment regimens comprise the following:

Safety Run-in Cohort 1 and Phase 2 Cohort 1

- Magrolimab 1 mg/kg intravenous (IV)
- Magrolimab 15 mg/kg IV
- Magrolimab 30 mg/kg IV
- Azacitidine 75 mg/m^2 subcutaneous or IV
- Venetoclax 100 mg oral tablets
- Venetoclax 200 mg oral tablets
- Venetoclax 400 mg oral tablets

Safety Run-in Cohort 2 and Phase 2 Cohort 2

- Magrolimab 1 mg/kg IV
- Magrolimab 15 mg/kg IV
- Magrolimab 30 mg/kg IV
- Mitoxantrone 8 mg/m^2 IV
- Etoposide 100 mg/m^2 IV
- Cytarabine 1000 mg/m^2 IV

Safety Run-in Cohort 3 and Phase 2 Cohort 3

- Magrolimab 1 mg/kg IV
- Magrolimab 15 mg/kg IV
- Magrolimab 30 mg/kg IV
- CC-486 300 mg oral tablets

Details about study treatments for each safety run-in cohort, dose de-escalation plans for each safety run-in cohort, and schedules of treatment administration are presented in the study protocol section 3.2.

Duration of treatment will be as follows:

- Cohorts 1 and 3: treatment until discontinuation criteria is met.
- Cohort 2: treatment for up to 12 months.

Clinical response will be assessed by the investigator using prespecified criteria (Appendix 2, also protocol Appendix 7).

Response assessments will be done in conjunction with bone marrow assessments, according to the schedule of assessments (protocol Appendix Table 2 and Appendix Table 3). Bone marrow assessments (including aspirate and core/trephine biopsy) are required for response assessments and may be used for blast evaluation, MRD assessment, cytogenetics, RO (to be collected at selected study sites), and correlative studies. Peripheral blood smears for blasts should be done on the day of the bone marrow assessments.

If the patient is cytopenic at the time of the bone marrow assessment, complete blood count (CBC) is to be monitored at least once per week until optimal count recovery is reached. The best accompanying laboratory CBC result within the ± 2-week window is to be used to support an efficacy response assessment, with the date of response assigned as the date of bone marrow assessment. If a patient achieves a CR, subsequent bone marrow biopsies are still required to be performed in accordance with the schedule of assessments.

Bone marrow aspirate and biopsy slides or blocks for efficacy assessments will be prepared for potential evaluation of response assessments by independent central review.

Response assessment will be obtained at the EOT visit, unless a prior response assessment has been performed within the last 30 days or progressive disease has been documented.

1.3. Sample Size and Power

Sample size calculations for each of the Phase 2 cohorts are as follows:

- For Cohort 1, a sample size of 46 (40 patients in Phase 2 Cohort 1 together with 6 patients in Safety Run-in Cohort 1) provides an 83.6% power for a 1-group Chi-square test at 1-sided alpha of 0.1 level to detect a CR rate of ≥ 53% for the combination compared with a historical control CR rate of 36.7% {DiNardo 2020}.

- For Cohort 2, a sample size of 36 (30 patients in Phase 2 Cohort 2 together with 6 patients in Safety Run-in Cohort 2) provides a 83.1% power for a 1-group Chi-square test at 1-sided alpha of 0.1 level to detect a CR rate of ≥ 35% for the combination compared with a historical control CR rate of 19% {Greenberg 2004}.

- For Cohort 3, a sample size of 46 (40 patients in Phase 2 Cohort 3 together with 6 patients in Safety Run-in Cohort 3) provides a 78.4% power for a 1-group Chi-square test at 1-sided alpha of 0.1 level to detect an MRD negative CR rate of ≥ 33% for the combination compared with a historical control MRD negative CR rate of 20% {Roboz 2020}.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

2.2. Primary Analysis

The primary analysis will be conducted after all patients have discontinued the study or have been on study for at least 24 weeks and completed the Week 24 response assessments, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis.

The primary analysis was conducted using data extracted on October 18, 2023 with the data cutoff date of June 1, 2023.

2.3. Final Analysis

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

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-patient listings will be presented for all patients in the All Enrolled Analysis Set, unless otherwise specified, and sorted by patient ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the patient. Age at Day 1 (ie, visit day 1, study day 1, first dosing date of study drug), 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 cohort.

A listing of reasons for exclusion from analysis sets will be provided by patient.

3.1.1. All Enrolled Analysis Set

The All-Enrolled Analysis Set includes all patients who receive a study patient identification (ID) number in the study after screening. This will be the primary analysis set for analyses of patient demographics and baseline characteristics, enrollment, and disposition.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled patients who receive at least 1 dose of any study treatment, with treatment group designated according to the assigned treatment. This is the primary analysis set for efficacy analysis.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all patients who receive at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints, as well as study treatment administration.

