CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination with Azacitidine versus Physician's Choice of Venetoclax in Combination with Azacitidine or Intensive Chemotherapy in Previously Untreated Patients with *TP53* Mutant Acute Myeloid Leukemia
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	147229
EudraCT Number:	2020-003949-11
Clinical Trials.gov Identifier:	NCT04778397
Indication:	Acute Myeloid Leukemia
Protocol ID:	GS-US-546-5857
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 21 September 2020 Amendment 1: 16 February 2021 Amendment 2: 28 April 2021 Amendment 3: 09 August 2021 Amendment 4: 31 March 2022 Amendment 5: 02 November 2023

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

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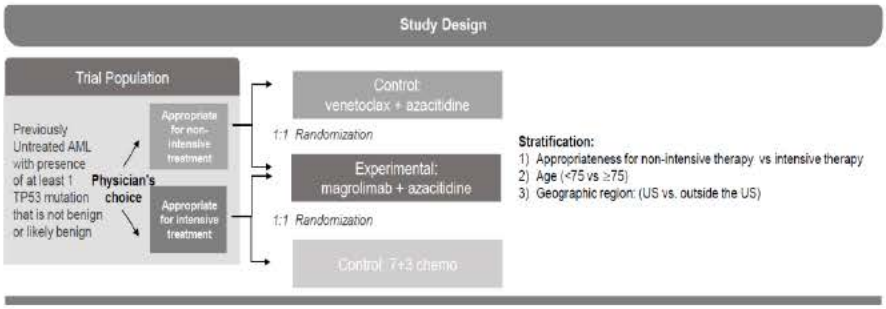
PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 3, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination with Azacitidine versus Physician's Choice of Venetoclax in Combination with Azacitidine or Intensive Chemotherapy in Previously Untreated Patients with TP53 Mutant Acute Myeloid Leukemia
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	147229 2020-003949-11 NCT04778397
Study Centers Planned:	Approximately 170 centers
Objectives:	The **primary** objective of this study is as follows: • To compare the efficacy of magrolimab + azacitidine versus venetoclax + azacitidine in patients with previously untreated *TP*53 mutant acute myeloid leukemia (AML) who are appropriate for non-intensive therapy as measured by overall survival (OS). The **secondary** objectives of this study are as follows: • To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients with previously untreated *TP*53 mutant AML as measured by OS. • To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients as measured by event-free survival (EFS). • To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy as measured by rate of complete remission (CR) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.

- To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy as measured by rate of CR without minimal residual disease (CR_{MRD-}) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.
- To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients as measured by the rate of CR + complete remission with partial hematologic recovery (CRh) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.
- To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy.
- To evaluate the duration of CR + CRh in patients who achieved CR or CRh within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy.
- To assess the safety and tolerability of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy.
- To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab.

CCI [redacted]

	[redacted]
Study Design:	This is a Phase 3, randomized, open-label, multicenter study comparing magrolimab + azacitidine versus venetoclax + azacitidine or 7 + 3 chemotherapy in patients with previously untreated *TP53* mutant AML. Approximately 346 patients will be randomized in 1:1 ratio to receive either magrolimab + azacitidine (experimental arm) or physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy (control arm). Randomization will be stratified by 3 factors: • appropriateness for non-intensive therapy versus intensive therapy • age (< 75 years, ≥ 75 years) • geographic region (United States [US], outside the US)  The primary endpoint is OS in the stratum of patients appropriate for non-intensive therapy. The primary analysis of OS will be conducted when 171 deaths have occurred in the stratum of patients appropriate for non-intensive therapy. An interim futility analysis and an interim superiority analysis will be conducted separately after approximately 69 and 128 deaths (40% and 75% of the expected 171 deaths, respectively) in the stratum of patients appropriate for non-intensive therapy have occurred. In the event the study meets futility, the sponsor may decide to terminate the study, and recommend patients receiving treatment transition to standard of care (SOC) therapy. The current study met futility and sites were informed of the outcome and sponsor's decision in a communication in September 2023.

	If an investigator believes that continued treatment with magrolimab + azacitidine is in the best interest of their patient(s), Gilead will continue to provide study drug, with a reduced schedule of assessments, pending final study closure; if an investigator believes that continued treatment with venetoclax + azacitidine is in the best interest of their patient(s), and the combination is not available locally as SOC, Gilead may continue to provide drug, pending final study closure.
Number of Patients Planned:	A minimum of 228 patients appropriate for non-intensive therapy. Approximately 346 patients in total.
Target Population:	Patients with untreated *TP53* mutant AML who are ≥ 18 years of age
Duration of Treatment:	Cycle length is 28 days for patients in the experimental arm and in the control arm venetoclax + azacitidine and all patients will continue on study treatment unless they meet study treatment discontinuation criteria. For 7 + 3 chemotherapy, cycle length is up to 42 days, and patients will stop treatment after 4 cycles of consolidation treatment.
Diagnosis and Eligibility Criteria:	**Inclusion Criteria:** 1) Patients with confirmation of AML by World Health Organization criteria, previously untreated for AML, and who have presence of: a) At least 1 *TP53* gene mutation that is not benign or likely benign based on evaluation by either central laboratory or an approved local laboratory (after central review of the bone marrow *TP53* mutation next-generation sequencing test results) b) Biallelic 17p deletions, loss of both 17p alleles, based on locally evaluated cytogenetics/karyotype/fluorescence in situ hybridization (FISH) report. 2) Patients with white blood cell (WBC) count ≤ $20 \times 10^3/\mu L$ prior to randomization. If the patient's WBC is > $20 \times 10^3/\mu L$ prior to randomization, the patient can be enrolled, assuming all other eligibility criteria are met. However, the WBC should be ≤ $20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each magrolimab dose for the first 4 weeks (if the patient is randomized to the experimental arm). NOTE: patients can be treated with hydroxyurea and/or leukapheresis throughout the study or prior to randomization to reduce the WBC to ≤ $20 \times 10^3/\mu L$ to enable eligibility for study drug dosing.

3) The hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment

   NOTE: Transfusions are allowed to meet hemoglobin eligibility.

4) Patient has provided informed consent.

5) Patient is willing and able to comply with clinic visits and procedure outlined in the study protocol.

6) Male or female, ≥ 18 years of age.

7) Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, except for patients less than 75 years of age and appropriate for non-intensive treatment. For these patients, the ECOG performance status score may be 0 to 3.

8) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula.

9) Adequate cardiac function as demonstrated by:

   a) Lack of symptomatic congestive heart failure and clinically significant cardiac arrhythmias and ischemic heart disease.

   b) Left ventricular ejection fraction (LVEF) > 50% for patients appropriate for intensive therapy.

10) Adequate liver function as demonstrated by:

   a) Aspartate aminotransferase ≤ 3.0 × upper limit of normal (ULN)

   b) Alanine aminotransferase ≤ 3.0 × ULN

   c) Total bilirubin ≤ 1.5 × ULN, or primary unconjugated bilirubin ≤ 3.0 × ULN if patient has a documented history of Gilbert's syndrome or genetic equivalent.

11) Pretreatment blood cross-match completed.

12) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

13) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (aspirate and trephines).

Exclusion Criteria:

1) Subjects that are unable to give consent. To give consent, the individual concerned must be of legal age and be able to understand the nature, significance and implications of the clinical study and form their rational intentions in light of these.
2) Positive serum pregnancy test
3) Breastfeeding female
4) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient
5) Prior treatment with any of the following:
   a) CD47 or signal regulatory protein alpha (SIRPα)-targeting agents
   b) Antileukemic therapy for the treatment of AML (eg, hypomethylating agent [HMA], low dose cytarabine and/or venetoclax), excluding hydroxyurea.

      NOTE: Patients with prior myelodysplastic syndrome (MDS) who have not received prior HMAs or chemotherapeutic agents for MDS are allowed on study. Other prior MDS therapies including, but not limited to, lenalidomide, erythroid stimulating agents, or similar red blood cell (RBC)-direct therapies, are allowed. Localized non-central nervous system (CNS) radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with luteinizing hormone-releasing hormone agonists for prostate cancer, hormonal therapy or maintenance for breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are also not criteria for exclusion.
   c) Patients who are appropriate for intensive treatment but who have been previously treated with maximum cumulative doses of idarubicin and/or other anthracyclines and anthracenediones will be excluded.
6) Patients receiving any live vaccine within 4 weeks prior to initiation of study treatments.
7) For patients appropriate for intensive therapy, patients treated with trastuzumab within 7 months prior to initiation of study treatments.
8) Current participation in another interventional clinical study.
9) Known inherited or acquired bleeding disorders.
10) Patients appropriate for non-intensive therapy, who have received treatment with strong and/or moderate cytochrome P450 enzyme (CYP)3A inducers within 7 days prior to the initiation of study treatments.

11) Patients appropriate for non-intensive therapy who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to the initiation of study treatment.

12) Patients appropriate for non-intensive therapy who have malabsorption syndrome or other conditions that preclude enteral route of administration.

13) Clinical suspicion of active CNS involvement with AML.

14) Patients who have acute promyelocytic leukemia.

15) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV.

16) Second malignancy, except MDS, treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapies and have had no evidence of active malignancy for at least ≥ 1 year.

    NOTE: patients on maintenance therapy alone who have no evidence of active malignancy for at least ≥ 1 year are eligible.

17) Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or HIV infection in medical history.

18) Active HBV, and/or active HCV, and/or HIV following testing at screening:

    a) Patients who test positive for hepatitis B surface antigen (HBsAg). Patients who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

    b) Patients who test positive for HCV antibody. These patients will require HCV RNA quantitative PCR for confirmation of active disease.

    c) Patients who test positive for HIV antibody.

    d) Patients not currently receiving antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study.

Study Procedures/ Frequency:

Following completion of screening and admission assessments, eligible patients will be randomized 1:1 to receive either magrolimab + azacitidine (experimental arm) or physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy (control arm).

The study treatments within each arm are as follows:

Dosing and Schedule for Magrolimab and Azacitidine Experimental Arm

Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
	Cycle 1	**Cycle 2**	**Cycle 3+**
Azacitidine 75 mg/m^2 SC or IV[a]	Days 1–7 or Days 1–5 and 8, 9[b]	Days 1–7 or Days 1–5 and 8, 9[b]	Days 1–7 or Days 1–5 and 8, 9[b]
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 x 5 weekly 30 mg/kg dose		
Magrolimab 30 mg/kg IV (over 2 hours)	Q2W beginning 1 week after the 5 weekly 30 mg/kg dose		

IV = intravenous; PO = orally; Q2W = every 2 weeks; QW = once a week; SC = subcutaneous
a Azacitidine administered per region-specific labeling.
b Or any other alternative schedule, as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.

Dosing and Schedule for Venetoclax and Azacitidine Control Arm

Control Arm	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	**Cycle 2**	**Cycle 3+**
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[b]	Days 1–7 or Days 1–5 and 8–9[b]	Days 1–7 or Days 1–5 and 8–9[b]

IV = intravenous; SC = subcutaneous
a Azacitidine administered per region-specific labeling.
b Or any other alternative schedule, as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.

Dosing and Schedule for 7 + 3 Chemotherapy Control Arm

Control Arm (7 + 3)	Drug/Dose/Route	7 + 3 Induction	5 + 2 Induction, if needed (after C1D15 bone marrow assessment)
Induction	Daunorubicin 60 mg/m^2 IVP or Idarubicin 12 mg/m^2 IV	Days 1–3	Days 1-2
	Cytarabine 100 or 200 mg/m^2 CI	Days 1–7	Days 1–5
Consolidation	Cytarabine (HiDAC) 1500 or 3000 mg/m^2 IV[a]	Every 12 hours on Days 1, 3, and 5 (up to 4 cycles)	
	Steroidal Eye Drops	As per institutional standard	

C1D15 = Cycle 1 Day 15; CI = continuous infusion; HiDAC = high-dose cytarabine; IV = intravenous; IVP = intravenous peripheral
a In some cases, patients ≥ 60 years of age can receive 1000 mg/m^2 based on local practice.

For the experimental arm and the control arm venetoclax + azacitidine, cycle lengths are 28 days and all patients will continue on study treatment until disease progression, relapse, loss of clinical benefit, or unacceptable toxicities occur.

Treatment with azacitidine as SOC is recommended for a minimum of 6 cycles. Therefore, in this study, for the patients in the magrolimab + azacitidine or venetoclax + azacitidine treatment arms, those without evidence of disease progression (including relapse after partial/complete remission [PR/CR]), loss of clinical benefit, or unacceptable toxicity should continue study treatment. For those in the 7 + 3 chemotherapy treatment arm, treatment should continue until the end of the induction cycle(s). 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 during the study treatment period for the magrolimab + azacitidine and venetoclax + azacitidine treatment arms. For the 7 + 3 control arm, response assessments will be performed:

- on Cycle 1 Day 15 (after 7 + 3 only; to determine if a new induction of 5 + 2 is needed); and
- at count recovery or Day 42 after the start of the most recent induction treatment, whichever is earlier; and

- if therapy is stopped at:
  - Consolidation Cycle 1, then at count recovery after consolidation Cycle 1 or Day 42 after the start of Consolidation Cycle 1, whichever is earlier, or
  - Consolidation Cycle 2, then at count recovery after Consolidation Cycle 2 or Day 42 after the start of Consolidation Cycle 2, whichever is earlier, or
  - Consolidation Cycle 3, then at count recovery after Consolidation Cycle 2 and Cycle 3, or Day 42 after the start of each Consolidation Cycle 2 and Consolidation Cycle 3, whichever is earliest, or
  - Consolidation Cycle 4, then at count recovery after Consolidation Cycle 2 and Cycle 4, or Day 42 after the start of each Consolidation Cycle 2 and Consolidation Cycle 4, whichever is earliest; and
- every 12 weeks thereafter.

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

In case patients discontinue the study treatment due to reasons other than disease progression or relapse, patients will be followed for response assessments until documented disease progression or relapse or initiation of new anti-AML therapy (excluding SCT and maintenance). For patients who discontinue the study treatment to receive a stem cell transplant, follow-up for response assessment and collection of bone marrow biopsy/aspirate results will continue every 12 weeks from the date of SCT, until documented disease progression or relapse or initiation of new anti-AML therapy (excluding maintenance therapy) occurs. Then patients will be observed for survival until death, withdrawal of consent, lost to follow-up, or the end of the study, whichever occurs first.

Treatment with magrolimab or venetoclax as single agent is not permitted. Patients who discontinue magrolimab + azacitidine, or venetoclax + azacitidine, 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. For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

	In the event the study meets futility, and the sponsor decides to terminate the study, all patients who discontinue study treatment for any reason will not be followed for response or survival.
Test Product, Dose, and Mode of Administration:	Magrolimab 1 mg/kg intravenous (IV) Magrolimab 15 mg/kg IV Magrolimab 30 mg/kg IV In combination with: Azacitidine 75 mg/m^2 IV or SC
Reference Therapy, Dose, and Mode of Administration:	Venetoclax 10 mg oral Venetoclax 50 mg oral Venetoclax 100 mg oral In combination with: Azacitidine 75 mg/m^2 IV or SC Or Cytarabine 100 or 200 mg/m^2 CI in combination with Daunorubicin 60 mg/m^2 IVP or Idarubicin 12 mg/m^2 IV followed by Cytarabine (HiDAC) 1000 or 1500 or 3000 mg/m^2 IV
Criteria for Evaluation:	
Safety:	Safety will be evaluated by data including the incidence of adverse events (AEs) for the duration of the study, assessment of clinical laboratory test findings, physical examination, 12-lead electrocardiogram, ECOG performance status, and vital signs measurements. Adverse events will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
Efficacy:	Efficacy will be evaluated by OS, EFS, transfusion independence rate, CR rate, CR_{MRD-} rate, GHS/QoL and physical functioning scale scores from EORTC QLQ-C30, CR + CRh rate, ORR, DCR, duration of CR + CRh, and DOR. Assessment of leukemia response in AML patients will be conducted using the European LeukemiaNet (ELN) 2017 recommendations for AML and the 2003 International Working Group (IWG) criteria with modifications.

Pharmacokinetics:	Magrolimab serum drug concentrations will be assessed in the magrolimab + azacitidine group at predose and at regular intervals postdose until study discontinuation. Samples will also be collected for the detection of antidrug antibodies (ADA) against magrolimab. Presence of neutralizing antibodies to magrolimab will also be assessed in the ADA positive samples.
Statistical Methods:	Analysis Data Set The Intent-to-Treat (ITT) Analysis Set includes all randomized patients according to the treatment arm to which the patient is randomized, unless otherwise specified. This is the primary analysis set for efficacy analysis. The Safety Analysis Set will include all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received. The PK Analysis Set will include all randomized patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab. The Immunogenicity Analysis Set will include all randomized patients who received at least 1 dose of magrolimab and had at least 1 evaluable anti-magrolimab antibody test result. The Biomarker Analysis Set includes all randomized patients who received at least 1 dose of any study drug and have at least 1 evaluable biomarker measurement available. This will be the primary analysis set for all biomarker data analyses. Efficacy Analysis Time-to-event endpoints, including OS, EFS, and DCR, will be summarized using Kaplan-Meier estimates, which include median and the proportion of event-free patients at benchmark time points such as 6 months and 12 months. The Kaplan-Meier plots will be provided. Hypothesis testing will be performed on the ITT Analysis Set for OS and EFS using the log-rank test stratified by randomization stratification factors. The hazard ratio (HR) with the corresponding 2-sided 95% CIs estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will also be presented for OS and EFS. Categorical endpoints including CR rate, CR_{MRD-} rate, CR + CRh rate, and transfusion independence conversion rate will be compared between arms using Cochran-Mantel-Haenszel test stratified by randomization stratification factors. The point estimate of these rates and the corresponding 2-sided exact 95% CIs based on the exact Clopper-Pearson method will be provided for each treatment arm.

The TTD on the EORTC QLQ-C30 GHS/QoL scale, defined as the time from date of randomization to the first time a patient experienced at least 1 threshold value deterioration from baseline or death, and TTD on the EORTC QLQ-C30 physical functioning scale may be summarized using the Kaplan-Meier method. The log-rank test stratified by randomization stratification factors will be conducted for comparison between treatment arms, and the HR estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will be provided.

To strongly control the overall type I error across the testing of primary and key secondary endpoints, a hierarchical testing strategy will be performed with a predefined order as listed in the protocol and the statistical analysis plan. A given hypothesis can only be tested and declared statistically significant if all previous hypotheses in the hierarchy are also statistically significant. The overall study-wide type I error is 1-sided 0.025. To protect the integrity of the study, an administrative 1-sided type I error of 0.0001 will be spent for the interim futility analysis. As a result, a 1-sided type I error of 0.0249 will be left for the superiority analysis of the primary and key secondary efficacy endpoints using the hierarchical testing approach.

Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications in the Safety Analysis Set by treatment arm. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized.

Interim Analysis

An interim futility analysis and an interim superiority analysis of OS will be performed separately when approximately 69 deaths and 128 deaths (40% and 75% of the expected 171 deaths, respectively) in the stratum of patients appropriate for non-intensive therapy have occurred.

Primary Analysis

If the null hypothesis on the primary endpoint of OS is not rejected in the interim efficacy analysis, the primary analysis of OS will be performed separately when approximately 171 deaths have occurred in the stratum of patients appropriate for non-intensive therapy.

In the event the study meets futility, and the sponsor decides to terminate the study, the planned interim superiority analysis and primary analysis will no longer be required.

Sample Size

It is assumed that administration of magrolimab + azacitidine to study patients will result in a median OS of approximately 9.77 months, improved from a median OS of 6.35 months in patients treated with venetoclax + azacitidine or 7 + 3 chemotherapy. This corresponds to an OS HR of 0.65. The median OS assumptions are based on the observations from Study 5F9005, which enrolled *TP53* mutant AML patients treated with magrolimab + azacitidine and the publication of studies for venetoclax in combination with hypomethylating agents in *TP53* mutant AML patients.

It is assumed 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, an HR of 0.65 under the alternative hypothesis of superiority of the magrolimab + azacitidine, a planned interim futility analysis when 40% OS events are observed, and an interim superiority analysis when 75% OS events are observed, 171 events (deaths) are required to achieve a power of 79.7% based on a log-rank test with an overall 1-sided significance level of 0.025 in the stratum of patients appropriate for non-intensive therapy; approximately 234 deaths may be observed in all patients when 171 events occur in the stratum of patients appropriate for non-intensive therapy. That provides a power of 90.4% for the OS test in all patients based on the log-rank test.

The study will enroll a minimum of 228 patients appropriate for non-intensive therapy to ensure adequate events (171 deaths) for the primary endpoint analysis. The study enrollment may stop after 228 patients in the non-intensive therapy group or approximately 346 of all patients are enrolled, whichever occurs later. The study duration and the total number of patients to be enrolled will depend on the prevalence of patients appropriate for non-intensive therapy in the overall population. When the enrollment of the required number of all patients finishes later than that of patients in the non-intensive therapy group, assuming a planned accrual period of 23 months, a study duration of 27 months, and an expectation that 10% of patients are likely to drop out by the end of study (annual dropout rate 4.8% assuming time to drop-out is exponentially distributed), approximately 173 patients in the experimental arm and 173 patients in the control arm (approximately 346 total) are to be enrolled. In the event the study meets futility, and the sponsor decides to terminate the study, no further patients will be enrolled.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ABO	any of the 4 blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CBC	complete blood count
Ccr	cytogenetic complete remission
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete count recovery
CR_{MRD-}	complete remission without 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
CYP	cytochrome P450 enzyme
DAT	direct antiglobulin test
DCR	duration of complete remission
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
ELN	European LeukemiaNet
EQ-5D-5L	5-level EuroQol 5 dimensions

EQ VAS	EQ visual analogue scale
EOT	end of treatment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GHS/QoL	global health status/quality of life
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HiDAC	high-dose cytarabine
HMA	hypomethylating agent
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IgG4	immunoglobulin G4
INR	international normalized ratio
IND	investigational new drug
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
IRR	infusion-related reaction
ITT	Intent-to-Treat
IV	intravenous
IVP	intravenous peripheral
IWG	International Working Group
LHRH	luteinizing hormone-releasing hormone
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MNS	a human blood group system based upon 2 genes (glycophorin A and glycophorin B) on chromosome 4
MOA	mechanism of action
MRD	minimal residual disease

MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial remission
PR/CR	partial/complete remission
PRO	patient-reported outcome
PT	prothrombin time
GLPS	Patient Safety
Q2W	every 2 weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
Rh	rhesus factor
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCT	stem cell transplant
SIRPα	signal regulatory protein alpha
SOC	standard of care
SOP	standard operating procedure
SSR	special situation reports
SUSAR	suspected unexpected serious adverse reaction
TTD	time to first deterioration
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Acute myeloid leukemia (AML) is a common hematologic malignancy whose incidence rises from 3:100,000 in young adults to greater than 20:100,000 in older adults. For patients < 60 years of age, 5-year overall survival (OS) is 40% to 50% but is only 5% for patients > 60 years of age. The majority of newly diagnosed previously untreated patients with AML are above the age of 60 years. In this patient population, standard intensive induction chemotherapy is often not an option due to increased treatment-related mortality as a result of age and co-morbidities. Standard of care (SOC) for AML patients unfit for combination chemotherapy is treatment with hypomethylating agents (HMAs) (azacitidine or decitabine) or low dose cytarabine. Venetoclax in combinations with either azacitidine, decitabine, or low dose cytarabine is also used as SOC in several regions. Despite these frontline treatments, median OS is only about 10 to 15 months. In all types of AML, disease relapse is common despite an initial therapeutic response and is the most common reason for death. Standard chemotherapy and stem cell transplant (SCT) (when used) often fail to eradicate all tumor-propagating cells and select for chemotherapy-resistant leukemia propagating subclones. Patients refractory to salvage therapy are treated palliatively, as current treatment options are extremely limited. These patients have a median survival of 2 months.

Acute myeloid leukemia patients harboring a *TP53* mutation comprise approximately 10% to 15% of all AML patients {Kadia 2016, Rucker 2012}. *TP53* mutant AML patients represent an extremely poor prognostic group that is highly refractory to standard therapies that include both intensive and non-intensive therapies. The median OS of *TP53* mutant patients is approximately 4 months, compared to 11 months for their wildtype counterparts {Rucker 2012}. In previously untreated AML patients who are unfit for intensive chemotherapy, *TP53* mutations predict a worse prognosis compared to all-comers with standard azacitidine therapy {Bally 2014}. In untreated *TP53* mutant unfit AML, azacitidine has demonstrated objective responses from 20% to 40% with a median OS of approximately 7 months {Dohner 2018, Sallman 2018}.

Despite recently approved therapies in AML, treatment for patients with *TP53* mutant AML remains a high unmet medical need. In 2018, venetoclax in combination with HMAs or low dose cytarabine was granted accelerated approval in the United States (US) for AML patients who are ineligible for intensive induction chemotherapy. While meaningful clinical benefit is observed in these AML patients, a subset of these patients, specifically those harboring a *TP53* mutation, have limited benefit. For Food and Drug Administration (FDA) approved venetoclax-based combinations with either HMA or low dose cytarabine, the complete remission (CR) and/or complete remission with incomplete count recovery (CRi) rate ranged from 30% to 55%. While responses are observed, the duration of response (DOR) (range: 5.6 to 6.4 months) is limited. Furthermore, median OS with venetoclax-based combinations is limited with a range of 3.6 to 7.2 months {DiNardo 2019, Kim 2020, Shoukier 2019}, which are similar to those observed with azacitidine alone {Hunter 2019}. In contrast, the median OS is approximately 10 months for all untreated AML patients unfit for intensive therapy treated with azacitidine {Dombret 2015} and approximately 15 months for all unfit patients treated with venetoclax + azacitidine {DiNardo 2020a}.

Patients treated with intensive chemotherapy have similarly poor outcomes (median survival 6.8 months vs 20.2 months and 2-year OS 9% vs 24% for *TP53* mutant AML and *TP53* wildtype AML, respectively) {Kadia 2016}. The CR rate after induction chemotherapy is only 28% in *TP53* mutant compared to 50% in wildtype patients, and the median OS was 4.1 months in *TP53* mutant AML {Rucker 2012}. Despite evaluation of multiple therapies in this *TP53* mutant population, the overall efficacy and prognosis remains consistently poor {Hunter 2019}, demonstrating the uniformly poor survival for this patient group. Thus, current available therapies have limited benefit for *TP53* mutant AML patients with no therapies approved specifically for this population.

Cluster of differentiation 47 (CD47) is a key molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic "eat me" signals {Jaiswal 2009, Majeti 2009}. The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal {Chao 2012}. Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint {Chao 2012}. Increased CD47 expression was identified first on leukemic stem cells in human AML {Majeti 2009}, and since then, it has been found that CD47 expression is increased on the surface of cancer cells in a diverse set of human tumor types.

In mouse xenograft models, CD47-blocking monoclonal antibodies (mAbs) inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors {Chao 2011a, Chao 2010a, Chao 2011b, Edris 2012, Kim 2012, Majeti 2009, Willingham 2012}. Binding of CD47 expressed by cancer cells to its ligand, signal regulatory protein alpha (SIRPα), expressed on phagocytes leads to inhibition of tumor cell phagocytosis. Thus, blockade of the CD47 SIRPα-signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of prophagocytic signals expressed mainly on tumor cells and not on normal cell counterparts {Chao 2010b}. In addition, the anti-CD47 antibody can induce an anti-cancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis {Liu 2015b, Tseng 2013}.

1.2. Magrolimab

1.2.1. General Information

Magrolimab is a humanized anti-CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells {Liu 2015a}. The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the immunoglobulin G4 (IgG4) Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells {Liu 2015a}. Nonclinical studies using

xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

The magrolimab program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia, non-Hodgkin lymphoma [NHL], myeloma, myelodysplastic syndrome [MDS], and others).

For further information on GS-4721 (magrolimab), refer to the current investigator's brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

The combination of magrolimab + azacitidine was evaluated in leukemic nonclinical models. Nonclinical synergy was observed based on the upregulation of prophagocytic signals (including calreticulin) on leukemic cells of a *TP53* mutated cell line by azacitidine combined with blockade of the anti-phagocytic signal CD47 with magrolimab {Feng 2018}. Magrolimab + azacitidine led to synergistic phagocytosis of leukemic cells in vitro and near 100% long-term durable remissions in an aggressive nonclinical leukemia mouse model, compared to modest effects with either monotherapy. These data support the mechanistic and nonclinical rationale for combining magrolimab with azacitidine in AML. Further nonclinical data including efficacy, toxicology, and pharmacology can be found in the IB.

1.2.3. Clinical Background for Magrolimab

1.2.3.1. Summary of Clinical Pharmacology

Clinical pharmacokinetic (PK) data have been collected in all ongoing studies of magrolimab conducted to date. Pharmacokinetic data have been analyzed in Phase 1 study (SCI-CD47-001) in patients with solid tumor. In this study, patients were treated with weekly magrolimab doses ranged from 0.1 to 45 mg/kg, with increasing plasma concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance was observed over this dose range. However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen, and trough levels associated with magrolimab efficacy in nonclinical studies were achieved. Nine of 88 (10%) evaluable patients tested positive for antidrug antibody (ADA) against magrolimab at any time point including baseline; ADA positivity had no impact on PK or clinical safety in these patients.

In the Phase 1 AML study (SCI-CD47-002), similar to the solid tumor Phase 1 study, nonlinear PK consistent with target-mediated clearance was observed. Three of 20 (15%) evaluable patients tested positive for ADA against magrolimab at any time point including baseline; ADA positivity had no impact on PK. Antidrug antibody positivity in either study was not associated with increased adverse events (AEs).

Preliminary PK data of magrolimab from other ongoing studies (5F9003, 5F9004, and 5F9005) of magrolimab indicates similar PK properties across all tumor populations and in the presence of coadministered drugs. Across all studies, 21 of 264 (8%) patients tested positive for ADA against magrolimab at any time point including baseline. Antidrug antibody positivity was not associated with changes in PK or AE profile.

A preliminary population PK analysis of combined magrolimab PK data indicated that results for magrolimab population PK were typical of other nonlinear antibodies. No clinically significant covariates of PK variability were identified.

1.2.3.2. Summary of Clinical Safety

Magrolimab is administered as an intravenous (IV) infusion and it is currently being studied in 7 clinical studies. Two completed single-agent Phase 1 studies include Study SCI-CD47-001 in patients with advanced solid tumors and lymphomas, and Study SCI-CD47-002 in patients with relapsed/refractory AML, along with 2 Phase 1b partnered studies in AML as well as urothelial carcinoma. Five combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with relapsed/refractory NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in solid tumor and colorectal cancer patients; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in AML and MDS patients; Study 5F9006, a Phase 1b study of magrolimab with avelumab in solid tumor and ovarian cancer patients, and Study 5F9009, ENHANCE: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome.

As of July 2020, over 500 patients have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no maximum tolerated dose (MTD) reached in any study with dosing up to 45 mg/kg. Two anticipated adverse reactions included on-target anemia and infusion-related reactions, which are expected with monoclonal antibodies. Importantly, on-target anemia due to CD47 blockade-mediated red blood cell (RBC) clearance was mitigated with a priming/maintenance dose strategy. The average hemoglobin decline with the first (priming) dose was 0.4 g/dL, with many patients improving their hemoglobin on therapy with a decrease in RBC transfusion requirements.

As of December 2020, 52 untreated induction chemotherapy-ineligible AML patients have been enrolled in Study 5F9005 and received the combination of magrolimab + azacitidine {Sallman 2020b}. The safety profile of magrolimab in combination with azacitidine was acceptable and consistent with azacitidine monotherapy, with no significant increases in cytopenias, or immune-related AEs. No MTD was reached with magrolimab dosing of 30 mg/kg weekly. The most common treatment-related AEs with magrolimab were anemia (31%), fatigue (19%), blood bilirubin increased (19%), neutropenia (19%), thrombocytopenia (17%), and nausea (15%). Treatment discontinuation due to any drug-related AEs occurred in 2 of 52 patients (3.8%).

1.2.3.3. Summary of Clinical Efficacy

In Study 5F9005, clinical activity was assessed for magrolimab + azacitidine in patients with treatment-naive/unfit AML and treatment-naive intermediate to higher risk (by Revised International Prognostic Scoring System [IPSS-R]) MDS {Sallman 2020b}. As of December 2020, a total of 52 AML patients (including 65% with *TP53* mutation) were treated with magrolimab + azacitidine and 34 of them were evaluable for efficacy. The objective response rate (ORR) was 65% (22 patients), with 44% achieving a CR, 12% achieving CRi, 3% achieving partial response, and 6% achieving morphologic leukemia-free state (MLFS). Time to response was rapid with a median of 2.04 months. Of the responding patients who had abnormal cytogenetics at baseline, 47% achieved complete cytogenetic response. Additionally, 37% of responding AML patients achieved minimal residual disease (MRD) negativity, as assessed by multiparametric flow cytometry {Sallman 2020b}.

In AML patients harboring *TP53* mutations, the ORR was 71% (15 of 21 patients) with a CR rate of 48% (10 of 21 patients), 19% (4 of 21 patients) of patients achieving CRi, and 5% (1 of 21 patients) achieving MLFS. Median follow-up for patients with *TP53*-mutant AML was 4 months, the median DOR was 9.9 months (range: 0.03+ to 15.1+ months ongoing), and the median OS for *TP53*-mutant patients (n = 34) was 12.9 months (range: 6.24 months, not reached) {Sallman 2020b}.

For further clinical efficacy and safety information for magrolimab in other indications, please refer to the magrolimab IB.

1.3. Information About Venetoclax and Azacitidine

1.3.1. Description of Venetoclax

Venetoclax is a selective, orally bioavailable, small-molecule Bcl-2 family inhibitor that binds with high affinity (inhibitory constant [Ki] < 0.010 nM) {Souers 2013}.

Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance {Fesik 2005}. Overexpression of Bcl-2 has been demonstrated in AML and chronic lymphocytic leukemia (CLL) cells where it mediates cell survival and resistance to chemotherapeutic agents. Venetoclax restores apoptosis by binding to Bcl-2 protein, thereby displacing proapoptotic proteins such as Bim, triggering mitochondrial outer membrane permeabilization and the activation of caspases. Venetoclax has demonstrated cell killing activity against patient-derived CLL cells and AML cells and a variety of lymphoma and leukemia cell lines.

In the US, venetoclax is approved for the treatment of adult patients with CLL or small lymphocytic leukemia. Venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine is approved for the treatment of newly diagnosed AML in adults who are age ≥ 75 years of age, or who have comorbidities that preclude use of intensive induction chemotherapy {VENCLEXTA 2020}.

In the European Union (EU), venetoclax monotherapy is approved for the treatment of adult patients with CLL, and for use in combination with hypomethylating agents for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. For additional information on venetoclax, please refer to the prescribing information.

1.3.2. Description of Azacitidine

Azacitidine is a nucleoside analog, specifically a chemical analog of cytidine. Azacitidine has 2 known primary antineoplastic MOAs: 1) inhibition of DNA methyltransferase leading to hypomethylation of DNA and 2) direct cytotoxicity of malignant hematopoietic cells through cell death via its incorporation into DNA and RNA.

Azacitidine is a SOC and approved in the US for treatment of subtypes of MDS including, but not limited to, MDS with refractory anemia with excess blasts, a subtype that is mostly composed of patients with intermediate to very high risk MDS by IPSS-R criteria {VIDAZA 2018}. Azacitidine is also an SOC therapy for previously untreated patients with AML who are ineligible for induction chemotherapy or SCT based on age, comorbidities, or other factors. In Europe, azacitidine is approved for patients with intermediate-2 and high-risk MDS according to International Prognostic Scoring System criteria and for patients with AML who are ineligible for SCT. For additional information on azacitidine, please refer to the prescribing information.

1.3.3. Clinical Data for Venetoclax + Azacitidine

Venetoclax in combination with azacitidine (N = 84) or decitabine (N = 31) was studied in M14-358, a non-randomized, open-label clinical studies with newly diagnosed AML {VENCLEXTA 2020}. Of those patients, 67 who received azacitidine combination were aged ≥ 75 years or had comorbidities that precluded the use of intensive induction chemotherapy. Patients received venetoclax via a daily ramp-up to a final 400 mg once daily dose and azacitidine at the standard dosing. Twenty-five percent (37 of 67) of patients receiving venetoclax + azacitidine achieved CR (95% CI: 26-50), and 16% (24 of 67 patients) (95% CI: 14-36) achieved CR with partial hematologic recovery (CRh). The median follow-up was 7.9 months (range: 0.4-36 months) for venetoclax in combination with azacitidine. At the time of analysis, for patients who achieved a CR, the median observed time in remission was 5.5 months (range: 0.4-30 months). Median time to first CR or CRh for patients treated with venetoclax in combination with azacitidine was 1.0 month (range: 0.7-8.9 months). Of patients treated with venetoclax in combination with azacitidine, 7.5% (5 of 67) subsequently received SCT. The study enrolled 35 additional patients (age range: 65-74 years) who did not have known comorbidities that preclude the use of intensive induction chemotherapy and were treated with venetoclax in combination with azacitidine (N = 17) or decitabine (N = 18). For the 17 patients treated with venetoclax in combination with azacitidine, the CR rate was 35% (95% CI: 14-62) and the CRh rate was 41% (95% CI: 18-67). Seven (41%) patients subsequently received SCT. For the 18 patients treated with venetoclax in combination with decitabine, the CR rate was 56% (95% CI: 31-79). The most common AEs of any grade observed with patients treated with venetoclax and azacitidine were nausea, diarrhea, constipation, neutropenia, thrombocytopenia, hemorrhage, peripheral edema, vomiting, fatigue, febrile neutropenia, rash, and anemia.

The Phase 3 randomized, double-blind, placebo-controlled study VIALE-A, investigating venetoclax in combination with azacitidine versus azacitidine + placebo in treatment-naive AML patients who are ineligible for intensive chemotherapy, confirms the efficacy of venetoclax + azacitidine with a statistically significant improvement in overall OS. Median OS of the venetoclax + azacitidine arm was 14.7 months, while the median OS of the azacitidine + placebo arm was 9.6 month leading to a hazard ratio (HR) of 0.66 (95% CI: 0.52-0.85; $P < 0.001$) {DiNardo 2020b}. Safety of the combination in VIALE-A was similar to what had been previously reported and can be managed with standard supportive care.

Despite these significant improvements in outcomes for these patients, *TP53*-mutated AML patients did not appear to benefit significantly from a venetoclax + HMA combination. Treatment with venetoclax in combination with an HMA as frontline therapy in *TP53*-mutated AML patients resulted in an improvement in CR with a CR/CRi rate of 47% but the durability was brief (median CR/CRi duration of 5.6 months). The median OS for newly diagnosed patients with *TP53*-mutated AML treated with venetoclax + HMA was 5.2 to 7.2 months, which is similar to treatment with HMA alone {DiNardo 2019, Kim 2020}.

1.4. Information About 7 + 3 Regimen

1.4.1. Description of Cytarabine

Cytarabine is a cytotoxic drug that primarily kills cells undergoing DNA synthesis (S phase) and under certain conditions blocks the progression of cells from G1 phase to S phase. It acts through the inhibition of DNA polymerase and incorporates in limited but significant amount in DNA and RNA.

Cytarabine in combination with other approved anticancer drugs (such as anthracyclines) is indicated for remission induction in AML.

For additional information on cytarabine, please refer to the prescribing information.

1.4.2. Description of Daunorubicin

Daunorubicin is an anthracycline cytotoxic antibiotic that has an antimitotic and cytotoxic activity through several mechanisms: it forms complexes with DNA by intercalation between base pairs, inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, inhibits polymerase activity, affects regulation of gene expression, and produces free radical damage to DNA.

Daunorubicin hydrochloride in combination with cytarabine is indicated for the remission induction in AML.

For additional information on daunorubicin, please refer to the prescribing information.

1.4.3. Description of Idarubicin

Idarubicin is a DNA-intercalating analog of daunorubicin that has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II.

Idarubicin hydrochloride in combination with cytarabine is indicated for the treatment of AML.

For additional information on idarubicin, please refer to the prescribing information.

1.4.4. Clinical Data for 7 + 3 Regimen

The standard induction regimen used for AML patients appropriate for intensive treatment is based on cytarabine plus an anthracycline. 7 + 3 induction chemotherapy is one of the most commonly used chemotherapy regimens for intensive treatment. In most studies, using this combination, 60% to 70% of patients with all-comers AML achieved CR {National Comprehensive Cancer Network (NCCN) 2020}. However, in *TP53*-mutated AML, the response rate with 7 + 3 chemotherapy or similar intensive chemotherapy results in a much lower CR rate (28%) with the median OS of 4.1 to 6.8 months {Kadia 2016, Rucker 2012}.

1.5. Rationale for This Study

Patients with *TP53*-mutated AML have very poor prognosis and are largely incurable both with intensive treatment and non-intensive therapies. The majority of patients previously untreated for AML are > 60 years of age. Due to age-related comorbidities, these patients often are ineligible for aggressive induction chemotherapy and hematopoietic SCT due to a significantly increased risk of treatment-related mortality. Instead, SOC for these patients is treatment with HMAs (eg, azacitidine), which have a lower risk of toxicity. However, these treatments are rarely curative and provide a treatment benefit of a median OS around only 10 months {Dombret 2015}. Venetoclax in combination with HMA or low-dose cytarabine was recently approved under the accelerated approval pathway by the US FDA, offering an efficacious alternative to HMAs alone. Despite these advances, AML patients harboring a *TP53* mutation have a particularly poor prognosis and are refractory to available therapies. To this point, median survival in *TP53* mutant AML patients ineligible for intensive induction chemotherapy is only about 5 to 7 months {DiNardo 2019} with similar outcomes in patients treated with intensive chemotherapy {Kadia 2016, Rucker 2012}. Thus, there is intense interest to improve the current SOC with therapies that augment antileukemic activity in previously untreated AML patients harboring a *TP53* mutation.

Given the encouraging preliminary efficacy demonstrated by magrolimab + azacitidine in previously untreated *TP53* mutant AML patients in the 5F9005 study, the magrolimab in combination with azacitidine provides a potential benefit in this patient population and is therefore the appropriate experimental arm. The control arm of venetoclax + azacitidine for non-intensive therapy is selected based on this combination being the current or emerging SOC therapy option for this patient population. This selection rationale is based on the fact that venetoclax + azacitidine is the current SOC option in the US based on accelerated approval by the FDA in 2018 for untreated AML patients who are ineligible for intensive induction

chemotherapy (inclusive of *TP53* mutation status). Furthermore, results from VIALE-A, a global randomized Phase 3 study comparing venetoclax + azacitidine compared with azacitidine + placebo has demonstrated OS superiority of venetoclax + azacitidine compared to azacitidine monotherapy in untreated AML patients who are ineligible for intensive induction chemotherapy {DiNardo 2020b}. Therefore, venetoclax + azacitidine is the recommended treatment option for this population in several region-specific practice guidelines. Venetoclax + HMA or cytarabine is a preferred regimen in the US {National Comprehensive Cancer Network (NCCN) 2020}. In Europe, venetoclax + HMA or cytarabine, while not yet approved, is considered superior to currently available first-line treatments, with a class IIIA evidence recommendation {Heuser 2020}. Venetoclax in combination with azacitidine for treatment of previously untreated AML patients who are ineligible for intensive induction chemotherapy is anticipated to be approved shorted in the EU as well as other regions. For patients who are appropriate for intensive chemotherapy, the most widely used SOC is 7 + 3 chemotherapy {Dohner 2017, National Comprehensive Cancer Network (NCCN) 2020}.