3.1.4. Dose-Limiting Toxicity (DLT) Evaluable Analysis Set

The DLT Evaluable Analysis Set includes all patients in the Safety Analysis Set who are enrolled in the safety run-in cohorts, have safety assessments through the protocol-specified DLT assessment window (first 4 weeks of study dosing, inclusive), and fulfill the criteria for evaluation for DLT specified in the protocol Section 3.1.1.

During the DLT assessment window, if a patient fails to receive sufficient study treatment for reasons other than DLT, another patient will be enrolled at the same dose level for replacement. For patients who are replaced but received at least 1 dose of any study drug, they will be included in the Safety Analysis Set and not in the DLT Evaluable Analysis Set.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 measurable (non-below the limit of quantitation [BLQ] numeric values) post-treatment serum concentration of magrolimab.

3.1.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 reported anti-magrolimab antibody test result.

3.2. Subject Grouping

For analyses based on the Full Analysis Set, patients will be grouped according to the treatment to which they were assigned. 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 assigned treatment only when their actual treatment differs from assigned 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

This study does not use a stratified randomization schedule when enrolling patients.
No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subgroups

Subgroup analyses based on baseline characteristics will not be explored.

3.5. Adjustment for Multiplicity

This study is CCI /proof-of-concept in nature and therefore no formal adjustments for multiplicity are made.

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.

Imputation rules for missing date of birth are described in Section 3.7. For missing last dosing date of study drug, imputation rules are described in Section 5.2.1. The handling of missing or incomplete dates for initial AML diagnosis is described in Section 5.4, for date of death and 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 Sections 5.10.1 and 5.10.2, respectively.

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 Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a patient, then age derived based on year of birth and the Day 1 visit date will be used instead. If an enrolled patient was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., 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 lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower 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 upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper 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 lower or upper LOQ, respectively).

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 study drug (ie, the first dosing date of any study drug) 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.

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 lab are provided in Table 3-1 and Table 3-2.

Table 3-1. Analysis Visit Windows for Lab (Excluding Hemoglobin) By-visit Summary

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 Prior to first dose date/time of any study drug
b Post first dose date/time of any study drug

Table 3-2. Analysis Visit Windows for Hemoglobin By-visit Summary

Analysis Visit	Nominal Study Visit or Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1[a]
Day 1 post-dose	Set 1 Day 1, post-dose Unscheduled[c], post-dose	1[b]	1
Day 2	2	2	2
Day 3	3	3	3
Day 4 pre-dose	Set 1 Day 4, pre-dose Unscheduled[d], pre-dose	NA	NA
Day 4 post-dose	Set 1 Day 4, post-dose Unscheduled[e], 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

Analysis Visit	Nominal Study Visit or Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
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 Prior to first magrolimab date/time if the patient is infused with magrolimab, otherwise use first dose date/time of any study drug
b Post first magrolimab date/time if the patient is infused with magrolimab, otherwise use first dose date/time of any study drug
c Hemoglobin collected at unscheduled post-dose visit on the same day of Set 1 Day 1 post-dose visit is mapped to Day 1 post-dose.
d Hemoglobin collected at unscheduled pre-dose visit on the same day of Set 1 Day 4 pre-dose visit is mapped to Day 4 pre-dose.
e Hemoglobin collected at unscheduled post-dose visit on the same day of Set 1 Day 4 post -dose visit is mapped to Day 4 post -dose.

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 study drug will be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade and anti-magrolimab antibody status.
- Response assessments performed at unscheduled visits after the date of first dose of study drug will be included in the analyses of the efficacy endpoints.

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, except hemoglobin, 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 (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For hemoglobin baseline (numerical value or grade), if a subject was not infused with magrolimab, the last nonmissing value on or prior to the first dosing date of study drug will be selected. If a subject was infused with magrolimab, the last nonmissing hemoglobin value on or prior to the first magrolimab dosing date will be selected. 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.

3.9. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some patients may have been unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. The following special situations due to COVID-19 will be handled in the analysis:

- Study treatment 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

4. PROTOCOL DEVIATIONS

A by-patient listing will be provided for those patients who did not meet at least 1 eligibility (inclusion or exclusion) criterion but enrolled in the study. 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, and the number and percentage of patients with important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by cohort for the All Enrolled Analysis Set. A by-patient listing will be provided for those patients with important protocol deviation.

5. SUBJECT INFORMATION

5.1. Patient Enrollment and Disposition

A summary of patient enrollment will be provided by cohort 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 summary of patient disposition will be provided by cohort. This summary will present the number of patients screened, the number of patients enrolled, and the number of patients in each of the categories listed below:

- All Enrolled Analysis Set
- Full Analysis Set
- Safety Analysis Set
- DLT-evaluable Analysis Set
- Completed study treatment (magrolimab, azacitidine, venetoclax, mitoxantrone, etoposide, cytarabine)
- Discontinued study treatment (magrolimab, azacitidine, venetoclax, mitoxantrone, etoposide, cytarabine) with reasons for discontinuation
- Completed Study
- Discontinued study with reasons for discontinuation

For the status of study drug and study completion and reasons for 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 Full Analysis Set corresponding to that column.