1.6. Rationale for Dose Selection of Magrolimab

The rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK-pharmacodynamic data, and modelling and simulation analyses based on data obtained from all ongoing and completed clinical studies with magrolimab in patients with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab (SCI-CD47-001) in patients with solid tumors and lymphomas, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. The use of an initial 1 mg/kg priming dose was integrated into the dosing regimen to mitigate the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged RBCs that are sensitive to CD47 blockade and triggers reticulocytosis of young RBCs that are not affected by CD47 blockade {Chen 2018}. Utilizing a priming dose leads to an initial, transient, and mild anemia that generally normalizes back to baseline over several weeks, even in the presence of repeated therapeutic doses of magrolimab {Advani 2018, Liu 2015a, Sikic 2019}. The maximum dose of 45 mg/kg has an acceptable safety profile, and no MTD was identified in this study. In Studies SCI-CD47-002 and 5F9005 in patients with AML/MDS, magrolimab was administered as a monotherapy at doses of up to 30 mg/kg twice weekly and in combination with azacitidine at doses of up to 30 mg/kg once weekly. In these studies, no significant dose-limiting toxicity was observed, and magrolimab had an acceptable safety profile over the tested dose range up to a maximum of 30 mg/kg twice a week. Furthermore, in these 2 studies, an intrapatient dose escalation approach was followed; after the priming dose, the patients received doses of 15 mg/kg on Day 8 during Week 2, after which the dose was escalated to 30 mg/kg on Day 11 and then weekly thereafter. This was based on nonclinical data indicating enhanced safety of intrapatient dose escalation. In Studies 5F9003 and 5F9004, magrolimab, in combination with rituximab and cetuximab, respectively, was found to have an acceptable safety profile at doses up to 45 mg/kg every week followed by every other week. The proposed dosing regimen of magrolimab in this study is expected to have an acceptable safety profile based on the entirety of safety data in multiple oncology populations including the MDS/AML population, both as a monotherapy and in combination with other tumor targeted antibodies and chemotherapeutics.

In Study SCI-CD47-002 and Study 5F9005, CD47 receptor occupancy (RO) by magrolimab was tested at baseline and at multiple time points on treatment, on both peripheral blood and bone marrow cells, including leukemic blasts. A PK-pharmacodynamics model linking dose exposure and blood and bone marrow RO was developed and described these data well. Simulations with the model predicted that > 90% RO would be achieved in the bone marrow cells at the magrolimab dosing regimen proposed in this study. This level of RO is typically associated with maximal efficacy for all immune-oncology antibodies. Therefore, the proposed dose regimen is expected to maximize efficacy in the MDS patient population. CCI

Based on results from the Phase 1b study of magrolimab in MDS and AML (Study 5F9005), the current study is designed to employ the same intrapatient dose escalation regimen for magrolimab in combination with azacitidine in treatment-naive patients with AML to mitigate on-target toxicities such as anemia and other toxicities observed in nonclinical AML models. The intrapatient dose escalation regimen uses initial twice-weekly dosing at a starting magrolimab dose of 1 mg/kg for Week 1 (Days 1 and 4), with escalation to 15 mg/kg on Day 8 and 30 mg/kg on Days 11, 15, and 22 of Cycle 1. In Cycle 2, the dose is 30 mg/kg weekly (Days 1, 8, 15, and 22), thereafter. In Cycle 3 and beyond, the dose is 30 mg/kg every 2 weeks (Q2W) on Days 1 and 15. Treatment should be continued until disease progression, relapse, loss of clinical benefit, or unacceptable toxicities occur. The strategy of intrapatient dose escalation was found to result in both mitigation of acute toxicities seen in nonclinical models and in expected RBC toxicities that were manageable for this patient population.

In summary, the proposed dose regimen has been shown to have an acceptable safety profile in multiple oncology patient populations, including MDS and AML patients. Based on PK-pharmacodynamics modelling, the proposed dose is predicted to result in optimal efficacy in this population. Further increases in dose beyond 30 mg/kg are not predicted to result in increased efficacy.

1.7. Risk/Benefit Assessment for the Study

Anemia, neutropenia, thrombocytopenia, and infections are known adverse drug reactions associated with both azacitidine and magrolimab. The monitoring and management guidelines for these potential overlapping toxicities are provided in Section 5.10.1. Based on the high frequency of disease-related anemia in AML patients and the ability to safely manage patients with anemia on magrolimab with transfusions in the 5F9005 study in AML patients, the potential overlapping toxicity of anemia can be managed to ensure patient safety in this study. Furthermore, more than 52 unfit AML patients, including 34 *TP53* mutant patients have been treated with magrolimab + azacitidine, in which the safety profile is generally comparable to azacitidine monotherapy. In addition, specific clinical and laboratory monitoring of magrolimab and azacitidine-related toxicities will be implemented to closely monitor potential AEs.

Magrolimab alone or in combination with azacitidine will be investigated in previously untreated AML patients. The nonclinical evidence of magrolimab activity (alone or in combination with azacitidine), the safety profile of magrolimab + azacitidine in AML patients, and preliminary clinical efficacy suggest that magrolimab has an acceptable risk-benefit profile for AML patients with *TP53* mutations.

The potential risks and mitigations associated with patients being unable to attend study visits as a result of a pandemic have been identified for this study and are described in Appendix 3. Given the risk mitigation measures that are being implemented, the expected benefit-risk assessment to the patient remains unchanged.

1.8. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are provided in Table 1.

Table 1 Study Objectives and Endpoints

Objective	Endpoint
Primary:	
To compare the efficacy of magrolimab + azacitidine versus venetoclax + azacitidine in patients with previously untreated *TP*53 mutant acute myeloid leukemia (AML) who are appropriate for non-intensive therapy as measured by overall survival (OS).	Overall Survival in the Stratum of Patients Appropriate for Non-intensive Therapy: The OS is measured from the date of randomization to the date of death from any cause. Those whose deaths are not observed during the study will be censored at their last known alive date.
Secondary:	
To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients with previously untreated *TP*53 mutant AML as measured by OS.	Overall Survival in All Patients: The OS is measured from the date of randomization to the date of death from any cause. Those whose deaths are not observed during the study will be censored at their last known alive date.
To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients as measured by event-free survival (EFS).	Event-Free Survival in All Patients: The EFS is defined as time from the date of randomization to the earliest date of documented relapse from CR, treatment failure (defined as failure to achieve CR within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or up to 2 months of treatment with 7 + 3 chemotherapy), or death from any cause. Response assessments or death post SCT or new anti-AML therapies will be included. Those who are not observed to have one of these events during the study will be censored at the date of their last response assessment with clear documentation of no relapse during the study. The date of randomization will be assigned as the event date for patients with treatment failure.
To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy as measured by rate of complete remission (CR) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.	Rate of CR within 6 months in All Patients (2 months for patients receiving 7 + 3 chemotherapy): The rate of CR is the proportion of patients who achieve a CR, including CR without minimal residual disease (CR_{MRD-}) and CR with positive or unknown minimal residual disease ($CR_{MRD+/unk}$) within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of treatment with 7 + 3 chemotherapy, as defined by investigators based on European LeukemiaNet (ELN) 2017 AML with modifications (Appendix 6), while on study prior to initiation of any new anti-AML therapy or SCT.

Objective	Endpoint
To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy as measured by rate of CR without minimal residual disease (CR_{MRD-}) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.	Rate of CR without Minimal Residual Disease within 6 months in All Patients (2 months for patients receiving 7 + 3 chemotherapy): The rate of CR_{MRD-} is the proportion of patients who achieve a CR_{MRD-} within 6 months treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of treatment with 7 + 3 chemotherapy, as defined by investigators based on ELN 2017 AML with modifications (Appendix 6), while on study prior to initiation of any new anti-AML therapy or SCT.
To compare the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy in all patients as measured by the rate of CR + complete remission with partial hematologic recovery (CRh) within 2 months of treatment for patients treated with 7 + 3 chemotherapy and within 6 months of treatment for other patients.	Rate of CR + CRh within 6 months in All Patients (2 months for patients receiving 7 + 3 chemotherapy): 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 6) within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of treatment with 7 + 3 chemotherapy while on study prior to initiation of any new anti-AML therapy or SCT.
To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy.	Duration of Complete Remission: The DCR is measured from the time the assessment criteria are first met for CR (including CR_{MRD-} and $CR_{MRD+/unk}$) within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of treatment with 7 + 3 chemotherapy 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. If patients start taking new anti-AML therapies (excluding maintenance therapy) before relapse, the DCR will be censored at the last response assessment before the initiation of the new anti-AML therapies.
To evaluate the duration of CR + CRh in patients who achieved CR or CRh within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy.	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 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of treatment with 7 + 3 chemotherapy 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. If patients start taking new anti-AML therapies (excluding maintenance therapy) before relapse, the duration of CR + CRh will be censored at the last response assessment before the initiation of the new anti-AML therapies.

Objective	Endpoint
To assess the safety and tolerability of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy.	Incidence of Grade ≥ 3 treatment-emergent adverse events Incidence of Grade ≥ 3 treatment-emergent laboratory abnormalities
To evaluate the pharmacokinetics and immunogenicity of magrolimab.	Serum concentration of magrolimab Rate of anti-magrolimab antibody incidence
CCI	

Objective	Endpoint
CCI	CCI

Objective	Endpoint
CCI	

Objective	Endpoint
	CCI

3. STUDY DESIGN

3.1. Endpoints

The endpoints of this study are described in Table 1.

3.2. Study Design

This is a Phase 3, randomized, open-label, multicenter study comparing magrolimab + azacitidine and venetoclax + azacitidine (for patients who are appropriate for non-intensive therapy) or 7 + 3 chemotherapy (for patients who are appropriate for intensive therapy) in patients with previously untreated *TP53* mutant AML. Approximately 346 patients will be randomized in 1:1 ratio to receive either magrolimab + azacitidine (experimental arm) or physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy (control arm). Randomization will be stratified by 3 factors: 1) appropriateness for non-intensive therapy versus intensive therapy; 2) age (< 75 years, ≥ 75 years); 3) geographic region (US sites, outside the US sites). The primary endpoint of this study is OS in the stratum of patients appropriate for non-intensive therapy and the key secondary endpoint will be OS in all patients. The primary analysis of OS will be conducted when 171 deaths have occurred in the stratum of patients appropriate for non-intensive therapy. An interim futility analysis and an interim superiority analysis will be conducted separately after approximately 69 and 128 deaths (40% and 75% of the expected 171 deaths, respectively) in the stratum of patients appropriate for non-intensive therapy have occurred.

In the event the study meets futility, the sponsor may decide to terminate the study, and recommend patients receiving treatment transition to SOC therapy. The current study met futility and sites were informed of the outcome and sponsor's decision in a communication in September 2023. Due to the study having met futility, patients are recommended to transition to SOC therapy. If an investigator believes that continued treatment with magrolimab + azacitidine is in the best interest of their patient(s), Gilead will continue to provide study drug, with a reduced schedule of assessments, pending final study closure; if an investigator believes that continued treatment with venetoclax + azacitidine is in the best interest of their patient(s), and the combination is not available locally as SOC, Gilead may continue to provide drug, pending final study closure.

Patient participation will include CCI prescreening component, screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment, during which time the patient's eligibility and baseline characteristics will be determined. Patients will receive study treatment per the dose schedule in Table 21, Table 22, Table 23, and Table 29. No cross-over between arms is allowed. Study treatment should be continued until disease progression, relapse, loss of clinical benefit, or unacceptable toxicities occur. In case patients discontinue the study treatment due to reasons other than disease progression or relapse, patients will be followed for response assessments until documented disease progression or relapse or initiation of new anti-AML therapy excluding SCT and maintenance. For patients who discontinue the study treatment to receive an SCT, follow-up for response assessment and collection of bone

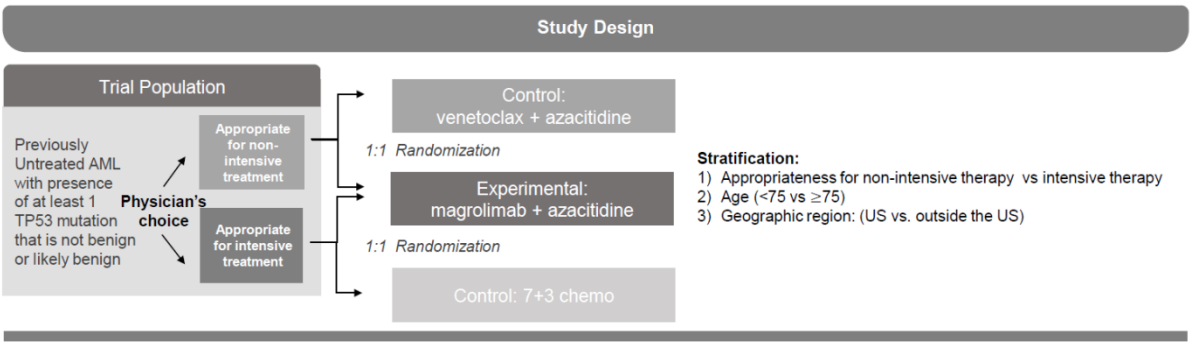
marrow biopsy/aspirate results will continue every 12 weeks from the date of SCT until documented disease progression or relapse or initiation of new anti-AML therapy (excluding maintenance therapy). Then patients will be observed for survival until death, withdrawal of consent, lost to follow-up, or the end of the study, whichever occurs first.

In the event the study meets futility, and the sponsor decides to terminate the study, all patients who discontinue study treatment for any reason will not be followed for response or survival.

Treatment with magrolimab or venetoclax as single agent is not permitted. Patients who discontinue magrolimab + azacitidine, or venetoclax + azacitidine, 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.

The study schematic is presented in Figure 1.

Figure 1. Study Schema



3.3. Study Treatments

Table 2. Dosing and Schedule for Magrolimab and Azacitidine Experimental Arm

Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
	Cycle 1	Cycle 2	Cycle 3+
Azacitidine 75 mg/m^2 SC or IV[a]	Days 1–7 or Days 1–5 and 8, 9[b]	Days 1–7 or Days 1–5 and 8, 9[b]	Days 1–7 or Days 1–5 and 8, 9[b]
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 x 5 weekly 30 mg/kg dose		
Magrolimab 30 mg/kg IV (over 2 hours)	Q2W beginning 1 week after the 5 weekly 30 mg/kg dose		

IV = intravenous; PO = orally; Q2W = every 2 weeks; QW = once a week; SC = subcutaneous
a Azacitidine administered per region-specific labeling.
b Or any other alternative schedule, as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.

Table 3. Dosing and Schedule for Venetoclax and Azacitidine Control Arm

Control Arm	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
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[b]	Days 1–7 or Days 1–5 and 8–9[b]	Days 1–7 or Days 1–5 and 8–9[b]

IV = intravenous; SC = subcutaneous
a Azacitidine administered per region-specific labeling.
b Or any other alternative schedule, as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.

Table 4. Dosing and Schedule for 7 + 3 Chemotherapy Control Arm

Control Arm (7 + 3)	Drug/Dose/Route	7 + 3 Induction	5 + 2 Induction, if needed (after C1D15 bone marrow assessment)
Induction	Daunorubicin 60 mg/m^2 IVP or Idarubicin 12 mg/m^2 IV	Days 1–3	Days 1-2
	Cytarabine 100 or 200 mg/m^2 Continuous Infusion	Days 1–7	Days 1–5
Consolidation	Cytarabine (HiDAC) 1500 or 3000 mg/m^2 IV[a]	Every 12 hours on Days 1, 3, and 5 (up to 4 cycles)	
	Steroidal Eye Drops	As per institutional standard	

C1D15 = Cycle 1 Day 15; HiDAC = high-dose cytarabine; IV = intravenous; IVP = intravenous peripheral
a In some cases, patients ≥ 60 years of age can receive 1000 mg/m^2 based on local practice.

The schedules of assessments are provided in Appendix 2.

3.4. Duration of Treatment

For patients treated with magrolimab + azacitidine or venetoclax + azacitidine, cycle length is 28 days and all patients without evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity should continue on study treatment unless they meet study treatment discontinuation criteria.

For patients treated with 7 + 3 chemotherapy (with or without 5 + 2 chemotherapy as indicated), induction followed by up to 4 cycles of consolidation with high-dose cytarabine (HiDAC) should be administered unless study treatment discontinuation criteria are met.

Patients will be discontinued from study treatment prior to starting SCT.

3.5. Discontinuation Criteria

The patient's health and welfare are the primary consideration in any determination to discontinue study treatment. In general, patients are expected to remain on study treatment until at least completion of Cycle 6 for azacitidine or venetoclax + azacitidine treatment, and through induction 7 + 3 chemotherapy treatment; however, patients (or a legally acceptable representative) may decline to continue receiving study treatment at any time during the study. Such patients will continue to participate in follow-up study visits unless they withdraw completely from the study.

Reasons for discontinuation of study treatment must include, but are not limited to, the following:

- Disease progression (including treatment failure and relapse)
- Unacceptable toxicity
- Loss of clinical benefit
- Death
- Pregnancy during the study
- Patient request, with or without a stated reason
- Patient noncompliance
- Initiation of anti-AML therapy
- SCT
- Investigator or treating physician decision
- Protocol violation
- Lost to follow-up
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB)/independent ethics committee (IEC)

Although disease progression is considered a sufficient reason for discontinuing a patient from study treatment, given the delayed treatment benefit commonly seen in immune therapies, the investigator is advised to continue to treat the patient until the investigator considers the study treatment to be no longer clinically beneficial to the patient, or the change of disease state renders the patient unacceptable for further treatment in the judgment of the investigator. All patients must be followed through completion of all study treatment.

If patients remain on study drugs beyond disease progression, a second bone marrow assessment, along with required laboratory tests for response assessment, should be done within 4 weeks. If disease progression is confirmed at the second bone marrow assessment, the patient should be discontinued from the study treatment.

Patients who discontinue study treatment are to return for an end of treatment (EOT) visit for evaluation of safety within 7 days of their last dose or the decision to end study treatment, whichever occurs later. In addition, patients are to have a safety follow-up telephone call 30 days and 70 days (± 7 days) after their last dose of study treatment. When a serious adverse event (SAE) or treatment-related AE is reported during the telephone call, the patient should come to the clinic for physical examination and blood tests, if clinically needed. Follow-up for ongoing SAEs or treatment-related AEs after the safety follow-up visit/call will stop if a patient begins another anti-AML therapy.

All patients who discontinue study treatment for reasons other than disease progression or relapse will participate in long-term follow-up for disease response until documented disease progression/relapse or until start of new anti-AML therapy, unless the patient withdraws consent for such follow-up and withdraws completely from the study. For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of bone marrow biopsy/aspirate results will continue until documented relapse occurs. When considering SCT, note that no significant magrolimab-related transplant complications have been observed in patients who have achieved a response and undergone SCT in an ongoing magrolimab study in AML and MDS (Study 5F9005); however, a 4-week wash-out period for magrolimab is recommended prior to SCT.

All patients will be followed for survival until the following events occur: death, withdrawal of formal consent, loss to follow-up, or the end of the study, whichever occurs first. For any patient who dies during this follow up period, the immediate cause of death must be reported to the sponsor. In the event the study meets futility, and the sponsor decides to terminate the study, all patients who discontinue study treatment for any reason will not be followed for survival; patients should have an EOT visit (within 7 days after last dose or EOT decision, whichever occurs later ± 7 days) and 30-day safety follow-up visit (± 7 days) after last dose, but the 70-day safety follow-up visit, post-treatment response assessments, long -term follow-up, long-term follow-up after SCT, and survival follow-up are not required. A final contact by telephone for patients who discontinued study therapy and are in long-term or survival follow-up prior to study termination for futility will be made.

The assessments to be performed at each of the posttreatment visits are listed in Table 24 and Table 28.

3.6. End of Study

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual Patients: Patients are considered to have reached the end of the study when they are no longer followed for long-term or survival follow-up due to the following reasons: death, loss to follow-up, withdrawal of consent, or sponsor termination of study.

3.7. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for survival and AEs as specified in Table 24 or Table 28.

For patients who start new anti-AML therapy (other than SCT and maintenance therapy) before a relapse, efficacy status will be collected until relapse. For patients discontinuing study treatment in the event of study termination due to futility, post-study anti-AML therapy status will not be collected and response assessments will no longer be required.

3.8. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), local and/or specialty (eg, PK, ADA, and/or pharmacodynamics) laboratory testing, and/or additional biomarker testing.

3.9. Biomarker Samples to Address the Study Objectives

Peripheral blood, bone marrow aspirate and trephine biopsy samples will be collected from all patients who have provided consent to participate in this study. They may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response, including efficacy and/or AEs, dosage selection, and to better understand the biological pathways, biology of *TP53* mutant AML or AML in general or the validation of a companion diagnostic for *TP53* mutant AML for magrolimab. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays described below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Blood and bone marrow samples will be collected to measure biomarkers which may include but will not be limited to the presence of or changes to immune cell populations, secreted protein factors, the expression of cell surface markers on either tumor cells or cells of the tumor microenvironment, and genetic mutations in tumor cells or subclones of tumor cells at the time points listed in the schedule of assessments (Table 20, Table 21, Table 23, and Table 24).

Samples to be collected for genomic research will be used to identify or validate genetic markers that may increase our knowledge and understanding of the biology of the study disease and related diseases, and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug

absorption and disposition. These specimens may also be used to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. Genomics research may include sequencing of genetic material derived from both cancer cells and normal cells.

The specimens collected for CCI future research will be destroyed no later than 15 years after the end of study or per country requirements.

In the event the study meets futility, and the sponsor decides to terminate the study, additional peripheral blood and bone marrow samples and buccal swab for biomarker research will no longer be collected.

CCI [redacted]

3.9.2. *TP53* Mutation Testing and Companion Diagnostic Development

Biological specimens will be collected from all patients who have provided consent to participate in this study, or the prescreening phase, to determine the mutational status of the *TP53* gene in leukemic cells and support diagnostic development using a next-generation sequencing (NGS) test. Patients will be enrolled based on *TP53* mutational status using a either Laboratory

Developed Test assay that has been analytically validated in accordance with Clinical Laboratory Improvement Amendments (CLIA)/Clinical Laboratory Standards Institute regulations in a CLIA-accredited central laboratory or an approved local laboratory using NGS on bone marrow aspirate (after central review of test results). The test in the EU central laboratory will carry a CE Mark. This central testing will be performed regardless of whether *TP53* status has been assessed as part of previous clinical diagnosis or an approved local laboratory using NGS. Collected samples from patients who prescreen, or screen fail due to a lack of *TP53* mutation may be stored and used for validation of a *TP53* companion diagnostic. Residual samples will be banked to validate diagnostic tests for *TP53* status for in vitro diagnostic development.

Samples collected for *TP53* mutational assessments will be destroyed no later than 15 years after the end of study or per country requirements.

In the event the study meets futility, and the sponsor decides to terminate the study, samples will not be used for validation of a *TP53* companion diagnostic or banked to validate diagnostic tests for *TP53* status for in vitro diagnostic development.

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

The study enrollment may stop after 228 patients in the non-intensive group or approximately 346 of all patients are enrolled, whichever occurs later. Approximately 346 patients will be enrolled in the study, with approximately 173 patients in the experimental arm and 173 patients in the control arm. In the event the study meets futility, and the sponsor decides to terminate the study, no further patients will be enrolled.

4.1.1. Patient Replacement

There will be no patient replacement on this study.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Patients with confirmation of AML by World Health Organization criteria, previously untreated for AML, and who have presence of:

   a) At least 1 *TP53* gene mutation that is not benign or likely benign based on evaluation by either central laboratory or an approved local laboratory (after central review of the bone marrow *TP53* mutation NGS test results)

   b) Biallelic 17p deletions, loss of both 17p alleles, based on locally evaluated cytogenetics/karyotype/fluorescence in situ hybridization (FISH) report.

2) Patients with white blood cell (WBC) count $\leq 20 \times 10^3/\mu L$ prior to randomization. If the patient's WBC is $> 20 \times 10^3/\mu L$ prior to randomization, the patient can be enrolled, assuming all other eligibility criteria are met. However, the WBC should be $\leq 20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each magrolimab dose for the first 4 weeks (if the patient is randomized to the experimental arm).

   NOTE: Patients can be treated with hydroxyurea and/or leukapheresis throughout the study or prior to randomization to reduce the WBC to $\leq 20 \times 10^3/\mu L$ to enable eligibility for study drug dosing.

3) The hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment.

   NOTE: Transfusions are allowed to meet hemoglobin eligibility (see Section 7.8.1).

4) Patient has provided informed consent.

5) Patient is willing and able to comply with clinic visits and procedure outlined in the study protocol.

6) Male or female ≥ 18 years of age.

7) Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 except for patients less than 75 years of age and appropriate for non-intensive treatment. For these patients, the ECOG performance status score may be 0 to 3.

8) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft-Gault formula (Appendix 11).

9) Adequate cardiac function as demonstrated by:

   a) Lack of symptomatic congestive heart failure and clinically significant cardiac arrhythmias and ischemic heart disease

   b) Left ventricular ejection fraction (LVEF) > 50% for patients appropriate for intensive therapy

10) Adequate liver function as demonstrated by:

   a) Aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN)

   b) Alanine aminotransferase (ALT) ≤ 3.0 x ULN

   c) Total bilirubin ≤ 1.5 x ULN, or primary unconjugated bilirubin ≤ 3.0 x ULN if patient has a documented history of Gilbert's syndrome or genetic equivalent.

11) Pretreatment blood cross-match completed (as detailed in Section 7.8.1).

12) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.

13) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (aspirate and trephines), unless not feasible as determined by the investigator and discussed with the sponsor.

4.3. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Subjects that are unable to give consent. To give consent, the individual concerned must be of legal age and be able to understand the nature, significance and implications of the clinical study and form their rational intentions in light of these.

2) Positive serum pregnancy test (Appendix 5).

3) Breastfeeding female.

4) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.

5) Prior treatment with any of the following:

   a) CD47 or SIRPα-targeting agents

   b) Antileukemic therapy for the treatment of AML (eg, HMA, low dose cytarabine and/or venetoclax), excluding hydroxyurea.

      NOTE: Patients with prior MDS who have not received prior HMAs or chemotherapeutic agents for MDS are allowed on study. Other prior MDS therapies including, but not limited to, lenalidomide, erythroid stimulating agents, or similar RBC-direct therapies, are allowed. Localized non-central nervous system (CNS) radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with luteinizing hormone-releasing hormone (LHRH) agonists for prostate cancer, hormonal therapy or maintenance for breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are also not criteria for exclusion.

   c) Patients who are appropriate for intensive treatment but who have been previously treated with maximum cumulative doses of idarubicin and/or other anthracyclines and anthracenediones will be excluded.

6) Patients receiving any live vaccine within 4 weeks prior to initiation of study treatments.

7) For patients appropriate for intensive therapy, patients treated with trastuzumab within 7 months prior to initiation of study treatments.

8) Current participation in another interventional clinical study.

9) Known inherited or acquired bleeding disorders.

10) Patients appropriate for non-intensive therapy who have received treatment with strong and/or moderate cytochrome P450 enzyme (CYP) 3A inducers within 7 days prior to the initiation of study treatments.

11) Patients appropriate for non-intensive therapy who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days prior to the initiation of study treatment.

12) Patients appropriate for non-intensive therapy, who have malabsorption syndrome or other conditions that preclude enteral route of administration.

13) Clinical suspicion of active CNS involvement with AML.

14) Patients who have acute promyelocytic leukemia.

15) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV.

16) Second malignancy, except MDS, treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapies and have had no evidence of active malignancy for at least ≥ 1 year.

    NOTE: Patients on maintenance therapy alone who have no evidence of active malignancy for at least ≥ 1 year are eligible.

17) Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or HIV infection in medical history.

18) Active HBV, and/or active HCV, and/or HIV following testing at screening:

    a) Patients who test positive for hepatitis B surface antigen (HBsAg). Patients who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

    b) Patients who test positive for HCV antibody. These patients will require HCV RNA quantitative PCR for confirmation of active disease.

    c) Patients who test positive for HIV antibody.

    d) Patients not currently receiving antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Patients who meet randomization eligibility criteria will be randomized in a 1:1 ratio using an integrated web response system to either the experimental arm or the control arm. The first dose of study drugs should be administered within 72 hours of randomization.

To achieve balance between treatment arms, randomization will be stratified according to the following factors:

- appropriateness for non-intensive therapy versus intensive therapy
- age (< 75 years, ≥ 75 years)
- geographic region (US sites, outside the US sites)

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study. A study data access plan will outline data access by various functions within the sponsor study team.

5.2. Description and Handling of Magrolimab

5.2.1. Formulation

Magrolimab is formulated as a sterile, clear, preservative-free liquid intended for IV administration containing 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20 at pH of 5.0. Each vial is manufactured to ensure a deliverable volume of 10 mL containing 200 mg of magrolimab at a concentration of 20 mg/mL.

5.2.2. Packaging and Labeling

Magrolimab is supplied in single-use, 10 mL glass vials with coated elastomeric stoppers and aluminum crimp overseals with a flip-off cap.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

Magrolimab should be stored at 2 C to 8 C (36 F to 46 F). Magrolimab should not be frozen. Protect from light during storage. Do not shake. Storage conditions are specified on the label. Until dispensed to the patients, study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Azacitidine

5.3.1. Formulation

Azacitidine is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.3.2. Packaging and Labeling

Commercial product of azacitidine 100 mg in a single-use vial will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.3.3. Storage and Handling

Commercial product of azacitidine will be used for the study. Further information regarding storage and handling are available in the local prescribing information for commercial products.

5.4. Description and Handling of Venetoclax

5.4.1. Formulation

Venetoclax is commercially sourced. Information regarding the formulation can be found in the current prescribing information {VENCLEXTA 2020}.

5.4.2. Packaging and Labeling

Commercially available venetoclax will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.4.3. Storage and Handling

Commercial product of venetoclax will be used for the study. Further information regarding storage and handling are available in the local prescribing information for commercial products.

5.5. Description and Handling of Cytarabine

5.5.1. Formulation

Cytarabine is commercially sourced. Information regarding the formulation can be found in the current prescribing information

5.5.2. Packaging and Labeling

Commercially available cytarabine will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.5.3. Storage and Handling

Commercial product of cytarabine will be used for the study. Further information regarding storage and handling are available in the local prescribing information for commercial products.

5.6. Description and Handling of Daunorubicin

5.6.1. Formulation

Daunorubicin is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.6.2. Packaging and Labeling

Commercially available daunorubicin will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.6.3. Storage and Handling

Commercial product of daunorubicin will be used for the study. Further information regarding storage and handling are available in the local prescribing information for commercial products.

5.7. Description and Handling of Idarubicin

5.7.1. Formulation

Idarubicin is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.7.2. Packaging and Labeling

Commercially available idarubicin will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.7.3. Storage and Handling

Commercial product of idarubicin will be used for the study. Further information regarding storage and handling are available in the local prescribing information for commercial products.

5.8. Dosage and Administration

The magrolimab and azacitidine dosing regimens for the experimental arm are presented in Table 2.

The treatment with magrolimab+azacitidine will be administered as inpatient/outpatient based on local guidelines for treatment of non-intensive treatment/investigator assessment of the patient's clinical status.

Azacitidine will be administered according to region-specific drug labeling, either subcutaneous (SC) or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle. Azacitidine may be administered on an alternative schedule (such as Days 1 to 5, Day 8, and Day 9 of a 28-day cycle) for flexibility and convenience as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days. When administered IV, the total dose of azacitidine (diluted in a 50 to 100 mL infusion bag of either 0.9% sodium chloride injection or lactated Ringer's injection solution) is infused over a period of 10 to 40 minutes (refer to the azacitidine prescribing information for detailed instructions for preparation and administration).

The first dose of study drugs should be administered within 72 hours after randomization.

Patients should be premedicated in accordance with Section 5.9.

Magrolimab, venetoclax, azacitidine, cytarabine, and daunorubicin or idarubicin should be prepared as outlined in the Pharmacy Manual for the study.

For patients taking concomitant CYP3A and P-gp inhibitors, refer to Table 12 for venetoclax dosing and administration.

Prior to initiation of venetoclax, WBC count must be $\leq 20 \times 10^3/\mu L$. Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea and/or leukapheresis throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$.

Venetoclax and azacitidine dosing regimens for the control arm are presented in Table 3. Venetoclax should be administered orally once daily with a meal and water, at approximately the same time each day. Patients should be advised to swallow the tablet whole, and not chew, crush or break the tablets. If a dose is missed and it has been less than 8 hours, patients should be advised to take their dose as soon as possible. If a dose is missed and more than 8 hours has passed, the missed dose should be skipped, and the next dose should be taken at the usual time. If a patient vomits after taking venetoclax, an extra dose should not be taken but rather the next dose should be taken at the usual time. Venetoclax will be dispensed to the patient on Day 1 of each treatment cycle.

The doses of magrolimab, azacitidine, daunorubicin or idarubicin, and cytarabine will be calculated based on actual weight at enrollment (using weight obtained either at screening or on Cycle 1 Day 1) and will remain constant throughout the study, unless there is a > 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a > 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

During the first 4 weeks of treatment, WBC count must be $\leq 20 \times 10^3/\mu L$ prior to each magrolimab dose. Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea (up to 4 g/day) and/or leukapheresis throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$.

Within 24 hours prior to each of the 2 first doses of magrolimab during initial treatment, *all patients* must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

Magrolimab will be administered by IV infusion. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. The reduced infusion time to 2 hours is utilized based on prior data demonstrating majority CD47 RO on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab. When both magrolimab and azacitidine are given on the same visit day, magrolimab will be administered at least 1 hour after the completion of azacitidine administration.

Magrolimab doses will be given twice weekly during priming and escalation (2 weeks), with a window of ± 3 days for each dose; however, **magrolimab doses are not to be given on consecutive days**.

All patients should be monitored hourly during infusion and for 1 hour post infusion for priming, repriming/reescalation, and maintenance doses during the first 4 weeks. Patients should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion-related reactions, which have been observed in previous magrolimab studies. Post infusion monitoring should begin after the infusion is complete. Post infusion monitoring is not required for doses after Day 22. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate. Management of infusion-related reactions is further described in Section 7.8.1.2.

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity (further details about treatment discontinuation in Section 3.5).

5.8.1. Repriming/Reescalation for Magrolimab

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming/re-escalation for magrolimab after a dose delay are provided in Section 5.10.1.1.

5.8.2. 7 + 3 Chemotherapy Administration

The treatment with 7 + 3 chemotherapy will be administered in the inpatient hospital setting.

The treatment plan will consist of daunorubicin at 60 mg/m^2 intravenous peripheral (IVP) or idarubicin 12 mg/m^2 by slow (10 to 15 min) IV injection on Days 1 to 3, and cytarabine at 100 mg/m^2 or 200 mg/m^2 given by continuous IV infusion on Days 1 to 7. In order to determine whether a second induction with 5 + 2 chemotherapy is needed, patients will have a bone marrow examination approximately 15 days after the start of systemic chemotherapy (Induction Cycle 1 Day 15 ± 5 days). At that time, if the cellularity is greater than 20% and the percentage of blasts are greater than 10%, then re-induction with "5 + 2" (daunorubicin at 60 mg/m^2 IVP or idarubicin 12 mg/m^2 by slow IV injection on Days 1 to 2 and cytarabine at 100 mg/m^2 or 200 mg/m^2 given by continuous IV infusion on Days 1-5) will be administered. Patients who achieve blast clearance (bone marrow blast < 5%) and a count recovery of absolute neutrophil count (ANC) > 1000 and platelet count > 75,000, will receive up to 4 cycles of consolidation with cytarabine (1500 or 3000 mg/m^2 over 3 hours every 12 hours on Days 1, 3, and 5 based on local guidelines/institutional practice. In some cases, patients ≥ 60 years of age can receive 1000 mg/m^2 based on local practice). Consolidation should occur between 1 to 4 weeks following count recovery of ANC > 1000 and platelet > 75,000 after induction and remission (must be confirmed by laboratory assessments to document maximal response) is established. Prior to starting each consolidation cycle, a count recovery of ANC > 1000 and platelet count > 75,000 should be established. If the patient is not able to meet the requirements to continue the treatment schedule, the patient will enter EOT (Table 21). Stem cell transplantation (autologous or allogeneic) may be performed as per institutional standards for consolidation.

Table 5. 7 + 3 Regimen Description

Induction			
Agent	**Dose**	**Route**	**Schedule**
Daunorubicin (7 + 3) or Idarubicin (7 + 3)	60 mg/m^2 12 mg/m^2	IVP 10-15 min IV	Days 1-3
Cytarabine (7 + 3)	100 or 200 mg/m^2	Continuous Infusion	Days 1-7
If 5 + 2 Regimen is needed (after Cycle 1 Day 15 bone marrow assessment)			
Daunorubicin (5 + 2) or Idarubicin (5 + 2)	60 mg/m^2 12 mg/m^2	IVP 10-15 min IV	Days 1-2
Cytarabine (5 + 2)	100 or 200 mg/m^2	Continuous Infusion	Days 1-5
Consolidation (up to 4 cycles)			
Cytarabine (HiDAC)	1500 or 3000 mg/m^2 [a]	IV	Every 12 hours on Days 1, 3, 5
Steroidal Eye Drops	As per institutional standard		

IV = intravenous; IVP = intravenous peripheral
a In some cases, patients ≥ 60 years of age can receive 1000 mg/m^2 based on local practice.

5.9. Premedication and Prophylaxis

Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming. Premedications should include oral acetaminophen 650 to 1000 mg, oral or IV diphenhydramine 25 to 50 mg, and IV dexamethasone 4 to 20 mg or comparable regimen. For patients who do not experience an infusion-related reaction (IRR) with the first 2 doses of magrolimab, steroid pretreatment can be discontinued at investigators' discretion. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion (Section 7.8.1.2).

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

Prophylactic antibiotics for the prevention of neutropenic fever are not required on study for magrolimab+azacitidine or venetoclax+azacitidine combination treatments but may be administered per local institutional guidelines or investigator discretion.

For 7 + 3 chemotherapy, antibiotic prophylaxes and prophylactic measures for tumor lysis syndrome are to be administered per local institutional guidelines.

5.10. Dose Modification and Delays

5.10.1. Magrolimab+Azacitidine (Experimental Arm)

5.10.1.1. Magrolimab Treatment Delays

A treatment delay is defined as a non–protocol specified interruption from treatment.

Clinical safety and PK data from dose finding studies in both solid tumor and hematologic malignancies have not demonstrated any dose-dependent toxicities associated with magrolimab.

Dose reduction/modification of magrolimab dosing may be allowed in certain circumstances (eg with certain AEs), with approval by the sponsor. If a dose reduction is considered, initial 33% dose reduction should be done (from 30 to 20 mg/kg).

Dose delay guidance for magrolimab due to severe neutropenia is provided below.

- Before achieving remission, for Grade 4 neutropenia (ANC < 500/µL) with or without fever or infection, delay of magrolimab dosing is not recommended. In cases of Grade 4 neutropenia with serious infection, hold magrolimab until the infection has resolved clinically. For serious infections that remain active for 14 or more days, consider discontinuation of magrolimab.

- After achieving remission, for Grade 4 neutropenia (ANC < 500/µL) with fever or infection, and lasting at least 7 days, magrolimab dosing delay should be considered. Upon resolution to Grade ≤ 2, resume magrolimab at the same dose should be considered.

Magrolimab does not need to be dose modified or delayed for Grade 4 thrombocytopenia.

When azacitidine is delayed due to toxicities, magrolimab should continue independently as per magrolimab administration schedule (Table 25). Continuous dosing of magrolimab is needed to maintain efficacious exposures and prolonged delays of greater than 1 week when magrolimab is dosed Q2W have been seen to result in lower clinical efficacy. Magrolimab may be delayed for severe neutropenia or serious infection as discussed above; otherwise, magrolimab may be delayed if other treatment-emergent and/or related AEs occur, and will require approval by the sponsor if the delay is longer than 3 days.

The repriming guidelines presented in Table 6 should be followed for patients with dose delays. In case of repriming, assessments should follow magrolimab repriming table (Table 25).

In the case of repriming, before the administration of the 2 first doses of magrolimab, hemoglobin should be ≥ 9 g/dL. Transfusion is allowed to meet this hemoglobin level.

Table 6. Repriming Guidelines for Magrolimab

Dose of Magrolimab	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	2 weeks
15 mg/kg	2 weeks
30 mg/kg	4 weeks

If planned surgical procedures that are needed for patients on study treatment, magrolimab will be delayed and restarted in accordance with Table 7.

Table 7. Magrolimab Dosing Guidance for Planned Surgical Procedures on Study

Planned Surgical Procedure	Magrolimab Dose Guidance
Minimally invasive procedure (Examples: biopsies [excluding lung/liver], skin/subcutaneous lesion removal, cataract/glaucoma/eye surgery, cystoscopy)	Hold magrolimab dose 3 days prior to procedure and restart after 3 days.
Moderately invasive procedure (Examples: lung/liver biopsy, hysterectomy, cholecystectomy, hip/knee replacement, minor laparoscopic procedures, stent/angioplasty)	Hold magrolimab dose 5 days prior to procedure and restart after 5 days.
Highly invasive procedure (Examples: CNS/spine surgery, major vascular surgery, cardiothoracic surgery, major laparoscopic surgery)	Hold magrolimab dose 7 days prior to procedure and restart after 7 days.

CNS = central nervous system

5.10.1.2. Azacitidine Treatment Delays

Treatment delay of azacitidine may not occur for patients in the initial 28-day period (Cycle 1).

After the initial 28-day period, in the absence of AML (as defined in Section 5.10.1.3.1.2), if hematologic toxicity is observed following azacitidine treatment, the next cycle of treatment should be delayed until platelets are $\geq 50 \times 10^9$/L and neutrophils are $\geq 1.0 \times 10^9$/L or if blood counts are improving from nadir or baseline. If recovery is achieved within 14 days, no dose adjustment is needed. However, if recovery is not achieved within 14 days (Day 42 of the cycle), the dose should be reduced according to the azacitidine dose modification guidelines in Table 8. For nonhematologic AEs ≥ Grade 3 that do not resolve to ≤ Grade 2 or baseline value, dosing will be delayed up to 14 days from onset. If recovery is achieved within 14 days, no dose adjustment is needed. However, if recovery is not achieved within 14 days, the dose should be reduced according to the azacitidine dose modification guidelines in Table 8. Following dose modifications, the cycle duration should return to 28 days. Azacitidine dosing may also be delayed for patients who experience hospitalization due to an AE that may preclude safe administration of azacitidine (eg, intensive care unit admissions, significant bleeding events, severe infections, or other such events).