The following information will be provided in by-patient listings by patient 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

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, venetoclax, azacitidine, mitoxantrone, etoposide and cytarabine. No formal statistical testing is planned.

5.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug (magrolimab, venetoclax, azacitidine, mitoxantrone, etoposide and cytarabine) will be defined for a patient 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 and percentage of patients exposed for at least the following time periods: 1 day, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, etc. Summaries will be provided for the Safety Analysis Set. If the last study drug dosing date is missing,

- If the study drug is permanently withdrawn, the latest date among the study drug end date, start date of AE leading to study treatment discontinuation, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for subjects included in the final analyses or the last available date in the database for subjects who were still on treatment at the time of final analysis.

- If the study drug completion status is unknown, the earlier of the date of death or data snapshot date for analysis will be used.

The number of cycles patients were exposed to venetoclax, azacitidine, mitoxantrone, etoposide and cytarabine will be summarized using descriptive statistics, as well as the number and percentage of subjects exposed to a given cycle category (eg, ≥1, ≥2, ≥3, etc).

The number and percentage of patients who have planned dose level different from the standard protocol dose level, infusion interruption, dose modification, dose delay, or dose missed for study drug and the reasons will be summarized.

A by-patient listing of magrolimab administration will be provided by cohort, patient ID number (in ascending order) and visit (in chronological order).

5.2.2. Relative Dose Intensity

Relative dose intensity (RDI) 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 patient's actual on-treatment period based on the study drug regimen.

For magrolimab:

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, and will be calculated for each cohort, respectively:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Cumulative Dosage of Magrolimab Administered (in mg/kg)}}{\text{Magrolimab Dosage Expected to be Administered on Treatment (in mg/kg)}}\right) \text{x } 100$$

Cumulative dosage (mg/kg) received for each patient is defined as the sum of dosages (mg/kg) of all infusions the patient received from Day 1 and onward.

Magrolimab dosage expected to be administered on treatment (mg/kg) for each patient is defined as the product of the assigned dose of magrolimab and number of doses the patient was scheduled to receive during the treatment period from Day 1, and it will include number of infusions administered plus the number of infusions not administered.

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, mitoxantrone, etoposide and cytarabine, take azacitidine RDI for example:

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

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.

5.2.2.1. On-Treatment Intensity Per Cycle

The level of on-treatment intensity per cycle will be determined by considering doses and durations of treatment cycle that a subject receives may vary between cycles or deviate from the planned 28-day cycle length. For each study drug venetoclax, azacitidine, mitoxantrone, etoposide and cytarabine, the actual cycle length of a cycle, except the last cycle of the treatment, is determined as the interval from Day 1 of the cycle to Day 1 of the subsequent cycle; the actual length of last cycle is determined by Day 1 of the last cycle, to the death date and last dosing date.

For azacitidine, mitoxantrone, etoposide and cytarabine:

$$\text{On-Treatment Intensity per 28-day Cycle (\%)} = \frac{\text{Amount of Doses Administered within a Cycle (mg/m}^2\text{)}}{\text{Amount of Doses Specified by Protocol within the Cycle (mg/m}^2\text{)}} \text{ x 100,}$$

averaged across all cycles treated.

$$\text{On-Treatment Intensity per Actual Cycle Duration (\%)} =$$

$$\frac{\text{Amount of Doses Administered within a Cycle (mg/m}^2\text{) /Actual Cycle Length}}{\text{Amount of Doses Specified by Protocol within the Cycle (mg/m}^2\text{) /28 Days}} \text{ x 100,}$$

averaged across all cycles treated.

For venetoclax:

$$\text{On-Treatment Intensity per 28-day Cycle (\%)} = \left(\frac{\text{Number of Days on Venetoclax within a Cycle}}{\text{28 Days}} \times 100\right),$$

averaged across all cycles treated

$$\text{On-Treatment Intensity per Actual Cycle Duration (\%)} = \left(\frac{\text{Number of Days on Venetoclax within a Cycle}}{\text{Actual Cycle Length (Days)}} \text{x100}\right),$$

averaged across all cycles treated

Additionally, the average dosing of venetoclax per cycle will be calculated as:

$$\text{Average Dosing per 28-day Cycle (mg)} = \frac{\sum \text{Dose of Venetoclax (mg)} \times \text{Number of Days on Venetoclax within a Cycle}}{\text{28 Days}},$$

averaged across all cycles treated.

$$\text{Average Dosing per Actual Cycle Duration (mg)} = \frac{\sum \text{Dose of Venetoclax (mg)} \times \text{ Number of Days on Venetoclax within a Cycle}}{\text{Actual Cycle Length (Days)}},$$

averaged across all cycles treated.