If ≤ 2 doses of azacitidine are missed during the 7-day dosing period, dosing should continue so that the patient receives the full 7 days of treatment, as long as these additional doses are given within 1 week of the previous dose. If ≥ 3 doses of azacitidine are missed during the 7-day dosing period, the investigator should contact the sponsor, and a dosing decision should be made on an individual case basis.

5.10.1.3. Azacitidine Dose Modifications Guidance

Dose modification of azacitidine may not occur for patients in the initial 28-day period (Cycle 1).

Dose modifications described below are in accordance with the azacitidine prescribing information, with 1 notable exception: while the US prescribing information allows for dose escalation to 100 mg/m^2 after the first 2 cycles, an azacitidine dose of 75 mg/m^2 is planned throughout this study for both treatment arms. Azacitidine dose increases above 75 mg/m^2 are not allowed.

5.10.1.3.1. Dose Modification Due to Hematologic Toxicity

5.10.1.3.1.1. Dose Modifications Due to Hematologic Toxicity in the Presence of AML

Treatment with azacitidine is associated with anemia, neutropenia, and thrombocytopenia. Thus, complete blood count (CBC) will be performed as described in the schedules of assessments and as needed to monitor toxicity. Importantly, these cytopenias are often a result of underlying hematologic disease. It is thus critical to distinguish between cytopenias due to azacitidine compared to underlying disease, so as to not limit potential treatment benefit. Hematologic cytopenias in the presence of AML disease are not defined as hematologic toxicities.

In accordance with this distinction, the dose of azacitidine should not be reduced if hematologic cytopenias are observed in the presence of persistent AML; ie, evidence of the following:

- ≥ 5% blasts in the bone marrow
- blasts with Auer rods
- circulating blasts

Nonhematologic toxicities may require dose modifications independent of the presence of persistent AML, given the clearer distinction of these toxicities relating to azacitidine as opposed to effects of AML. Dose modifications for hematologic toxicity, decreased bone marrow cellularity, and nonhematologic toxicities are described in the sections below.

5.10.1.3.1.2. Dose Modifications Due to Hematologic Toxicity in the Absence of AML

Azacitidine should be dose modified or delayed for hematologic toxicities without evidence of persistent AML (defined in Section 5.10.1.3.1).

If hematologic toxicity is observed following azacitidine treatment, the next cycle of therapy should be delayed for up to 14 days until the platelet count and the ANC have improved. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery is not achieved within 14 days (Day 42 of the cycle), the dose should be reduced according to Table 8. Following dose modifications, the cycle duration should return to 28 days. Patients with a dose reduction will be reassessed after 2 additional cycles per protocol. For patients with persistent cytopenia, treatment should be delayed for up to 14 days (Day 42 of the cycle); if counts have recovered, no further dose modification is needed. If counts have not recovered, then a further dose reduction is recommended, in accordance with Table 8. The reduced dose should be maintained during subsequent cycles unless further toxicity develops (defined in Table 8 as further occurrences). Azacitidine may be re-escalated back to a higher dose if toxicities have improved.

Separate dose modifications for hematologic toxicity are provided in Table 8 for patients who do not have reduced blood counts at baseline (ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L) and who have reduced baseline blood counts (ANC $< 1.5 \times 10^9$/L or platelets $< 75 \times 10^9$/L).

Table 8. Azacitidine Dose Modification for Patients With and Without Cytopenia at Baseline

Nadir Counts		% Dose in the Next Cycle if Recovery[a] is Not Achieved Within 14 Days
ANC ($\times 10^9$/L)	**Platelets ($\times 10^9$/L)**	
Dose Modification for Patients Without Reduced Blood Counts (ANC $\geq 1.5 \times 10^9$/L and Platelets $\geq 75 \times 10^9$/L) at Baseline		
First occurrence		
≤ 1.0 or	≤ 50.0	67% (50 mg/m^2)
Second occurrence[b]		
≤ 1.0 or	≤ 50.0	50% (37.5 mg/m^2)
Third occurrence[b]		
≤ 1.0 or	≤ 50.0	33% (25 mg/m^2)
Dose Modification for Patients with Reduced Blood Counts (ANC $< 1.5 \times 10^9$/L or Platelets $< 75 \times 10^9$/L) at Baseline		
First occurrence		
< 0.5[c] or	< 25[c]	67% (50 mg/m^2)
Second occurrence[b]		
< 0.5[c] or	< 25[c]	50% (37.5 mg/m^2)
Third occurrence[b]		
< 0.5[c] or	< 25[c]	33% (25 mg/m^2)

ANC = absolute neutrophil count; AML = acute myeloid leukemia.

a Recovery is defined as a ≥ 25% recovery in the nadir count.

b After initial dose reduction, patients will be reassessed after 2 additional cycles per protocol, and if persistent cytopenias are observed, a further dose reduction of azacitidine should be considered as outlined.

c No dose adjustment is needed if the baseline blood counts are below an ANC $< 0.5 \times 10^9$/L and/or platelets $< 25 \times 10^9$/L.

Following dose modifications, the cycle duration should return to 28 days.

If per dosing modification Table 8, the patient is eligible to start the cycle, but the cycle is delayed, investigator should contact the medical monitor.

The start of the subsequent cycle should not be delayed beyond 2 weeks if the patient's clinical condition allows safe resumption of the cycle. If the start of the subsequent cycle is delayed beyond 2 weeks, the investigator should contact the medical monitor.

5.10.1.3.1.3. Dose Modifications Due to Decreased Bone Marrow Cellularity in the Absence of AML

Azacitidine alone or in combination with magrolimab may result in a decrease in bone marrow cellularity. No dose modification is required if a decrease in bone marrow cellularity is observed without reduced peripheral blood counts or if persistent AML is still observed (defined in Section 5.10.1.3.1.1). If hypocellularity AND reduced peripheral blood counts are observed, then the azacitidine dose should be modified in accordance with the instructions in Table 9.

Table 9. Azacitidine Dose Modification: Patients With Reduced Bone Marrow Cellularity and Reduced Peripheral Blood Counts

Bone Marrow Cellularity	Azacitidine Dose Instruction if Recovery[b] Is Not Achieved Within 14 Days			
	First Occurrence	Second Occurrence	Third Occurrence	Recovery[b]
≥ 50% decrease from baseline with a cellularity < 30% in the presence of reduced peripheral blood counts[a] OR Decrease to < 15% cellularity with a baseline cellularity > 20% in the presence of reduced peripheral blood counts[a]	Dose reduce azacitidine to 50 mg/m^2 administered Days 1–7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity after 2 cycles	Dose reduce azacitidine to 37.5 mg/m^2 administered Days 1-7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity after 2 cycles	Dose reduce azacitidine to 25 mg/m^2 administered Days 1–7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity within 2 cycles Upon reassessment after 2 cycles, if reduced cellularity persists, then decrease azacitidine dose to 25 mg/m^2 on Days 1–5 per cycle and reassess bone marrow cellularity after 2 cycles	Continue at current azacitidine dose. For subsequent cycles, the azacitidine dose can be escalated up to the next highest dose (ie, escalate to 75 mg/m^2 if initially dose reduced to 50 mg/m^2; escalate to 50 mg/m^2 if previously dose reduced to 37.5 mg/m^2; or escalate to 37.5 mg/m^2 if previously dose reduced to 25 mg/m^2). AND Repeat bone marrow biopsy to assess bone marrow cellularity at the next protocol-defined bone marrow assessment.

ANC = absolute neutrophil count; AML = acute myeloid leukemia

a Reduced peripheral blood counts are defined as ANC < 0.5 × 10^9/L and platelets < 25 × 10^9/L in the absence of AML disease (ie, < 5% bone marrow blasts)

b Recovery in bone marrow cellularity is defined as an increase in bone marrow cellularity ≥ 25% from the nadir, increase in bone marrow cellularity to ≥ 15%, or improvement of peripheral blood counts to ANC > 0.5 × 10^9/L and platelets > 25 × 10^9/L.

Following dose modifications, the cycle duration should return to 28 days.

If per dosing modification Table 9, the patient is eligible to start the cycle, but the cycle is delayed, investigator should contact the medical monitor.

The start of the subsequent cycle should not be delayed beyond 2 weeks if the patient's clinical condition allows safe resumption of the cycle. If the start of the subsequent cycle is delayed beyond 2 weeks, the investigator should contact the medical monitor.

5.10.1.3.2. Dose Modifications Due to Nonhematologic Toxicity Irrespective of Presence of AML

Renal abnormalities ranging from elevated serum creatinine to renal failure have been reported with rare frequency in patients treated with azacitidine. In addition, renal tubular acidosis, defined as a decrease in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L), has been rarely observed. If unexplained reductions in serum bicarbonate (< 20 mmol/L) occur, the azacitidine dose should be reduced by 50% on the next cycle. Similarly, if unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2-fold above baseline values and above the ULN occur, the next cycle should be delayed until values return to normal or baseline, and the azacitidine dose should be reduced by 50%. The reduced dose should be maintained during subsequent cycles unless toxicity develops.

For other azacitidine-related nonhematologic toxicities that are ≥ Grade 3 that do not resolve to ≤ Grade 2 or baseline levels, azacitidine dosing should be delayed up to 14 days until resolution to ≤ Grade 2 or baseline levels. If ≥ Grade 3 toxicities continue despite this dose delay, dose modification of azacitidine should be performed in accordance with Table 10.

Following dose modifications, the cycle duration should return to 28 days.

Table 10. Azacitidine Dose Modification: Nonhematologic Toxicities

Toxicity	Azacitidine Dose Instruction if Recovery[a] is Not Achieved within 14 Days		
	First Occurrence[b]	**Second Occurrence[b]**	**Third Occurrence[b]**
Grade 3 or higher nonhematologic adverse event	Dose reduce azacitidine to 50 mg/m^2 administered Days 1–7 per cycle AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, proceed to second occurrence.	Dose reduce azacitidine to 37.5 mg/m^2 administered Days 1–7 per cycle AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, proceed to third occurrence.	Dose reduce azacitidine to 25 mg/m^2 administered Days 1–7 per cycle AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, then administer azacitidine at 25 mg/m^2 on Days 1–5 per cycle. Reassess toxicity on subsequent cycle. <u>Fourth occurrence and beyond</u>: If toxicity still persists, then contact the medical monitor for azacitidine dosing instructions.

a Recovery is defined as improvement of nonhematologic toxicity to ≤ Grade 2 or baseline value within 14 days of dose delay.
b Azacitidine may be dose-escalated back to the original dose or next higher dose level if there is resolution of the toxicity to ≤ Grade 2 or back to baseline level.

5.10.2. Venetoclax + Azacitidine (Control Arm for Patients Appropriate for Non-intensive Treatment)

Patients treated with venetoclax may develop tumor lysis syndrome. Assess blood chemistry (potassium, uric acid, phosphorous, calcium, and creatinine) and correct preexisting abnormalities prior to initiation of treatment with venetoclax. Blood chemistry must be monitored for tumor lysis syndrome at predose, 6 to 8 hours after each new dose during ramp-up (Days 1, 2, 3), and 24 hours after reaching maintenance dose. Dose modifications and delays for venetoclax due to AEs should follow Table 11 or the venetoclax prescribing information.

The treatment with venetoclax + azacitidine will be administered as inpatient/outpatient based on local guidelines for treatment of non-intensive treatment/investigator assessment of the patient's clinical status.

At the start of each cycle, both venetoclax and azacitidine are administered on the same day.

5.10.2.1. Dose Modifications and Treatment Delays

Table 11. Dose Modifications and Delays for Venetoclax Due to Adverse Events

Event	Occurrence	Action Taken
Hematologic toxicities		
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission[a]	In most instances, do not interrupt venetoclax and azacitidine due to cytopenias prior to achieving remission.
	First occurrence after achieving remission[a] and lasting at least 7 days	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax therapy at the same dose in combination with azacitidine.
	Subsequent occurrences in cycles after achieving remission[a] and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax therapy at the same dose and reduce the duration by 7 days for each subsequent cycle.

a. Bone marrow assessment to be performed as per Table 21 and results reviewed to know the remission status needed for the dosing modifications per this table.

5.10.3. 7 + 3 (or 5 + 2) Chemotherapy (Control Arm for Patients Appropriate for Intensive Treatment)

There will be no dose delays permitted for cytarabine, daunorubicin, or idarubicin. If deemed clinically necessary to reduce cytarabine, daunorubicin, and/or idarubicin doses (eg, hyperbilirubinemia, neurotoxicity), please contact the medical monitor.

5.11. Prior and Concomitant Medications

5.11.1. Permitted Concomitant Medications

Premedication, and prophylaxis for AEs as described in Section 5.9, is permitted while on study treatment. Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with LHRH agonists for prostate cancer, hormonal maintenance therapy for breast cancers, and treatment with bisphosphonates receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are permitted. Red blood cell and platelet transfusions are permitted during screening and prior to randomization to ensure adequate hemoglobin level and as per investigator clinical judgment. Blood transfusions are also permitted during the study as clinically indicated for management of cytopenias and should be recorded in the electronic case report form (eCRF) dedicated to on study transfusions. Hydroxyurea and/or leukapheresis can be used throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$. In nonclinical studies, coadministration of magrolimab and hydroxyurea in human leukemia engrafted immunodeficient mice did not cause phagocytosis of normal bone marrow cells, suggesting limited on-mechanism toxicity in patients. No gross safety abnormalities were observed in these nonclinical studies. While no formal analyses have been performed, in clinical studies, no significant safety concerns have been observed in patients who have received concomitant magrolimab and hydroxyurea or magrolimab, azacitidine, and hydroxyurea.

All concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 30 days before the first dose of study treatment through the 70-day safety follow-up call/visit should be recorded in the eCRF.

5.11.2. Prohibited Concomitant Medications

Antileukemic therapies including chemotherapy (with the exception of hydroxyurea), targeted therapies, and immunotherapy are not permitted while patients are on study treatment.

Live vaccines are prohibited during the study, and for 3 months after the last dose of study treatment {Rubin 2014}.

Drugs with cardiotoxic potential are prohibited because of the potential cardiotoxicity with the use daunorubicin, idarubicin, and azacitidine.

For patients randomized to receive venetoclax and azacitidine, avoid concomitant use of venetoclax with strong CYP3A inducers or moderate CYP3A inducers, as use with a strong CYP3A inducer decreases venetoclax C_{max} which may decrease venetoclax efficacy. Preparations containing St John's wort are not allowed during study treatment.

Any investigational drugs other than magrolimab are prohibited during study treatment.

Conversely, concomitant use of strong and moderate CYP3A inhibitors with venetoclax increase exposure of venetoclax and therefore may increase the risk of venetoclax related toxicity including tumor lysis syndrome. Table 12 describes venetoclax dose modification based on concomitant use of strong or moderate CYP3A inhibitor or P-gp inhibitor at initiation, during or

after the ramp-up phase. Resume the venetoclax dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor. Avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax, as they contain inhibitors of CYP3A.

For additional information drug interactions with venetoclax refer to the local prescribing information.

Table 12. Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Coadministered Drug	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)
Posaconazole	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	Reduce venetoclax dose to 70 mg.
Other strong CYP3A inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%	
P-gp inhibitor		

CYP = cytochrome P450 enzyme; P-gp = P-glycoprotein

5.11.3. COVID-19 Vaccine

There is no contraindication to the COVID-19 vaccine with magrolimab. Given that immunocompromised individuals on myelosuppressive treatment may have attenuated responses to vaccines, investigators should, after consultation with local guidelines, consider delay of COVID-19 vaccination until recovery of a neutropenic individual's ANC and determine the ideal timing of the subsequent dose of vaccine based on count recovery. Investigators should document vaccinations. Investigators should notify patients of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection.

5.12. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (kits, vials, etc). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to patients must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits (kits, vials, etc)
- The date, patient number, and the study lot number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

Patients should be reminded to bring the venetoclax dosing diary card, all used and unused study drug, along with the packaging, to each study visit for review by site staff.

5.12.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient enrolled in the study are presented in tabular form in Appendix 2 (Table 20, Table 21, Table 22, Table 23, Table 24, Table 28 and Table 29), and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Patient Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment onto the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Prescreening Visit

In order to minimize impact of screening procedures to patients, an optional prescreening consent form will be offered to patients at the investigator's discretion in order to conduct bone marrow biopsy and aspirate to assess *TP53* mutational status and for blast evaluation, correlative studies, and cytogenetics. Once a patient's *TP53* mutational status has been confirmed, the patient will then be offered the full consent form for the study after which screening procedures will be completed.

6.2.2. Screening Visit

Patients will be screened within 30 days after signing of the main informed consent, prior to randomization to determine eligibility for participation in the study. The following will be performed and documented at screening as per Table 20:

- Obtain written informed consent.
- Central testing of *TP53* mutational status (if not performed during prescreening, refer to the laboratory manual for details) from a bone marrow aspirate sample. If local *TP53* testing performed on a bone marrow aspirate sample from an approved local laboratory is available, patients can be enrolled following a central review of the local test results without waiting for the confirmation of the mutation from central testing.
- Obtain medical and cancer history (including demographic information, AML molecular marker results at diagnosis, and echocardiogram/multigated acquisition [scan] [MUGA] or pulmonary function tests if done within the 3 months prior to signing the informed consent form [ICF])

- Serum pregnancy test (screening pregnancy test may be used as Cycle 1 Day 1 test if performed within 72 hours prior to administration of the first dose)
- Complete physical examination including vital signs, body weight, and height
- CBC with differential, platelets, reticulocytes, blasts
- Serum or plasma chemistry
- Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) or PTT
- Red blood cell ABO/Rh type and screen (any of the 4 blood groups A, B, AB, and O comprising the ABO system [ABO]/rhesus factor [Rh]), direct antiglobulin test (DAT) and RBC extended phenotyping or genotyping. Refer to Section 6.4.4 for more information.
- Urinalysis
- Peripheral blood for MRD assessment
- Bone marrow biopsy and aspirate for blast evaluation, correlative studies, cytogenetics, and MRD assessment (not required if the patient was prescreened)
- Peripheral blood smear (for blasts)
- HBV, HCV, and HIV
- ECOG performance status (Appendix 10)
- Perform 12-lead electrocardiogram (ECG) (single)
- Echocardiogram or MUGA (for patients appropriate for intensive therapy)
- Record all SAEs and any AEs related to protocol-mandated procedures occurring after signing of the ICF
- Record prior and concomitant medications
- Eligibility criteria

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AEs eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be considered medical history. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Randomization

Randomization procedures are described in Section 5.1.1

6.4. On Study-Treatment Assessments

6.4.1. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of ≥ 12 months of amenorrhea, a single FSH measurement is insufficient. A negative serum pregnancy test is required at screening, and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours prior to study treatment administration. Serum or urine pregnancy tests will also be required at Day 1 of each subsequent cycle. For further details, refer to Appendix 5.

6.4.2. Complete Blood Counts

Samples for CBCs should be collected per the schedules of assessments in Appendix 2. White blood cell count needs to be $\leq 20 \times 10^3/\mu L$ prior to randomization and prior to each magrolimab dose for the first 4 weeks (see Section 4.2, Inclusion Criterion 2 for details). Additional samples for CBC may be collected outside of the protocol-specified time points to ensure WBC level $\leq 20 \times 10^3/\mu L$ for the first 4 weeks and repriming/reescalation cycle. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

6.4.3. Peripheral Blood Smear Assessment

Peripheral blood smears should be collected per the schedules of assessments and assessed for standard general cell morphology (first 4 weeks and in case of repriming) and for blast (along with bone marrow assessment). These samples should be collected from the arm contralateral to the arm being used for drug infusion/injection, if possible. All other observed findings should be reported according to local laboratory hematopathology standard procedures. Peripheral blood smears will be assessed locally.

In the event the study meets futility, and the sponsor decides to terminate the study, peripheral blood smears will no longer be required. Peripheral blood smear assessment may be performed per institutional SOC.

6.4.4. Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult due to expected coating of the RBC membrane, ABO/Rh type, antibody screen, blood phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab, as described in Section 7.8.1.

RBC phenotyping/genotyping, ABO type and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the patient was transfused since that time.

6.4.5. Vital Signs

Vital signs will include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height should be recorded during screening only. Weight should be recorded during screening and on Day 1 of each cycle. Vital signs are to be recorded prior to dosing with study treatment at the visits specified in the schedules of assessments in Table 21, Table 22, and Table 23.

6.4.6. Physical Examination

Complete physical examination will be performed at screening. Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and neurologic system.

6.4.7. Electrocardiograms

A single 12-lead ECG will be performed at screening for all patients.

For patients undergoing treatment with 7 + 3 intensive chemotherapy, 12-lead ECGs will also be performed at the end of Consolidation Cycles 1 and 4, at the EOT visit, and approximately every 12 weeks during long-term follow-up, as per Table 23 and Table 24.

In the event the study meets futility, and the sponsor decides to terminate the study, ECGs will no longer be required. ECG evaluation may be performed per institutional SOC.

6.4.8. Echocardiogram or MUGA

An echocardiogram or MUGA will be performed at screening for patients appropriate for intensive therapy for determination of LVEF.

For patients undergoing treatment with 7 + 3 intensive chemotherapy, an echocardiogram or MUGA will also be performed at the end of Consolidation Cycles 1 and 4, at the EOT visit, and approximately every 12 weeks during long-term follow-up, as per Table 23 and Table 24.

In the event the study meets futility, and the sponsor decides to terminate the study, echocardiograms and MUGAs will no longer be required. Evaluations may be performed per institutional SOC.

6.4.9. Bone Marrow Assessments

Bone marrow assessments (including aspirate ± core/trephine biopsy) are required for response assessments (eg, blast evaluation) (refer to Section 6.6, Table 21, and Table 23), including conventional cytogenetic analysis per institutional standards. In addition, bone marrow specimens may be used for correlative studies, MRD monitoring, CCI [redacted], and biobanking. Minimal residual disease testing will be performed by a central laboratory. Details for preparation and distribution of aspirate and biopsy/trephine specimens to the testing laboratories will be provided in the laboratory manual for this study.

In the event the study meets futility, and the sponsor decides to terminate the study, bone marrow assessments may continue locally as per the schedule outlined in Table 13 and Appendix 2 Table 26, Table 27, and Table 28 or as per investigator discretion. MRD testing will not be required nor performed by the central laboratory but may be done locally per SOC. Cytogenetic testing may be performed locally per SOC but will not be required.

Bone marrow assessments include collection of both aspirate ± core biopsy (trephine) specimens at each time point according to the schedules of assessments in Appendix 2 and as summarized in Table 13.

Table 13. Timing of Response Assessments

Response Assessment from: Bone Marrow, Aspirate/Biopsies, and Peripheral Blood Smear (for Blasts)[a]	**Experimental Arm: Magrolimab + Azacitidine**	**Control Arm: Venetoclax + Azacitidine**	**Control Arm: 7 + 3 Chemotherapy Regimen**
At Screening	Prior to first dose of study treatment	Prior to first dose of study treatment	Prior to first dose of study treatment
During Study Treatment	D28 bone marrow can be performed on D1 of the subsequent cycle if the delay of starting the subsequent cycle is not foreseen to be more than 7 days. Results of bone marrow assessment to be reviewed to determine the timing of subsequent cycles and schedule modifications as recommended in Table 8 and Table 9 for the magrolimab + azacitidine arm, and Table 11 for the venetoclax +azacitidine arm.		
	C1D28 (± 7 days)	C1D28 (± 7 days)	Cycle 1 Day 15 (± 5 days) (after 7 + 3 only; to determine if a new induction cycle of 5 + 2 is needed); and
	C2D28 (± 7 days)	C2D28 (± 7 days)	At count recovery following induction or Day 42 after the start of the most recent induction treatment, whichever is earlier; and

Response Assessment from: Bone Marrow, Aspirate/Biopsies, and Peripheral Blood Smear (for Blasts)[a]	**Experimental Arm: Magrolimab + Azacitidine**	**Control Arm: Venetoclax + Azacitidine**	**Control Arm: 7 + 3 Chemotherapy Regimen**
	C4D28 (± 14 days)	C4D28 (± 14 days)	If therapy is stopped at Consolidation Cycle 1, then at count recovery after Cycle 1 or not later than Day 42 after the start of Consolidation Cycle 1, whichever is earlier, *or* If therapy is stopped at Consolidation Cycle 2, then at count recovery after Cycle 2 or not later than Day 42 after the start of Cycle 2, whichever is earlier, *or* If therapy is stopped at Consolidation Cycle 3, then at count recovery after Cycles 2 and 3 or not later than Day 42 after the start of each Cycle 2 and Cycle 3, whichever is earliest for each cycle, *or* If therapy is stopped at Consolidation Cycle 4, then at count recovery after Cycles 2 and 4 or not later than Day 42 after the start of each Cycle 2 and Cycle 4, whichever is earliest for each cycle.
	C6D28 (± 14 days)	C6D28 (± 14 days)	
	and every 3 cycles (± 14 days) thereafter	and every 3 cycles (± 14 days) thereafter	
End of Treatment (EOT)	Last Dose or EOT (± 14 days), *if not performed within the last 30 days*		
Long-term Follow-up	Every 12 weeks thereafter (± 14 days), from last CXD1		
Post SCT	Every 12 weeks thereafter, from SCT Day 1		

C = Cycle; D = Day; SCT = stem cell transplant
a. Bone marrow biopsies will be collected at screening and Day 28 of Cycles 2 and 6.

For the experimental arm magrolimab + azacitidine and control arm venetoclax + azacitidine, the Day 28 bone marrow assessment may be performed on Day 1 of the subsequent cycle if the delay of starting the subsequent cycle is not foreseen to be more than 7 days.

A response assessment at the EOT visit is not required if it has been performed within the last 30 days, if progressive disease has been documented, or if patient continues on long-term follow-up. Bone marrow aspirate and response assessments should continue during long-term follow-up approximately every 12 weeks until progressive disease is documented or until start of a new anti-AML therapy. In the event the study meets futility, and the sponsor decides to terminate the study, bone marrow assessments at EOT and during long-term follow-up is not required.

For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of bone marrow biopsy/aspirate results will continue every 12 weeks, until documented disease progression or relapse occurs. In the event the study meets futility, and the sponsor decides to terminate the study, bone marrow assessments for patients undergoing SCT is not required.

6.4.10. Patient-reported Outcomes

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 patient should complete these questionnaires before any other study procedures at required visits. Please refer to schedule of assessments (Table 21, and Table 23) for timing of PRO assessments.

In the event the study meets futility, and the sponsor decides to terminate the study, PRO assessments will no longer be required.

6.4.10.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a reliable and valid measure of PRO and has been widely used among cancer patients. 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) {Fayers 2001}. The recall period is 1 week (past week). It will require approximately 11 minutes to complete. An example is provided in Appendix 7.

6.4.10.2. EQ-5D-5L

The EQ-5D-5L is an instrument for use as a measure of health outcome {EuroQol Research Foundation 2017, Janssen 2013}. The EQ-5D-5L consists of 2 sections: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). An example is provided in Appendix 8.

The 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.

6.4.10.3. PGIS/PGIC

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 {Department for Health and Human Services (DHHS) 2018}. These questionnaires are provided in Appendix 9. In the event the study meets futility, and the sponsor decides to terminate the study, PGIS and PGIC assessments are not required to be used in determining the thresholds but will be analyzed descriptively.

6.4.11. Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur after the first dose of study treatment through 70 days after the last dose of study treatment are to be reported using the applicable eCRF (Section 7.1.1). Full details on the definitions, assessment and reporting instructions for AEs are provided in Section 7.

In the event the study meets futility, and the sponsor decides to terminate the study, AEs that occur following initiation of study medication, regardless of cause or relationship, will be collected until 30 days (± 7 days) after last administration of study drug and reported on the eCRFs as instructed.

6.4.12. Concomitant Medications

All concomitant medications taken by the patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after informed consent through the study treatment period, and up until 70 days after treatment discontinuation. Concomitant medication associated with procedure-related AEs will be captured from the time of informed consent and onward. Information to be collected includes therapy name, indication, route, start date, and stop date and must be reported using the applicable eCRF. Note that any anti-AML therapies after the study treatment period should also be collected per the schedule of assessments (Table 24).

In the event the study meets futility, and the sponsor decides to terminate the study, concomitant medications will be collected until 30 days (± 7 days) after last administration of study drug and reported on the eCRFs as instructed. Post-study anti-AML therapy status will not be collected for patients discontinuing study treatment in the event of study termination due to futility.

6.5. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories at screening are presented in Table 14. See Appendix 10 for ECOG assessment information.

Table 14. Laboratory Analyte Listing (to be Performed at Screening)

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate[a] Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Uric acid Total bilirubin Direct bilirubin Indirect bilirubin Haptoglobin LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	Hemoglobin Hematocrit Platelets WBC differential Absolute neutrophil count (ANC) Eosinophils Basophils Lymphocytes Monocytes Reticulocytes Blasts **Peripheral blood smear**: Blasts *(with bone marrow assessments)* **Coagulation:** PT INR aPTT or PTT	RBC Protein	Serum pregnancy Blood phenotyping or genotyping[b] Type and screen (ABO/Rh), DAT HIV antibody **Hepatitis B and hepatitis C assessments:** HBsAg, anti-HBc, HCV antibody, HBV DNA, and HCV RNA, as applicable **Bone marrow aspirate and biopsy:** Blast evaluation Correlative studies[c] Cytogenetics MRD[c] **Peripheral blood:** MRD[c]

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; Rh = rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.
Note: Refer to Appendix 2 for collection time points.
a If available at the local laboratory.
b Genotyping can be performed locally or centrally.
c These assays will be performed at a central laboratory. MRD assessment will not be required if the patient was prescreened.

Analytes to be assessed by the local laboratory or specialty laboratories during the study are presented in Table 15.

Table 15. Laboratory Analyte Listing (to be Performed During the Study)

Chemistry (Serum or Plasma)	Hematology	Other Laboratory Measurements
Sodium	Hemoglobin	Serum or urine pregnancy
Potassium	Platelets	Pharmacokinetics[a]
Calcium	WBC differential	Antidrug antibodies[b]
Chloride	Absolute neutrophils count (ANC)	
Bicarbonate[a]	Lymphocytes	**Bone marrow aspirate and biopsy:**
Albumin	Reticulocytes	Blast evaluation
Phosphorus	Blasts	Correlative studies[b]
Glucose		Cytogenetics[c]
BUN or urea	**Peripheral blood smear[d]:**	MRD[b]
Creatinine	General morphology	
Uric acid	Experimental Arm or Venetoclax + Azacitidine: C1D1, C1D2, C1D11 only	**Peripheral blood:**
Total bilirubin	7 + 3 chemotherapy: C1D1, C1D2, C1D15 only	Correlative studies[b]
Direct bilirubin		MRD[b]
Indirect bilirubin	Blasts *(with bone marrow assessments)*	
Haptoglobin		
LDH		
AST (SGOT)		
ALT (SGPT)		
Alkaline phosphatase		

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; D = day; DAT = direct antiglobulin test; LDH = lactate dehydrogenase; MRD = minimal residual disease; RBC = red blood cell; Rh = rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SOC = standard of care; WBC = white blood cell.
Note: Refer to Appendix 2 for collection time points.
a If available at the local laboratory.
b These assays will be performed at a central laboratory. In the event the study meets futility, and the sponsor decides to terminate the study, MRD assessments and correlative studies will no longer be required; MRD assessments may be performed locally per SOC for patients remaining on study treatment.
c In the event the study meets futility, and the sponsor decides to terminate the study, cytogenetics will no longer be required; it may be performed locally per SOC for patients remaining on study.
d In the event the study meets futility, and the sponsor decides to terminate the study, peripheral blood smears will no longer be required.

6.6. Efficacy Assessments

Clinical response will be assessed using the guidelines in Appendix 6 which are based primarily on ELN AML recommendation and IWG AML response criteria {Cheson 2003, Dohner 2017} with modifications.

Response assessments will be performed in conjunction with bone marrow assessments, according to the schedule of assessments (Table 21 and Table 23). The timing of these assessments is also summarized in Table 13. Accompanying laboratory results ± 2 weeks from the protocol-specified bone marrow efficacy assessment can be used to support an efficacy assessment, but peripheral blood smears for blasts should be done on the day of the bone marrow

assessments. Response assessments for magrolimab + azacitidine and venetoclax + azacitidine are scheduled at Cycle 1 Day 28, Cycle 2 Day 28, Cycle 4 Day 28, Cycle 6 Day 28, and then at the end of every 3 cycles thereafter during study treatment. For patients who receive control treatment with 7 + 3 (5 + 2) chemotherapy, response assessments will be performed as summarized in the schedule of assessments and Table 13. These supporting laboratory results will be entered into the eCRF. If a patient achieves a CR, subsequent bone marrow assessments are still required to be performed as per the schedule of assessments and Table 13.

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, or if patient continues on long-term follow-up. Response assessments should continue during long-term follow-up approximately every 12 weeks until progressive disease is documented or start of a new anti-AML therapy. For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of bone marrow biopsy/aspirate results will continue every 12 weeks from the date of SCT, until documented disease progression or relapse or initiation of new anti-AML therapy (excluding maintenance therapy) occurs.

In the event the study meets futility, and the sponsor decides to terminate the study, response assessments may continue locally as per the schedule outlined in Table 13, Table 26, or Table 28 or as per investigator discretion.

6.7. Pharmacokinetics

Pharmacokinetic samples will be evaluated for magrolimab concentrations. Serum magrolimab assessment will be done using a validated assay.

Pharmacokinetic samples will be collected as described per schedule of assessments (Table 21 and Table 22).

In the event the study meets futility, and the sponsor decides to terminate the study, pharmacokinetic samples will no longer be collected.

6.8. Immunogenicity (Antidrug Antibodies)

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described per schedule of assessments (Table 21 and Table 22). When collected on the day of study treatment dosing, the blood sample must be collected at the same time as the predose PK specimen. Neutralizing antibodies to magrolimab will also be assessed in samples that test positive for ADA.

In the event the study meets futility, and the sponsor decides to terminate the study, immunogenicity (ADA) samples will no longer be collected.

6.9. Pharmacodynamics and Biomarker Assessments

6.9.1. Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to study the biological activity of the treatment. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating immune cells, and other studies. Samples for correlative studies in the peripheral blood will be collected per schedule of assessments (Table 21 and Table 23).

In the event the study meets futility, and the sponsor decides to terminate the study, correlative blood samples will no longer be collected.

6.9.1.1. Measurement of Plasma Cytokines

Cytokine release by immune cells is one surrogate measure of immune cell activation (including T-cells and macrophages). Since magrolimab activates both macrophages and T-cells, it is hypothesized that a specific cytokine profile relating to immune cell activation will correlate with clinical response to therapy. Fluorescence-based platforms allow for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity {Swartzman 1999}. A predefined multiplex panel of human cytokines will be measured from a small, thawed vial of plasma, detecting and quantifying the soluble proteins and peptides that help control cellular function. The observed systemic biochemical changes in the blood may provide a further correlate with tumor progression and therapeutic response and help provide a much broader understanding of disease. Cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be specifically interrogated.

6.9.1.2. Characterization of Circulating Immune Cells

In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation {Tseng 2013}. It is therefore predicted that magrolimab administration may lead to T-cell activation in patients. Peripheral blood samples will be collected, and T-cell activation/repression markers/studies may be performed by flow cytometry, mass cytometry, in vitro T-cell activation assays, and/or T-cell receptor sequencing. Additional peripheral blood mononuclear cells and plasma at the specified time points will also be cryopreserved and biobanked for future analyses.

6.9.2. Minimal Residual Disease Monitoring

Minimal residual disease monitoring has become a powerful prognostic factor that is beginning to play a central role in the treatment of patients with MDS and AML both in the pretransplant and post-transplant settings. In multiple large studies of previously untreated patients with MDS and AML, as well as in advanced MDS patients who achieved CR, MRD positivity post-therapy was an independent poor prognostic factor and a predictor of relapse {Buccisano 2012, Freeman 2013, Platzbecker 2018, Sievers 2003}. In a large prospective study of MRD monitoring in both MDS and AML patients who achieved CR and received post-remission azacitidine, the 12-month

relapse-free survival for those who were MRD positive was 46% compared to 88% in patients who were MRD negative. Several methods for MRD monitoring have been utilized in AML including: 1) multiparameter flow cytometry for detection of aberrant hematopoietic surface antigens, 2) molecular monitoring of leukemia-specific mutational burden, and 3) cytogenetic monitoring of leukemia-associated chromosomal abnormalities.

Multiparameter flow cytometry will be utilized as the main method of MRD analysis and, CCI [redacted] may be compared to NGS or cytogenetic approaches to MRD monitoring. Minimal residual disease testing will be performed by a central laboratory, and incorporated for response assessments, where appropriate.

Minimal residual disease assessments in the bone marrow will be collected at the same time as the bone marrow efficacy response assessments, as outlined in schedule of assessments (Table 21 and Table 23) and Table 13.

In the event the study meets futility, and the sponsor decides to terminate the study, MRD samples will no longer be collected; MRD assessment may be performed locally per SOC for patients remaining on study treatment.

CCI [redacted]

CCI [redacted]

6.9.4. Post-treatment Assessments

Post-treatment assessments can be found in Table 24. In the event the study meets futility, and the sponsor decides to terminate the study, post-treatment assessments can be found in Table 28.

6.10. Assessments for Early Discontinuation from Study

If a patient discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures (Section 6.10.1). If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study. For patients who discontinue from the study prior to completion of all protocol-required visits for study assessments or survival follow-up as described in the schedule of assessments (Table 24), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status. This ensures reduced risk of missing critical efficacy data.

In the event the study meets futility, and the sponsor decides to terminate the study, all patients who discontinue study treatment for any reason will not be followed for survival; patients should have an EOT visit (within 7 days after last dose or EOT decision, whichever occurs later ± 7 days) and 30-day safety follow-up visit (± 7 days) after the last dose, but 70 day safety follow-up visit, post-treatment response assessments, long-term follow-up after SCT, and survival follow-up are not required.

6.10.1. Criteria for Discontinuation of Study Treatment

Reasons for discontinuation of study treatment are provided in Section 3.5.

6.11. End of Study

The end of the entire study for all patients and for individual patients is defined in Section 3.6.

6.12. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Poststudy treatment assessments are described in Table 24 and Table 28.

For patients who start new anti-AML therapy (other than SCT and maintenance therapy) before a relapse, efficacy status will be collected until relapse. Post-study anti-AML therapy status and status will not be collected and response assessments will no longer be required for patients discontinuing study treatment in the event of study termination due to futility.

6.13. Sample Storage

The stored biological samples may be used by Gilead or its research partners for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years. If subjects provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AEs is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.

- A congenital anomaly/birth defect.

- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Adverse Event/Serious Adverse Event Clarifications

Given the primary and secondary endpoints of the study, in order to maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered AEs/SAEs:

- Progression of AML

- Deaths related to progression of AML

Events that are considered to represent progression of the underlying AML should not be recorded as AEs/SAEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE.

Death that is attributed by the investigator as solely due to progression of AML and that occurs during the protocol-specified AE reporting period should be recorded only on the death eCRF (ie, not collected as an SAE on the AE eCRF).

7.1.2.1.1. Deaths Not Related to AML Progression

All other deaths (ie, deaths that are not due to AML progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the AE eCRF and reported within 24 hours of awareness and no later than the next business day.

When recording a death on the eCRF, the event or condition that is considered the primary cause of death should be the AE term, and the outcome should be death. A patient can only have 1 AE (SAE) with outcome of death and severity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 5.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, will be collected until 70 days after last administration of study drug and reported on the eCRFs as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

In the event the study meets futility, and the sponsor decides to terminate the study, AEs that occur following initiation of study treatment, regardless of cause or relationship, will be collected until 30 days (± 7 days) after last administration of study drug and reported on the eCRFs as instructed.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and Patient Safety (GLPS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 70 days of the last dose of study drug, regardless of causality, should also be reported. In the event the study meets futility, and the sponsor decides to terminate the study, SAEs that occur after the 30 days (± 7 days) posttreatment follow-up visit may be reported if the SAE is considered as related to study drug by the investigator.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead (GLPS).

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to GLPS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

  Gilead GLPS
  Email: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead GLPS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.
- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female patients that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead GLPS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.
- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the Gilead GLPS.

- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

- Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line-listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the NCI CTCAE, Version 5.0. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all patients.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, pre-existing or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment if the investigator determines that it is not in the patient's best interest to continue. Discontinuation of treatment should be considered if there is an indication of severe liver injury according to Hy's Law, defined by FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health & Human Services (DHHS) 2009}, as:

- Treatment-emergent ALT or AST elevation (≥ 3 x ULN), AND
- Treatment-emergent total bilirubin elevation (> 2 x ULN), and absence of cholestasis (defined as alkaline phosphatase < 2 x ULN), AND
- No other good explanation for the injury (hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure, worsening liver metastases).

7.8. Toxicity Management

7.8.1. Magrolimab

7.8.1.1. Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBC's membrane. Therefore, when magrolimab binds to CD47, it is likely to interfere with routine blood bank tests needed in case of transfusion. Notify blood transfusion centers/blood banks of this interference with blood bank testing and inform them that a patient will receive magrolimab.

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. Significant drops (up to 3 g/dL or more) have also been observed in early doses. For patients with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life-threatening or fatal.

Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, *all patients* must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Patients with a low baseline hemoglobin level, especially those with cardiac history or risk factors, must be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. Red blood cell transfusions are permitted prior to study treatment to ensure adequate hemoglobin level and as per the investigator's clinical judgment.

Prior to initiation of magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) must be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with a recent transfusion). Results must be available before the first dose of magrolimab.

7.8.1.1.1. For Patients After Exposure to Magrolimab

An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

7.8.1.1.2. Blood Components for Transfusion

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines.

For RBC phenotype/genotype matched units are preferred. However, cytomegalovirus (CMV)-seronegative units for CMV-seronegative patients are not required for this study.

In case ABO/Rh type cannot be resolved, use units matched for pretreatment (historical) phenotype/genotype matched units and for minor RBC antigens (CcDEe and Kk, to the feasible extent). Regarding the ABO type, historical blood group or O type can be used as per the institutional guidelines.

For emergency transfusions, the transfusion centers may consider using emergency Group O red cells if phenotype/genotype matched units are not available.

Whenever possible, blood plasma therapy should be blood type specific. Platelets should be blood type compatible whenever possible and, if not, should have been tested and found not to have high titer anti-A or anti-B. Otherwise, plasma and platelet products can be provided as per the institutional policy.

A recent report has suggested that cross-match interference by RBCs due to treatment with magrolimab may be resolved by using gamma-clone anti-IgG and multiple alloadsorptions with papain-treated RBC samples, pooled single donor apheresis platelets or commercial human platelet concentrate product if required {Troughton 2018, Velliquette 2019}.