5.3. Demographics and Baseline characteristics

Patient demographic variables (eg, age, sex, race, ethnicity) and baseline characteristics (eg, body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], Body Surface Area [BSA; in m^2]) and Eastern Cooperative Oncology Group [ECOG] status at baseline will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The ECOG status at baseline is the ECOG status at screening. The summary of demographic data will be provided for the All Enrolled Analysis Set.

A by-patient demographic listing, including the informed consent date, will be provided by cohort and patient ID number in ascending order.

Other baseline characteristics, including but not limited to ECOG performance status will also be listed.

5.4. Medical History

Medical history (i.e. conditions not specific to the disease being studied) will be collected at screening for disease-specific and general conditions. A by-patient listing of medical history will be provided by cohort and patient ID number in ascending order.

AML diagnosis history will be summarized by cohort based on the All Enrolled Analysis Set. Time since AML diagnosis (months) will be calculated by (date of first dosing date of study drug (or enrollment date if patient is not treated with any study drug) – date of diagnosis) / 30.4375. Time since AML relapse diagnosis will be calculated as well, if applicable. Time since diagnosis will be summarized using summary statistics for a continuous variable. No formal statistical testing is planned. A by-patient listing of disease-specific medical history will be provided.

In deriving time since disease diagnosis, partial dates of diagnosis 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.

5.5. Prior Anti-Cancer Therapy

Prior anti-cancer therapies that patients received, including prior anti-AML therapy and prior anti-MDS therapy, will be listed separately. The details of prior anti-cancer therapy will be listed by patient ID number in ascending order including, regimen name, regimen start/stop date and best response of the regimen.

5.6. Post Study Treatment Stem Cell Transplant

Number and percentage of patients who received post study treatment stem cell transplant will be summarized.

The details of SCT will be listed by patients ID number in ascending order, including date and type of SCT.

5.7. Prior and Concomitant Radiation therapy

No summary or listing of prior and concomitant 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

Number and percentage of patients who received prior transfusions will be summarized. The number of transfusion received within 4 weeks and 8 weeks prior to the first dose will be summarized for whole blood/RBC and platelet as well.

A by-patient listing of transfusion will be provided by cohort and patient ID number in ascending order.

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 begun before a subject took the first study drug.

No summary of prior medications will be provided.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the 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 in the prior medication, unless otherwise specified.

5.10.2. Concomitant Medications

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

No summary of concomitant medications will be provided.

For the purposes of analysis, 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 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 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 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 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.

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

5.11. Post Treatment Anti-cancer Therapy

Post treatment anti-cancer therapies will not be summarized. A by-patient listing will be sorted by cohort, patient ID number and administration date in chronological order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoints

The primary endpoints are as follows:

- CR Rate (Cohorts 1 and 2): The CR rate is defined as the proportion of patients who achieve CR (CR_{MRD-} or complete remission with positive or unknown MRD [$CR_{MRD+/unk}$]) as determined by the investigator based on prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

The primary efficacy hypothesis for Cohort 2 to be tested is:

H_0: CR rate $\leq$ 19%

H_1: CR rate $>$ 19%

6.1.3. Analysis of the Primary Efficacy Endpoint

The analyses of primary efficacy endpoint will be based on the FAS.

The point estimates of the CR rate and the corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method will be provided for Cohorts 1 and 2. The CR data will also be tested against the historical control rates 19% (Cohort 2) at 1-sided alpha of 0.1 significance level using 1-group Chi-square test.

6.1.4. Sensitivity Analysis of the Primary Efficacy Endpoint

No sensitivity analysis for the primary efficacy endpoint is planned.

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6.1.6. Additional Analysis Supporting the Primary Efficacy Endpoint

Assessments for peripheral blood smear, which are used for response criteria for the primary efficacy endpoint will be summarized using:

- Baseline value
- 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

In addition, by-patient data listings will be provided.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- ORR (Cohorts 1 and 2): The ORR is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$), CRi, CRh, PR, or MLFS as determined by the investigator based on prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).
- CR/CRi Rate (Cohorts 1 and 2): The CR/CRi rate is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRi as determined by the investigator based on prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).
- CR_{MRD-} Rate (Cohorts 1 and 2): The CR_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} as determined by the investigator based on prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).
- CR/CRh Rate (Cohorts 1 and 2): The CR/CRh rate is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRh as determined by the investigator based on prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).
- cCR Rate (Cohorts 1 and 2): The cCR rate is the proportion of patients who achieve cCR determined by investigator based on the prespecified criteria (Appendix 2) while on study prior to initiation of any new anti-AML therapy (including SCT).
- DOR (Cohorts 1 and 2): The DOR is measured from the time assessment criteria are met for CR (CR_{MRD-} or $CR_{MRD+/unk}$), CRi, CRh, PR, or MLFS, whichever is first recorded, until the first date of AML relapse, progressive disease, or death (including assessments post SCT). Those who are not observed to have a relapse, progressive disease, or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse/PD/death, duration of response will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Duration of CR (Cohorts 1 and 2): The duration of CR is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse/death, duration of CR will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Duration of CR/CRi (Cohorts 1 and 2): The duration of CR/CRi is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRi until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse/death, duration of CR/CRi will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Duration of CR/CRh (Cohorts 1 and 2): The duration of CR/CRh is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRh until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse/death, duration of CR/CRh will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- EFS (Cohorts 1 and 2): EFS is defined as the time from the date of the first dose of study treatment to the earliest date of documented relapse from CR, treatment failure (TF) defined as failure to achieve CR during the response assessment window (the first treatment dosing date until before the fifth cycle of magrolimab+venetoclax+azacitidine in Cohort 1 and the first treatment dosing date until before the third cycle of magrolimab + MEC in Cohort 2), or death from any cause. Response assessments post SCT or new anti-AML therapies will be excluded from deriving treatment failure. 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 the response assessment window*	No relapse or death	Censored	Last assessment date
	Had relapse or death	Event (Relapse/death)	Relapse date or death date which occurs earlier
Within the response assessment window, had at least one post-baseline response assessment, but didn't achieve the CR	Had progression, death or new anti-AML therapies within the window	Event (TF)	Day 1 of treatment
	No progression, death or new anti-AML therapies within the window, and have been on study beyond the up limit of the window	Event (TF)	Day 1 of treatment
	No progression, death or new anti-AML therapies within the window, and haven't been on study beyond the up limit of the window	Censored	Day 1 of treatment
Within the response assessment window, had no post-baseline response assessment	Had death or new anti-AML therapies within the window	Event (TF)	Day 1 of treatment
	No death or new anti-AML therapies within the window	Censored	Day 1 of treatment

*Response assessment window: the first treatment dosing date to the fifth cycle of magrolimab+venetoclax+azacitidine in Cohort 1 and the first treatment dosing date to the third cycle of magrolimab + MEC in Cohort 2

- OS: The OS is measured from the date of the first dose of study treatment to the date of death from any cause. Those who are not observed to die during the study will be censored at last date they are known to be alive.

- RBC Transfusion Independence Rate: The RBC transfusion independence rate is the proportion of patients who have a 56-day or longer period with no RBC or whole blood transfusion at any time between the date of the first dose and discontinuation of study treatment among all patients who are RBC transfusion-dependent at baseline, defined as having received an RBC or whole blood transfusion within the 28 days prior to the first dose of study treatment (conversion rate), and among all patients who are RBC transfusion-independent at baseline (maintenance rate).

- Platelet Transfusion Independence Rate: The platelet transfusion independence 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 the first dose and discontinuation of study treatment among all patients who are platelet transfusion-dependent at baseline, defined as having received a platelet transfusion within the 28 days prior to the first dose of study treatment (conversion rate), and among all patients who are platelet transfusion independent at baseline (maintenance rate).

The date of the last known alive will be determined by selecting the last available visit date, including unscheduled visits, across all datasets.

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.

When the date of initiation of a new anti-AML therapy/SCT other than the study treatment 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 last dose date of study drug +1, whichever is later.
- If day and month are missing but year is available, then the imputed day and month will be 01Jan, first dose date of study drug +1, or the last day of the month for the last adequate disease assessment if they have the same year, whichever is later.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

The point estimates of the ORR, CR rate, CR/CRi rate, CR_{MRD-} rate, cCR rate, and CR/CRh rate and the corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method will be provided for Cohorts 1 and 2. The analyses of RBC and platelet transfusion independence rates (conversion rate and maintenance rate) will be similar to those of ORR.

Medians, first quartile (Q1), and third quartile (Q3) of EFS distribution, and the proportion of patients who are event free at Weeks 12, 24, and 48 from the first dosing date will be estimated by cohort using the KM method and the corresponding 95% CIs will be reported. Kaplan-Meier plots will be provided. Analyses of OS will be similar to those of EFS.

For the time-to-event endpoints of duration of CR, duration of CR/CRi, duration of CR/CRh, DOR, analyses will be conducted on the subsets for which the outcome measures are defined. Specifically, the duration of CR, duration of CR/CRi, duration of CR/CRh, and DOR will be based on patients in Cohorts 1 and 2 who achieve CR, CR/CRi, CR/CRh, and OR, respectively. The KM method will be used to estimate median durations and 95% CIs, and KM plots will be provided.