7.8.1.2. Management of Infusion-related Reactions

Infusion-related reactions 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" (Appendix 4). For the purposes of this study, the time frame for infusion-related reaction assessment is the 24- hour period beginning from the start of the infusion. Premedication use described in Section 5.9 will be used to manage infusion-related reactions preemptively.

Recommendations for the management of infusion-related reactions are in Table 16:

Table 16. Management of Infusion-related Reactions

Infusion-related Reactions	
CTCAE Grade	**Management**
Grade 1 Mild transient reaction.	Remain at bedside and monitor patient until recovery from symptoms. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
Grade 2 Requiring symptomatic treatment and prophylactic medications for ≤ 24 hours.	Interrupt magrolimab therapy per protocol and begin an IV infusion of normal saline and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg of oral acetaminophen. Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be given at the discretion of the investigator. If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate. If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely. If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. The amount of magrolimab infused must be recorded on the eCRF. Patients who experience a Grade 2 infusion-related reaction during the postinfusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.
Grade 3-4 Grade 3: Prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae. Grade 4: Life-threatening consequences, where urgent intervention is indicated.	Immediately discontinue infusion of magrolimab. Begin an IV infusion of normal saline and consider treating the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Infusion-related Reactions	
CTCAE Grade	**Management**
	Patients who experience Grade 3 IRRs must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician. Patients who receive premedication and still experience a recurrent Grade 3 IRR or patients who experience a Grade 4 IRR at any time should be permanently discontinued from the study treatment. For anaphylaxis, investigators should follow their institutional guidelines for treatment. All patients with a Grade 3 or higher IRR will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AE.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IV = intravenous

7.8.1.3. Thromboembolic Events

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use. Patients should be closely monitored for the symptoms of thromboembolic events and treated accordingly.

7.8.1.4. Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (Appendix 2, Table 22, Table 27) including neutrophils is required for all patients treated with magrolimab. Prophylactic antibiotics and/or antimycotics should be considered. Administer granulocyte-colony stimulating factor, if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia is provided in Section 5.10.1.1

7.8.1.5. Serious Infections

Serious infections have been reported in patients treated with magrolimab. Grades 3 and 4 infections have been reported in patients treated with magrolimab, including fatal events of pneumonia and sepsis. Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (eg fluoroquinolone) or antifungal agents (eg oral triazoles or parenteral echinocandin) in accordance with current guidelines

For serious infections, hold the next dose of magrolimab until the infection has resolved clinically. For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab.

7.8.1.6. Management of Pneumonitis

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its antitumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies.

In instances of suspected pneumonitis, first rule out non-inflammatory causes (eg, infections). If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging (eg, chest x-ray or computed tomography) and pulmonary consultation.

Management of potential pneumonitis is detailed in Table 17 and follows the American Society of Clinical Oncology (ASCO) guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3-4 pneumonitis will be permanently discontinued from study treatment.

Table 17. Pneumonitis Management Algorithm

Pneumonitis		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 1 Radiographic changes (CXR or CT) only.	Monitor for signs and symptoms weekly and consider monitoring with CXR. Consider pulmonary and infectious disease consults.	Consider re-imaging with CT in 3-4 weeks as clinically indicated. May resume magrolimab with radiographic evidence of improvement or resolution. If no clinical improvement or worsening, treat as Grade 2.
Grade 2 Mild to moderate new symptoms.	Interrupt magrolimab therapy per protocol. Pulmonary and infectious disease consults. Consider empirical antibiotics. Monitor signs and symptoms every 2-3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. If improving to baseline, taper corticosteroids over 4-6 weeks and resume magrolimab therapy per protocol. If no clinical improvement after 48-72 hours or worsening, treat as Grade 3-4.

Pneumonitis		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening.	Discontinue magrolimab therapy. Hospitalize. Pulmonary and infectious disease consults. 1-2 mg/kg/day methylprednisolone IV or IV equivalent. Add empirical antibiotics and consider prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improving to baseline, taper corticosteroids over 4-6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest x-ray; IV = intravenous.

7.8.2. Venetoclax

Safety management guidelines for venetoclax are described in 5.10.2. Additional safety guidelines are provided in the venetoclax prescribing information.

7.8.3. Azacitidine

Safety management guidelines for azacitidine are described in Section 5.10.1.2. Additional safety guidelines are provided in the azacitidine prescribing information.

7.8.4. Cytarabine

Safety management guidelines for cytarabine are provided in the cytarabine prescribing information.

7.8.5. Daunorubicin

Safety management guidelines for daunorubicin are provided in the daunorubicin prescribing information.

7.8.6. Idarubicin

Safety management guidelines for idarubicin are provided in the idarubicin prescribing information.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The study objectives and endpoints are provided in Table 1.

8.2. Planned Analyses

The overall study-wide type I error is 1-sided 0.025. To protect the integrity of the study, an administrative 1-sided type I error of 0.0001 will be spent for the interim futility analysis (Section 8.2.1.1). As a result, a 1-sided type I error 0.0249 will be left for the superiority analysis of the primary and key secondary efficacy endpoints.

8.2.1. Interim Analyses

Two interim analyses are planned. The first interim analysis is the analysis of OS futility. The second interim analysis is for OS superiority. In the event the study meets futility, and the sponsor decides to terminate the study, the planned interim analysis for OS superiority will no longer be required.

8.2.1.1. Interim Futility Analysis

This interim analysis for futility will be performed after approximately 69 deaths (40% of the expected 171 OS events) in the stratum of patients appropriate for non-intensive therapy have occurred. The analysis will include a stratified log-rank test for OS in the stratum of patients appropriate for non-intensive therapy and will be reviewed by an external data monitoring committee (DMC). An administrative 1-sided type I error 0.0001 will be allocated to this analysis to protect the study integrity. A non-binding futility rule with a boundary HR = 1.1 will be implemented. The DMC may make a recommendation to terminate the study for futility if the observed HR for the OS in patients appropriate for non-intensive therapy is larger than 1.1. When the true OS HR in patients appropriate for non-intensive therapy is 0.74, the probability of observing HR > 1.1 at the interim analysis is less than 5%.

8.2.1.2. Interim Efficacy Analysis for Superiority

An interim efficacy analysis for OS superiority will be performed after approximately 128 deaths (75% of the expected 171 OS events) in the stratum of patients appropriate for non-intensive therapy have occurred, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

The Lan-DeMets approach with O-Brien-Fleming type alpha spending function will be used for the interim analysis and primary analysis for OS in the stratum of patients appropriate for non-intensive therapy. The stopping boundaries for each analysis are provided in Table 18.

Table 18. Stopping Boundaries for Efficacy Analyses for Superiority

Efficacy Analysis	Events (%[a])	Stopping Boundary	
		HR	1-Sided *P*-Value
IA	128 (75%)	0.661	0.010
Primary Analysis	171 (100%)	0.735	0.022

HR = hazard ratio; IA = interim analysis; OS = overall survival
a Information fraction = number of events/total number of events × 100

To strongly control the overall type I error across the testing of the primary and key secondary efficacy endpoints, a hierarchical testing strategy will be performed with a predefined order as listed in the protocol and the statistical analysis plan (SAP). The primary efficacy endpoint of OS in the stratum of patients appropriate for non-intensive therapy will be tested for superiority first at the significance level specified in Table 18. If the superiority is established, analysis of key secondary efficacy endpoints will be performed. For each key secondary endpoint, an O'Brien-Fleming boundary will be derived based on the information fraction defined at the interim analysis and the remaining type I error, respectively, per Table 19.

Table 19. Definition of Information Fraction

Secondary Endpoint	Information Fraction at the Interim Analysis
OS in all patients	75%, same with that of primary efficacy endpoint
EFS in all patients	75%, same with that of primary efficacy endpoint
Transfusion independence conversion rate in all patients	Proportion of patients who have at least 9 months follow-up since randomization
Rate of CR within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)	Proportion of patients who have at least 7 months follow-up since randomization (3 months for patients receiving 7 + 3 chemotherapy)
Rate of CR_{MRD-} within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)	Proportion of patients who have at least 7 months follow-up since randomization (3 months for patients receiving 7 + 3 chemotherapy)
Rate of CR + CRh within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)	Proportion of patients who have at least 7 months follow-up since randomization (3 months for patients receiving 7 + 3 chemotherapy)

CR = complete remission; CRh = complete remission with partial hematologic recovery; CR_{MRD-} = complete remission without minimal residual disease; EFS = event-free survival

The key secondary endpoints will be tested in the following order:

- OS in all patients
- EFS in all patients
- Transfusion independence conversion rate in all patients

- Rate of CR within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)
- Rate of CR_{MRD-} within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)
- Rate of CR + CRh within 6 months of treatment (2 months for patients receiving 7 + 3 chemotherapy)

A given hypothesis can only be tested and declared statistically significant if all previous hypotheses tested in the hierarchy are also statistically significant.

At the time of each planned interim analysis, the DMC will review the analysis results, and provide recommendations. The process details are described in Section 8.12. Details for the planned interim analyses will be provided in the DMC Charter and the SAP.

8.2.2. Primary Analysis

If the null hypothesis on the primary endpoint of OS is not rejected in the interim efficacy analysis, the primary analysis will be conducted when 171 deaths have occurred in the stratum of patients appropriate for non-intensive therapy. The analysis will be conducted after all outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. The same hierarchical testing strategy with the order as defined in Section 8.2.1.2 will be used.

If the null hypothesis of the primary endpoint OS is rejected in the interim efficacy analysis, the primary analysis timing will be determined by the maturity of the key secondary endpoints that have not been rejected in the interim analysis.

In the event the study meets futility, and the sponsor decides to terminate the study, the planned primary analysis will no longer be required.

8.2.3. Final Analysis

The final analysis will be performed after all patients have completed the study and outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint of OS may be conducted at this time but this will be descriptive in nature.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is the Intent-to-Treat (ITT) analysis set, defined as all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified.

8.3.1.2. Safety

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

All data collected during treatment up to 70 days after treatment discontinuation will be included in the safety summaries.

8.3.1.3. Pharmacokinetics

The PK analysis will be conducted on Pharmacokinetic Analysis Set, defined as all randomized patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.3.1.4. Immunogenicity

The Immunogenicity Analysis Set is defined as all randomized patients who received at least 1 dose of magrolimab and had at least 1 evaluable anti-magrolimab antibody test result.

8.3.1.5. Biomarker

The Biomarker Analysis Set includes all randomized patients who received at least 1 dose of any study drug and have at least 1 evaluable biomarker measurement available. This will be the primary analysis set for all biomarker data analyses.

8.3.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by treatment arm.

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study treatment. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include age, sex, race/ethnicity, and randomization stratification group. Baseline data will include a summary of body weight, height, body surface area, body mass index, World Health Organization AML classification, and ECOG performance status.

8.5. Efficacy Analysis

8.5.1. Primary Endpoint Analysis

Formal hypothesis testing will be performed to test the statistical hypothesis that the distribution of OS between the experimental arm and the control arm in patients appropriate for non-intensive therapy is the same (null hypothesis) versus that the experimental arm is superior to the control arm in terms of survival function (alternative hypothesis).

A log-rank test stratified by the randomization stratification factors will be used to compare the treatment differences in OS. A stratified Cox proportional hazard regression model will be used to estimate HR and its 2-sided 95% CI. In addition, the Kaplan-Meier method will be used to estimate median OS with its 95% CI, and the Kaplan-Meier plots will be provided.

8.5.2. Secondary Efficacy Endpoints Analyses

Analyses will be performed based on the patient populations on which the endpoints are defined. Analyses of OS in all patients and EFS will be similar to that of the primary efficacy endpoint OS in the stratum of patients appropriate for non-intensive therapy.

The point estimate of the CR rate and the corresponding 2-sided exact 95% CI based on Clopper-Pearson method will be provided for each treatment arm. The difference in CR rates between the 2 arms will be tested using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors. The CR_{MRD-} rate, CR + CRh rate, transfusion independence conversion rate will be evaluated in a similar manner as CR rate, except that transfusion independence conversion rate will be based on a subset of randomized patients who are transfusion-dependent at baseline.

For the time-to-event endpoints of DCR and duration of CR + CRh in all patients, analyses will be conducted based on the subsets on which the outcome measures are defined. Specifically, the DCR will be based on patients who achieved CR within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy. Duration of CR + CRh will be based on patients who achieved CR or CRh within 6 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or within 2 months of 7 + 3 chemotherapy. The Kaplan-Meier method will be used to estimate median duration with its 95% CI and Kaplan-Meier plots will be provided.

CCI [redacted]

[redacted]

8.5.4. Analyses by Appropriateness for Intensive or Non-intensive Therapy

Analyses of OS, EFS, rate of CR, rate of CR_{MRD-}, rate of CR + CRh, transfusion independence conversion rate, and TTD on the GHS/QoL scale and the physical functioning scale of the EORTC QLQ-C30 will be conducted in the stratum of patients appropriate for non-intensive therapy and those appropriate for intensive therapy, separately. The objective is to demonstrate that the efficacy in patients appropriate for intensive therapy is consistent with that in patients appropriate for non-intensive therapy. In the event the study meets futility, and the sponsor decides to terminate the study, the planned analysis as described will no longer be required.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug + 70 days will be summarized by treatment group (according to the study drug received). Data for the pretreatment and treatment-free safety follow-up periods will be included in data listings. For categorical safety data including incidence of AEs and categorizations of laboratory data, count and percent of patients will be summarized. For continuous safety data including laboratory data, the number of patients, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized.

8.6.1. Extent of Exposure

A patient's extent of exposure to study drugs data will be generated from the study drugs administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to and including the date of last dose of study treatment plus 70 days or the day before initiation of new anticancer therapy including SCT, whichever comes first.

Summaries (number and percentage of patients) of treatment-emergent AEs (by System Organ Class and PT) will be provided by treatment group.

Adverse events that occurred before exposure to study treatment will be reported in the AE line listings and appropriately identified as non-treatment-emergent AEs.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline, up to and including the date of last dose of study treatment plus 70 days or the day before initiation of any new anticancer therapy including SCT, whichever comes first will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the patient has been discontinued from treatment for at least 70 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and physical examination findings will be summarized at select time points. Details will be provided in the SAP.

8.7. Pharmacokinetic Analysis

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Due to the sparse nature of PK collection, PK parameters will not be calculated.

Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as zero in summary statistics and reported as is in data listings.

All data from this study may be combined with PK data from other company sponsored clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

8.8. Analysis of Patient-Reported Outcome Data

The PRO endpoints, TTD on domain scales of the EORTC QLQ-C30, are defined based on the ITT Analysis Set. The TTDs will be summarized using the Kaplan-Meier method. 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.

Additional analyses may be conducted on PRO data, including absolute scores and changes from baseline for scales and single items of the EORTC QLQ-C30 instrument, the EQ-5D-5L instrument, and PGIS/PGIC at each assessment time point for each arm. A linear mixed effect model with treatment, time, treatment by time interaction, stratification factors, and baseline scores as fixed factors may be fitted for analyses of selective PRO endpoints.

8.9. Immunogenicity Analysis

Immunogenicity will be assessed using a 3-tier (screen, confirmatory, and titer) approach on study samples using a validated immunoassay. The rate and magnitude of anti-magrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Titer summaries may also be generated, if relevant. CCI [redacted]

Neutralizing antibody analysis will be conducted using a validated assay on ADA positive samples and results will be summarized.

8.10. Biomarker Analysis

The baseline level, absolute level, and change from baseline level over time may be summarized using descriptive statistics for each biomarker at the sample collection time point by treatment arm, as appropriate. CCI [redacted].

8.11. Sample Size Rationale

Based on data from Study 5F9005, which enrolled 47 *TP53* mutant AML patients treated with magrolimab + azacitidine with a median OS of 12.9 months {Sallman 2020a}, and from studies for venetoclax in combination with hypomethylating agents that have shown a median OS ranging from 5.2 to 7.2 months in *TP53* mutant AML patients {DiNardo 2019, Kim 2020}, it is assumed that administration of magrolimab + azacitidine to study patients will result in a median OS of approximately 9.77 months, improved from a median OS of 6.35 months in patients treated with venetoclax + azacitidine or 7 + 3 chemotherapy. This corresponds to an OS HR of 0.65.

It is assumed 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, an HR of 0.65 under the alternative hypothesis of superiority of the magrolimab + azacitidine, a planned interim futility analysis when 40% of OS events are observed, and an interim superiority analysis when 75% of OS events are observed, 171 events (deaths) are required to achieve a power of 79.7% based on a log-rank test with an overall 1-sided significance level of 0.025 in the stratum of patients appropriate for non-intensive therapy; approximately 234 deaths may be observed in all patients when 171 events occur in the stratum of patients appropriate for non-intensive therapy. That provides a power of 90.4% for the OS test in all patients based on the log-rank test.

The study will enroll a minimum of 228 patients appropriate for non-intensive therapy to ensure adequate events (171 deaths) for the primary endpoint analysis. The study enrollment may stop after 228 patients in the non-intensive therapy group or approximately 346 of all patients are enrolled, whichever occurs later. The study duration and the total number of patients to be enrolled will depend on the prevalence of patients appropriate for non-intensive therapy in the overall population. When the enrollment of the required number of all patients finishes later than that of patients in the non-intensive therapy group, assuming a planned accrual period of 23 months, a study duration of 27 months, and an expectation that 10% of patients are likely to drop out by the end of study (annual dropout rate 4.8% assuming time to drop-out is exponentially distributed), approximately 173 patients in the experimental arm and 173 patients in the control arm (approximately 346 total) are to be enrolled. In the event the study meets futility, and the sponsor decides to terminate the study, no further patients will be enrolled.

8.12. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data on a regular basis and provide recommendation to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the patients, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

In addition, the DMC will meet after approximately 69 and 128 OS events in the stratum of patients appropriate for non-intensive therapy have occurred to review the results from the interim futility analysis and superiority analysis, respectively. Based on the prespecified futility and superiority rules, the DMC may make recommendations to Gilead as to whether the study should be terminated early due to futility, should be stopped due to overwhelming efficacy, or should continue as planned.

The DMC's specific activities will be defined by a mutually agreed charter, which will describe 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.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last patient completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform patients about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement or to allow the use of the remainder of their already collected specimens for CCI future research, in accordance with applicable regulations. The results of the tests performed on the samples will not be given to the patient or the investigator.

9.1.5. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, case report forms (CRFs)/eCRFs, IRB/IEC and governmental approval with correspondence, the ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each patient:

- Patient identification
- Documentation that patient meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)

- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each patient consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor.

Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications may be made only by the sponsor.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.6).

- Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at investigator meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the patients, appropriate regulatory authority, IRBs, and IECs. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

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11. APPENDICES

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Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGMENT

A Phase 3, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination with Azacitidine versus Physician's Choice of Venetoclax in Combination with Azacitidine or Intensive Chemotherapy in Previously Untreated Patients with *TP53* Mutant Acute Myeloid Leukemia

GS-US-546-5857 Protocol Amendment 5; 02 November 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD Medical Monitor	*[See appended electronic signature]* Signature
[See appended electronic signature] Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Schedules of Assessment

Table 20. Schedule of Assessments – Screening[a]

Assessment	Study Day −30 to −1
Bone marrow aspirate for central assessment of *TP53* mutation status[b]	X
Informed consent[a]	X
Demographics	X
Medical and cancer history	X
Serum pregnancy test[c]	X
CBC with differential, platelets, reticulocytes, blasts	X
Serum or plasma chemistry	X
PT, INR, and aPTT (or PTT)	X
Blood phenotyping or genotyping,[f] type, and screen (ABO/Rh), DAT	X
Urinalysis	X
Peripheral blood for MRD assessment[d]	X
Bone marrow biopsy and aspirate for blast evaluation, correlative studies, cytogenetics, and MRD assessment[b,e]	X
Peripheral blood smear (for blasts)[e]	X
ECOG performance status	X
Vital signs, height, and weight	X
Complete physical examination	X
HBV, HCV, and HIV	X
12-lead ECG (single)	X
Echocardiogram or MUGA (for patients appropriate for intensive therapy)	X
Adverse events related to protocol-mandated procedures	X
Prior and concomitant medications	X
Eligibility criteria	X
Randomization [a]	X

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRD = minimal residual disease; MUGA = multigated acquisition (scan); PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; RBC = red blood cells; Rh = rhesus factor

a Screening must be completed before 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 Bone marrow biopsy and aspirate for blast evaluation, correlative studies, cytogenetics and to assess *TP53* mutational status may take place as a prescreening assessment and will require an additional consent form. In that case, the MRD assessment will not be required.

c Screening pregnancy test may be used as the Cycle 1 Day 1 test if performed within 72 hours prior to first dose; additional guidance is provided in Section 6.4.1. FSH test is required for female subjects 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.

d Peripheral blood sample for MRD assessment must be collected prior to the first dose of study treatment at the latest.

e A trephine (biopsy) is to be collected for baseline. This procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for blast evaluation, MRD assessment, correlative studies, and biobanking. Bone marrow aspirate samples are to be obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics to be tested per institutional standards. Peripheral blood smear for blasts are to be collected along with bone marrow aspirate/biopsy.

f ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) must be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for patients with a recent transfusion). Results must be available before the first dose of magrolimab.