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6.4. Changes From Protocol-Specified Efficacy Analyses

The following changes are made from the protocol-specified efficacy analyses:

- Analyses on Cohort 3 will not be conducted since no patients are enrolled in the cohort.
- Given the sample size calculation determined by patients in both Safety Run-in and Phase 2 in Cohorts 1 and 2 and all safety Run-in patients were dosed with the Recommended Phase 2 Dose for both cohorts 1 and 2, the Primary analysis of CR will be conducted on Patients in Cohorts 1 and 2, including patients in both Safety Run-in and Phase 2. Since the enrollment of Cohort 1 terminated earlier, and the number of patients enrolled in Cohort 1 is smaller than the sample size, hypothesis testing of CR rate in Cohort 1 will not be conducted.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

All Adverse Events (AEs) will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs).

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. 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 NCI 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 Treatment

Related AEs are those for which the investigator selected "Related" 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-patient data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured 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 Drug Safety and Public Health Department 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 AEs with an onset date on or after the study drug start date and no later than 70 days after the study drug last dosing date or the day before initiation of new anticancer therapy including SCT, whichever comes first.

7.1.5.2. Missing or 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 70 days after the study drug last dose date or the day before initiation of new anticancer 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 day of the month or the first dosing date if they have the same month and year, whichever is later.
- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

7.1.6. Summaries of Adverse Events and Deaths

TEAEs and deaths will be summarized by cohort based on the Safety Analysis Set.

7.1.6.1. Summaries of TEAEs

A brief, high-level summary of the number and percentage of patients who experienced at least 1 TEAE in the categories described below will be provided. All deaths observed in the study will also be included in this summary. Similar brief summaries will be provided for each category of adverse events of interest and other important safety topics listed in Section 7.1.7.3, 7.1.7.4 and 7.1.7.5.

- TEAEs
- TEAEs with Grade 3 or higher

- TE treatment-related AEs for any study drug and for each study drug, including magrolimab, venetoclax, azacitidine, mitoxantrone, etoposide and cytarabine
- TE treatment-related AEs with Grade 3 or higher for any study drug and for each study drug
- TE SAEs
- TE treatment-related SAEs for any study drug and for each study drug
- Infusion related reaction AE by investigators
- TEAEs leading to discontinuation of any study drug and each study drug
- TEAEs leading to interruption of any study drug and for each study drug
- TEAEs leading to dose reduction of any study drug and for each study drug
- TEAEs leading to death

For the TEAE categories described below, summaries will be provided by SOC and PT (and maximum severity where applicable):

- TEAEs
- TEAEs with Grade 3 or higher (by SOC, PT and severity)
- TE treatment-related AEs for any study drug and for magrolimab
- TE treatment-related AEs with Grade 3 or higher for magrolimab
- TE SAEs
- TE treatment-related SAEs for any study drug and for magrolimab
- TEAEs leading to discontinuation of any study drug and for magrolimab
- TEAEs leading to interruption of any study drug and for magrolimab
- TEAEs leading to dose reduction of any study drug and for magrolimab
- TEAEs leading to death

The number and percentage of patients who experienced at least 1 TEAE will be provided and summarized by PT and severity in descending order of total frequency:

- TEAEs by PT and Severity
- TE treatment-related AEs for magrolimab

For the AE categorizes described below, summaries will be provided by PT in descending order of total frequency:

- TEAEs
- Grade 3 or higher TEAEs
- TE treatment-related AEs for magrolimab
- TE SAEs
- TEAEs leading to discontinuation of any study drug and for magrolimab
- TEAEs leading to death

Multiple episodes of the same event will be counted only once per patient 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 PT, multiple events will be counted only once per patient for each preferred term. For summaries by severity, the highest severity will be used for those AEs that occurred more than once in a given patient during the study.

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

- All AEs
- All SAEs
- All AEs leading to death
- All AEs with severity of Grade 3 or higher
- Infusion related reaction AE by investigators

A flag will be included in the listings to indicate whether the event is treatment emergent.

7.1.6.2. Summaries of Deaths

A summary (number and percentage of patients) of all deaths will be provided. The 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
- Deaths after stem cell transplant.

A by-patient listing of all deaths occurred during this study will be listed by cohort and patient ID number in ascending order.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

A DLT is defined as any Grade 4 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity (that has worsened in severity from pretreatment baseline) during the 4-week DLT assessment period and is related to magrolimab or magrolimab combination.

For each cohort being evaluated for safety and tolerability based on DLT assessment, DLT evaluable patients are identified as those who either experienced a DLT any time during the DLT Assessment Period or completed at least certain amount of the drug administration during the DLT Assessment Period. A summary of DLT will be presented by Preferred Term and Severity.

A listing of the DLT AEs will be provided by cohort including cohort number, patient ID, actual dose amount prior to or on the start date of the AE, DLT term from investigator as well as CTCAE term and associated severity grade, if available.

7.1.7.2. Infusion Reaction Adverse Events (IRAEs)

The incidence of infusion reaction AEs will be examined. Infusion reaction AEs are defined by the NCI CTCAE Version 5.0 (under the category “General disorders and administration site conditions”) as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances”. For the purpose of this study, they are defined as AEs that occur within the 24-hour period beginning from the start of the infusion.

A by-patient listing of infusion reaction AEs will be listed by cohort and patient ID number in ascending order.

7.1.7.3. Treatment-Emergent Adverse Events of Interest (AEI)

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

- Anaemia (MedDRA Search Term [MST]-Anemia Extravascular Transient Hemolysis) (Gilead's MST)
- Infusion Related Reaction (IRR) (SMQ-Hypersensitivity Narrow Terms + within one day of the 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 (MST-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)

Number and percentage of subjects with the following TEAEs of interest will also be summarized by AE onset time within 2 weeks, >2weeks to 2 months, >2 months to 6 months, >6 months to 12 months, and >12 months of first dosing of any study drug.

7.1.7.4. Other Important Safety Topics

Number and percentage of patients 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)

Number and percentage of patients with the following AEs of important safety topics will also be summarized by AE onset time within 2 weeks, >2weeks to 2 months, >2 months to 6 months, >6 months to 12 months, and >12 months of first dosing of study drug.

7.1.7.5. Regrouped Treatment-Emergent Adverse Events

For the regrouped AE PT terms described below, summaries will be provided by cohort:

- Regrouped Thrombocytopenia and Platelet Count Decreased
- Regrouped Neutropenia and Neutrophil Count Decreased
- Regrouped Anemia and Hemoglobin 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 and including the date of last dose of study drug plus 70 days or the day before initiation of any new anticancer therapy including SCT, whichever comes first. 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-patient listing for laboratory test results will be provided by cohort, patient ID number and time point 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.

Line plots for selected lab test results over time will be provided by cohort and patient for the Safety Analysis Set.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort for laboratory tests (eg, chemistry, hematology, coagulation) as follows:

- Baseline value
- 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 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 cohort 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.

Local labs will be graded based on central lab normal ranges with in-house macro.

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 any new anticancer therapy including SCT, whichever comes first. 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 lab test and cohort; patients will be categorized according to the most severe postbaseline abnormality grade for a given lab 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 any new anticancer therapy including SCT, whichever comes first.

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

7.2.3. Shifts Relative to the Baseline Grade

Shift tables will be presented by showing change in severity grade from baseline to the worst postbaseline grade 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 (ECG) analysis results will be provided.

7.5. Premedication

Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming. Premedication during subsequent infusions may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent infusions is required.

Prior to first dose of venetoclax, patients must be provided with prophylactic measures including adequate hydration and antihyperuricemic agents and continue during the ramp-up phase (Days 1, 2, and 3).

Premedications for mitoxantrone, etoposide, and cytarabine can be administered per local institutional guidelines.

A by-patient listing of premedication will be provided by patient ID number in ascending order.

7.6. Other Safety Measures

A by-patient listing of ECOG performance status will be provided by cohort and patient ID number in ascending order.

7.7. Changes From Protocol-Specified Safety Analyses

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

- AEs occurring one day before initiation of new anticancer therapy (including SCT) is added in TEAE definition to be aligned with magrolimab studies.
- AEs occurring within the date of last dose of study drug plus 70 days or the day before initiation of new anticancer therapy (including SCT) is added in TE lab abnormality definition to be aligned with TEAE definition change.

8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No additional changes are made from protocol-specified analyses.

9. PHARMACOKINETIC (PK) AND IMMUNOGENICITY ANALYSES

9.1. PK Sample Collection

Blood samples for evaluating magrolimab serum concentrations will be collected as described in Protocol Appendix Table 4.

9.2. 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 non-missing 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.

9.3. Immunogenicity Analysis

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

ADA Prevalence: the proportion of patients 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 patients who had negative baseline ADA sample and at least one positive post-treatment ADA sample based on patients 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 patients 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 patients who had treatment-induced or treatment-boosted ADA based on patients 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 patients 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 patients who had transient ADA is based on the patients evaluable for ADA incidence.

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

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

10. BIOMARKER ANALYSIS

CCI [redacted]

11. REFERENCES

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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.

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Roboz GJ, Ravandi F, Wei AH, Dombret H, Dohner H, Thol F, et al. CC-486 Prolongs Survival for Patients with Acute Myeloid Leukemia (AML) in Remission after Intensive Chemotherapy (IC) Independent of the Presence of Measurable Residual Disease (MRD) at Study Entry: Results from the QUAZAR AML-001 Maintenance Trial. Blood 2020;136 (Supplement 1):32-3.

12. SOFTWARE

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

13. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
17 OCT 2023	6.2.1	EFS censoring rules	Update EFS algorithm
31 MAY 2024	1.2	Removed response assessments in long-term follow-up	Reflect changes in protocol amendment 6
	7.1.7.3, 7.1.7.4	Updated AE of interest and important safety topics	Consistent within Magrolimab studies
	9	Added PK/ADA analyses	Update for final synoptic CSR
	universal	Reduced outputs for final synoptic CSR	Update for final synoptic CSR

Appendix 1. 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 primary and key secondary endpoints is presented in the estimand framework. Appendix Table 1 summarizes the attributes of estimands and estimators defined for main analyses.

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

Appendix Table 1. List of Estimands and Estimators of Main Analyses

Treatments	Variable (Endpoint)	Intercurrent Events & Strategies	Population Level Summary	Estimators
magrolimab + venetoclax + azacitidine, magrolimab + MEC	OS	• Discontinuation of treatment: treatment policy • SCT, New anti-cancer therapy: treatment policy	Kaplan-Meier estimates (medians, Q1, and Q3 of OS distribution, and the proportion of patients who are event free at Weeks 24, 48, and 96 from the first dosing date)	**Main Estimator:** median OS and 95% CI for each cohort.
magrolimab + venetoclax + azacitidine, magrolimab + MEC	EFS	• Discontinuation of treatment: treatment policy • Death, Treatment failure: composite • SCT, New anti-cancer therapy: treatment policy	Kaplan-Meier estimates (medians, Q1, and Q3 of EFS distribution, and the proportion of patients who are event free at Weeks 12, 24, and 48 from the first dosing date)	**Main Estimator:** median EFS and 95% CI for each cohort.
magrolimab + venetoclax + azacitidine, magrolimab + MEC	CR rate / CR_{MRD-} rate / rate of CR+CRi / rate of CR+CRh/ ORR	• Discontinuation of treatment: treatment policy • SCT, New anti-cancer therapy: while-on-treatment • Loss to follow-up: while-on-treatment	Point estimates of the rate and the corresponding 2-sided exact 95% CIs	**Main Estimator:** Estimate rate and CIs based on the Clopper-Pearson method for each cohort; Test rate against the historical control rate using 1-group Chi-square test for each cohort separately.
magrolimab + venetoclax + azacitidine, magrolimab + MEC	RBC/platelet transfusion independence	• Discontinuation of treatment: while-on-treatment • Dose reduction or temporary delay: treatment policy • Loss to follow-up: while-on-treatment	Point estimates of the rate and the corresponding 2-sided exact 95% CIs	**Main Estimator:** Estimate rate and CIs based on the Clopper-Pearson method for each cohort.

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

Assessment of leukemia response in patients with acute myeloid leukemia (AML) will be conducted based on the European Leukemia Net (ELN) 2017 recommendations for AML {Dohner 2017}, with modifications for the purposes of this protocol (protocol Appendix Table 10). Response classifications include complete remission without minimal residual disease (CR_{MRD-}), complete remission with positive or unknown minimal residual disease ($CR_{MRD+/unk}$), complete remission 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 (protocol Appendix Table 11) {Cheson 2003}.

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 2. Response Criteria in Acute Myeloid Leukemia (Based on 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%	MRD negative (determined using multiparameter flow cytometry with a sensitivity of < 0.1%). Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
Complete remission with positive or unknown minimal residual disease ($CR_{MRD+/unk}$)	> 1.0×10^9/L	> 100×10^9/L	< 5%	MRD positive (determined using multiparameter flow cytometry with a sensitivity of < 0.1%) or unknown. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
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. (All CR criteria except residual neutropenia [< 1.0×10^9/L] or thrombocytopenia [< 100×10^9/L]).
Complete remission with partial hematologic recovery (CRh)	> 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)[a]			< 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
Stable disease	Absence of CR_{MRD-}, $CR_{MRD+/unk}$, CRi, CRh, PR, MLFS; and criteria for progressive disease not met			

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Progressive disease	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] non-transfused); 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.			

ANC = absolute neutrophil count; 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 positive or unknown minimal residual disease; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PR = partial remission; WBC = white blood cell.
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: Based on ELN 2017 guidelines {Dohner 2017}, with modifications for the purposes of this protocol.

Appendix Table 3. Additional Response Definitions Used in This Study (2003 IWG Criteria)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Cytogenetic CR (cCR)	> 1.0 × 109/L	> 100 × 109/L	< 5%	Cytogenetics normal and no evidence of extramedullary disease

cCR = cytogenetic complete remission; CR = complete remission; IWG = International Working Group
Source: {Cheson 2003}

Treatment Failure

Treatment failure is defined as failure to achieve complete remission or complete remission with incomplete hematologic recovery (CR) before the fifth cycle of magrolimab+venetoclax+azacitidine in Cohort 1 and before the third cycle of magrolimab + MEC in Cohort 2.

GS-US-546-5920-Final-SAP-V3.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Global Development Lead (GDL) eSigned	31-May-2024 16:34:25
PPD	Biostatistics eSigned	31-May-2024 20:55:31