Table 21. Schedule of Assessments - Treatment Period for Azacitidine (Experimental Arm) and Venetoclax + Azacitidine Regimens

	Cycle (28-day cycles)																																		
	Cycle 1													Cycle 2												Cycle 3+									
Visit Window	None		± 3 Days											± 3 Days												± 3 Days									
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**
PRO Assessment[b]	X													X												X									
Serum or Urine Pregnancy Test[c]	X													X												X									
CBC with Differential, Platelets, Reticulocytes, Blasts[d,e]	X	X		X				X	X	X	X	X	X	X							X	X	X	X	X	X							X	X	X
Haptoglobin and LDH[d]	X	X		X				X						X																					
Serum or Plasma Chemistry[d]	X[f]	X[f]	X[f]	X[f]				X		X	X			X								X				X							X		
Peripheral Blood Smear (for General Morphology)[d,g]	X	X							X																										
Peripheral Blood Smear (for Blasts)[h]												X												X										C4D28, C6D28 then Q3C	
Buccal Swab[i]	X																																		

	Cycle (28-day cycles)																																				
	Cycle 1													Cycle 2												Cycle 3+												
Visit Window	None		± 3 Days											± 3 Days												± 3 Days												
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**
Peripheral Blood Sample for Correlative Studies[j]	X							X				X		X[k]										X										C6D28	
Peripheral Blood Sample for MRD Assessment[h]												X												X										C4D28, C6D28 then Q3C	
Bone Marrow Aspirate for Cytogenetics, MRD Monitoring and Response Assessment[h,l,m]												X												X										C4D28, C6D28 then Q3C	
Bone Marrow Aspirate and Biopsy for Correlative Studies[h]																								X										C6D28	
Vital Signs[n]	X	X						X	X	X	X			X							X	X	X			X							X				
Weight[n]	X													X												X											
Symptom-directed Physical Examination[d]	X							X		X				X												X										
Adverse Events, Concomitant Medications (Including Blood Transfusions)[o]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	

	Cycle (28-day cycles)																																		
	Cycle 1													Cycle 2												Cycle 3+										
Visit Window	**None**		**± 3 Days**											**± 3 Days**												**± 3 Days**										
Cycle Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[a]**
Study Treatment Dispensing																																			
Venetoclax[p]	X													X												X										
Study Treatment Administration																																			
Azacitidine[q]	X	X	X	X	X	X	X							X	X	X	X	X	X	X						X	X	X	X	X	X	X				
Venetoclax[p,r]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

C = cycle; CBC = complete blood count; D = day; EOT = end of treatment; EORTC QLQ- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire -Core Questionnaire; EQ-5D-5L = 5-level EuroQol 5 dimensions; LDH = lactate dehydrogenase; MRD = minimal residual disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; Q3C = every 3 cycles; WBC = white blood cell

a 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 CBC (including prior Day 28 CBC) is within 3 days of Day 1.

b 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.

c Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 6.4.1.

d Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment except for CBC, which must be performed within 24 hours prior to magrolimab dosing. Thereafter, pretreatment assessments are to be collected within 24 hours prior to any intravenous or subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.

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

f 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.

g Peripheral blood smears will be collected at predose and assessed locally.

h Day 28 assessments can be done on Day 1 of the next cycle if there is no foreseen delay of more than 7 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 (Section 5.10, and Table 8, Table 9, and Table 11). Collection of bone marrow aspirate and biopsy for correlative studies will be allowed within 7 days (rather than a 3-day window).

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

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

k Peripheral blood samples for correlative studies do not need to be repeated at D1, if performed in the past 7 days. Collection of peripheral blood for correlative studies will be allowed within 7 days (rather than a 3-day window).
l Conventional cytogenetics to be tested per institutional standards.
m An aspirate sample will be collected for response assessment and MRD assessment. Response assessments may be adjusted by up to 1 week prior to Cycle 1 Day 28, and Cycle 2 Day 28. After Cycle 2 Day 28, the window is up to 14 days ± from Day 28. Bone marrow results are to be reviewed as required for determining schedule modifications.
n Vital signs will be assessed prior to infusion/injection of each study treatment on the days marked in the table. Weight will be assessed on Day 1 of each cycle. Details are provided in Section 6.4.5.
o Collected at all regularly scheduled visits.
p Venetoclax will be dispensed to the patient on Day 1 of each treatment cycle.
q Azacitidine administration should be completed at least 1 hour before magrolimab administration on days when both drugs are administered. Azacitidine may be administered on an alternative schedule such as Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.
r Venetoclax is administered daily. Please refer to Section 5.4.

Table 22. Magrolimab Administration and Associated Assessment Schedule-Treatment Period

Visit Window (Days)	None[a]			± 3[a]				
Day	**1**	**2**	**4**	**8**	**11**	**15**	**Weekly × 5**	**Every 2 Weeks**
Vital signs[b]	X		X	X	X	X	X	X
Hemoglobin[c]	Pre and post dose		Pre and post dose					
PK	Within 72 hours prior to magrolimab dosing			Within 12 hours prior to magrolimab dosing			Within 12 hours prior to magrolimab dosing for 2nd weekly dose	Within 12 hours prior to magrolimab dosing before 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg[d]
Antidrug antibodies[e]								
Magrolimab Administration								
Premedication	X		X	X	X			
Magrolimab[g]	X		X	X	X	X	X	X

ADA = antidrug antibodies; PK = pharmacokinetic(s)

a In cases of magrolimab repriming/re-escalation following a treatment delay (Section 5.8.1), follow magrolimab schedule of assessment and administration for repriming Table 25.

b Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.4.5.

c Hemoglobin must be performed within 24 hours prior to magrolimab dosing on Days 1 and 4 to ensure hemoglobin is ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 magrolimab doses. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (see Section 5.8).

d On the first day of the biweekly maintenance dose, an additional sample for postdose PK will be collected at 1 hour (± 15 minutes) after the end of infusion of magrolimab.

e 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. Antidrug antibodies will not be collected on Day 8.

f Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication for subsequent doses 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 doses is required (Section 7.8.1.2).

g Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion for priming, repriming/re-escalation, and maintenance doses during the first 4 weeks. For magrolimab dosing, refer to Table 2.

Table 23. Schedule of Assessments - Treatment Period for the 7 + 3 Regimen

Visit Window	Induction Cycle(s)										Consolidation Cycles (up to 4 cycles)				
	None		± 3[a] Days								± 3[a] Days				
Cycle Day	1	2	3	4	5	6	7	15	21 and Twice Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]	1	3	5	21 and Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]
PRO Assessment[c]	X										X				
Serum or urine Pregnancy Test[d]	X										X				
CBC with Differential, Platelets, Reticulocytes, Blasts[e,f]	X	X		X			X	X	X	X	X			X	X
12-lead ECG (single)															X[g]
Echocardiogram or MUGA															X[g]
Haptoglobin and LDH[e]	X						X				X				
Serum or Plasma Chemistry[e]	X						X	X	X	X	X			X	X
Peripheral Blood Smear (for General Morphology)[e,h]	X	X						X							
Peripheral Blood Smear (for Blasts)[b, i]								X[i]		X					X
Buccal Swab[k]	X														
Peripheral Blood Sample for Correlative Studies[l]	X							X[j]		X					Consolidation C4 only
Peripheral Blood Sample for MRD Assessment[b]								X[j]		X					X

Visit Window	Induction Cycle(s)										Consolidation Cycles (up to 4 cycles)				
	None		± 3[a] Days								± 3[a] Days				
Cycle Day	1	2	3	4	5	6	7	15	21 and Twice Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]	1	3	5	21 and Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]
Bone Marrow Aspirate for Cytogenetics, MRD Monitoring and Response Assessment[b,i,m]								X[j]		X					X
Bone Marrow Aspirate and Biopsy for Correlative Studies[n]										X					Consolidation C4 only
Vital Signs[o]	X	X	X	X	X	X	X	X	X	X	X			X	X
Weight[o]	X										X				
Symptom-Directed Physical Examination[e]	X						X	X		X	X				X
Adverse Events, Concomitant Medications (Including Blood Transfusions)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment Administration															
7 + 3															
Daunorubicin or Idarubicin[q]	X	X	X												
Cytarabine[r]	X	X	X	X	X	X	X								
5 + 2															
Daunorubicin or Idarubicin[q]	X	X													
Cytarabine[r]	X	X	X	X	X										

Visit Window	Induction Cycle(s)										Consolidation Cycles (up to 4 cycles)				
	None		± 3[a] Days								± 3[a] Days				
Cycle Day	1	2	3	4	5	6	7	15	21 and Twice Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]	1	3	5	21 and Weekly Thereafter Until Count Recovery or Day 56, Whichever Occurs First	At Count Recovery[b]
Consolidation															
Cytarabine (HiDac)[s]											X	X	X		

C = cycle; CBC = complete blood count; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EQ-5D-5L = 5-level EuroQol 5 dimensions; LDH = lactate dehydrogenase; MRD = minimal residual disease; MUGA = multigated acquisition (scan); PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; WBC = white blood cell

a ± 3-day visit window does not apply to specimen collection during induction for correlative studies, nor to study drug administration.
b Response assessments will be performed as described in Table 13.
c 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.
d Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 6.4.1.
e 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 intravenous or subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.
f Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level $\leq 20 \times 10^3/\mu L$ prior to initiation of study treatment.
g At the end of Consolidation Cycles 1 and 4.
h Peripheral blood smears will be collected at predose and assessed locally.
i A bone marrow sample is to be collected for response assessment. An aspirate sample will be collected for response assessment and MRD assessment. Response assessments may be adjusted by ± 5 days for Cycle 1 (Day 15). The window for post consolidation or post transplantation is ± 14 days.
j Response assessment (including bone marrow biopsy/aspirate) at C1D15 should be performed only after 7 + 3 induction to determine if second induction with 5 + 2 is needed. After 5 + 2 induction, there is no need to perform Day 15 bone marrow assessment and bone marrow assessment should be performed only at count recovery (not beyond 42 days after the initiation of 5 + 2).
k Single sample to be collected on Day 1 of the first induction cycles or at any time during the study.
l Samples will be collected predose within 12 hours prior to study treatment administration. Collection of peripheral blood for correlative studies will be allowed within 7 days (rather than a 3-day window).
m Conventional cytogenetics to be tested per institutional standards.
n Collection of bone marrow aspirate and biopsy for correlative studies will be allowed within 7 days (rather than a 3-day window).
o Vital signs will be assessed prior to infusion of each study treatment. Weight will be assessed on Day 1 of each cycle. Details are provided in Section 6.4.5.
p Collected at all regularly scheduled visits.
q For 7 + 3 regimen, daunorubicin or idarubicin is administered on Days 1-3 and for 5 + 2 regimen, daunorubicin or idarubicin is administered on Days 1 and 2.
r For 7 + 3 regimen, cytarabine is administered on Days 1-7 and for 5 + 2 regimen, cytarabine is administered on Days 1-5.
s Cytarabine (HiDAC) is administered every 12 hours in the consolidation cycles.

Table 24. Schedule of Assessments – Post treatment

	End of Treatment Visit	Safety Follow-up Visit/Call (Telephone)[a]	Safety Follow-up Visit/Call (Telephone)[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[b]	Until Disease Progression or Start of New Anti-AML Therapy[c], Whichever Occurs First[d]	Until Disease Progression[b] or Start of a New Anti-AML Therapy[c], Whichever Occurs First[d]	Every 2 Months Until Death or End of Study
Visit Window	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 14 Days**	**± 14 days**	
Serum or Urine Pregnancy Test[e]	Q4W	→	→	→	→	→
CBC with Differential, Platelet Count, Reticulocytes, Blasts	X			Q12W	Q12W	
Serum or Plasma Chemistry	X					
Peripheral Blood for Correlative Studies[f]	X					
Pharmacokinetics	X					
Antidrug Antibodies	X					
Bone Marrow Aspirate[i] for MRD Monitoring, Response Assessment[g], and Cytogenetics[h]	X[i]			Q12W	Q12W	
Peripheral Blood Smear (for Blasts)[g]	X[e]			Q12W	Q12W	
12-lead ECG (single) (for patients treated with 7 + 3)[j]	X			Q12W	Q12W	
Echocardiogram or MUGA (for patients treated with 7 + 3)[j]	X			Q12W	Q12W	
ECOG performance status	X					
Vital Signs	X					
Symptom-Directed Physical Examination	X					
PRO Assessment[k]	X				Q12W	
Adverse Events[l]	X	X	X			
Concomitant Medications	X	X	X			
New Anti-AML Therapy[m]	X	X	X	X	X	X
Survival Follow-up						X

AE = adverse event; CBC = complete blood count; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete count recovery; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire; EOT = end of treatment; MLFS = morphologic leukemia-free state; MUGA = multigated acquisition (scan); PGIS/PGIC = Patient Global Impression of Severity/Patient Global Impression of Change; PR = partial remission; PRO = Patient Report Outcome; Q4W = every 4 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SCT = stem cell transplant; SOC = standard of care

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 For patients who do not initiate new anti-AML therapy after the last dose. See Section 6.4.11. for adverse event reporting details.
c For patients who start new anti-AML therapy (other than SCT) before a relapse, efficacy status (done as SOC) will be collected until relapse.
d Disease progression includes relapse after CR/CRi/CRh or disease progression after PR, stable disease, or MLFS.
e Pregnancy tests should be taken at monthly intervals until end of contraception requirement.
f Peripheral blood for correlative studies should not be repeated at EOT if done at the end of the Consolidation Cycle 4.
g Response assessment at EOT is required at last dose or EOT decision (± 14 days) and is not required if performed within the last 30 days or if progressive disease has been documented or start of new anti-AML therapy, whichever comes first. (SCT and maintenance therapy are not considered new anti-AML therapy.)
h Conventional cytogenetic testing (per institutional standards) is required for all patients.
i Bone marrow aspirate and biopsy for correlative studies is required at EOT if not done at the end of the Consolidation Cycle 4.
j Only for patients undergoing treatment with 7 + 3 intensive chemotherapy. ECG and echocardiogram/MUGA should not be repeated at EOT visit if performed in the past 4 weeks.
k EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC.
l Report all AEs through the safety follow-up visit/call, and any treatment-related SAEs thereafter.
m Collect data for the first new anti-AML therapy following the last dose of study treatment.

Table 25. Schedule of Assessments - Repriming/Reescalation Cycle (Required after Magrolimab Delays of > 4 Weeks)

Visit Window (Days)[a]	None			± 3				
Day	1	2	4	8	11	15	22[b]	29, then every 2 weeks OR 57, then every 2 weeks[b]
Safety								
CBC with differential, platelets, reticulocytes[c,d]	X	X	X	X	X	X	X	
Haptoglobin and LDH[c]	X	X	X	X				
Chemistry[c]	X	X	X	X		X		
Peripheral blood smear for general morphology[c,e]	X	X			X			
Vital signs[f]	X		X	X	X	X	X	X
Weight	X							
Symptom-directed physical examination[c]	X			X		X		
Adverse events[g]	→	→	→	→	→	→	→	→
Concomitant medications[g]	→	→	→	→	→	→	→	→
PK/Immunogenicity								
PK[j]	X			X			X[j]	X[j]
Antidrug antibodies[k]	X						X[k]	X[k]
Magrolimab Administration								
Premedication[l]	X		X	X	X			
Magrolimab[m]	X		X	X	X	X	X	X

ADA = antidrug antibodies; CBC = complete blood count; EOT = end of treatment; LDH = lactate dehydrogenase; PK = pharmacokinetic(s); Q4W = every 4 weeks; WBC = white blood cell

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

b In case the repriming occurs during the first 4 weeks of magrolimab treatment, patient should receive magrolimab 30 mg/kg weekly × 5 after receiving Day 15 dose. All Day 22 safety assessments should be completed weekly x 5. One week after the 5th weekly dose, dosing of magrolimab will be 30 mg/kg Q2W.

c Pretreatment assessments for the initial dose may be collected up to 72 hours before administration of any study treatment. Pretreatment laboratory assessments are to be collected within 24 hours prior to any intravenous or subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.

d 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 dose during first 4 weeks of repriming. In the case of repriming, before the administration of the 2 first doses of magrolimab, hemoglobin should be ≥ 9 g/dL. Transfusions are allowed to meet this hemoglobin level.

e Peripheral blood smears for general morphology will be collected predose and assessed locally.

f Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.4.5.

g Adverse events and concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

j Samples will be collected within 72 hours before the first dose of magrolimab and within 12 hours before subsequent doses of magrolimab. In addition to Day 1, and Day 8, predose samples will also be collected before the Day 29 dose (only applicable if the repriming schedule has 4 additional weekly doses post Day 22), as well as before the 1st, 5th, 9th, 15th, and 21st biweekly maintenance doses of 30 mg/kg, respectively, and at EOT. On the first day of the biweekly maintenance dose, an additional sample for postdose PK will be collected at 1 hour (± 15 minutes) after the end of infusion of magrolimab.

k When collected on the day of magrolimab dosing, the blood sample for ADA must be collected at the same time as the predose PK sample. ADA samples will be collected at predose on Day 1 and Day 29 (only applicable if the repriming schedule has 4 additional weekly doses post Day 22), as well as before the 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg, respectively, and at EOT.

l Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment in case of reintroduction with repriming. Premedication for subsequent cycles 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 doses is required (Section 7.8.1.2).

m Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion, during first 4 weeks for repriming. For magrolimab dosing, please refer to Table 2.

Table 26. Schedule of Assessments - Treatment Period for Azacitidine (Experimental Arm) and Venetoclax + Azacitidine Regimens, in the Event the Study Meets Futility, and the Sponsor Decides to Terminate the Study

Visit Window	Cycle (28-day cycles)																																		
	Cycle 1													Cycle 2												Cycle 3+									
	None	± 3 Days												± 3 Days												± 3 Days									
Cycle Day	1	2	3	4	5	6	7	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]	1	2	3	4	5	6	7	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]	1	2	3	4	5	6	7	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]
Serum or Urine Pregnancy Test[b,]	X													X												X									
CBC with Differential, Platelets, Reticulocytes, Blasts[c, d]	X	X		X				X	X	X	X	X	X	X							X	X	X	X	X	X							X	X	X
Serum or Plasma Chemistry[e]	X[e]	X[e]	X[e]	X[e]				X		X	X			X								X				X							X		
Bone Marrow Aspirate for Response Assessment[f, g, h]												X												X										C4D28, C6D28 then Q3C	
Vital Signs[i]	X	X						X	X	X	X			X							X	X	X			X							X		
Weight[i]	X													X												X									
Symptom-directed Physical Examination[c]	X							X		X				X												X									
Adverse Events, Concomitant Medications (Including Blood Transfusions)[j]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

Visit Window	Cycle (28-day cycles)																																				
	Cycle 1													Cycle 2												Cycle 3+											
	None	± 3 Days												± 3 Days												± 3 Days											
Cycle Day	1	2	3	4	5	6	7	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]	1	2	3	4	5	6	7	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]	1	2	3	4	5	6	7	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[a]
Study Treatment Dispensing																																					
Venetoclax[k]	X													X												X											
Study Treatment Administration																																					
Azacitidine[l]	X	X	X	X	X	X	X							X	X	X	X	X	X	X						X	X	X	X	X	X	X					
Venetoclax[k, m]	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			

C = cycle; CBC = complete blood count; D = day; MRD = minimal residual disease; Q3C = every 3 cycles; SOC = standard of care; WBC = white blood cell

a. 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 CBC (including prior Day 28 CBC) is within 3 days of Day 1.

b. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 6.4.1.

c. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment except for CBC, which must be performed within 24 hours prior to magrolimab dosing. Thereafter, pretreatment assessments are to be collected within 24 hours prior to any intravenous or subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.

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

e. 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.

f. Bone marrow assessments may continue locally as per the schedule outlined in Table 13 and Table 26 or as per investigator discretion. MRD testing will not be required nor performed by the central laboratory but may be done locally per SOC. If continuing response assessments per Table 13 and Table 26, Day 28 assessments can be done on Day 1 of the next cycle if there is no foreseen delay of more than 7 days. Bone marrow response information from Day 28 may be used to decide start of the next cycle per dosing modification guidelines in the protocol (Section 5.10, and Table 8, Table 9, and Table 11).

g. Conventional cytogenetics testing may be performed locally per SOC but will not be required.

h. If continuing assessments per Table 13 and Table 26, response assessments may be adjusted by up to 1 week prior to Cycle 1 Day 28, and Cycle 2 Day 28. After Cycle 2 Day 28, the window is up to 14 days ± from Day 28. Bone marrow results should be reviewed as required for determining schedule modifications.

i. Vital signs will be assessed prior to infusion/injection of each study treatment on the days marked in the table. Weight will be assessed on Day 1 of each cycle. Details are provided in Section 6.4.5.

j. Collected at all regularly scheduled visits. In the event the study meets futility, and the sponsor decides to terminate the study, AEs that occur following initiation of study medication, regardless of cause or relationship, will be collected until 30 days (± 7 days) after last administration of study drug and reported on the eCRFs as instructed.
k. Venetoclax will be dispensed to the patient on Day 1 of each treatment cycle.
l. Azacitidine administration should be completed at least 1 hour before magrolimab administration on days when both drugs are administered. Azacitidine may be administered on an alternative schedule such as Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience as long as the 7 doses of azacitidine of the cycle are administered within 9 consecutive days.
m. Venetoclax is administered daily. Please refer to Section 5.4.

Table 27. Magrolimab Administration and Associated Assessment Schedule-Treatment Period, in the Event the Study Meets Futility, and the Sponsor Decides to Terminate the Study

Visit Window (Days)	None[a]			± 3[a]				
Day	**1**	**2**	**4**	**8**	**11**	**15**	**Weekly × 5**	**Every 2 Weeks**
Vital signs[b]	X		X	X	X	X	X	X
Hemoglobin[c]	Pre and post dose		Pre and post dose					
Magrolimab Administration								
Premedication[d]	X		X	X	X			
Magrolimab[e]	X		X	X	X	X	X	X

a. In cases of magrolimab repriming/re-escalation following a treatment delay (Section 5.8.1), follow magrolimab schedule of assessment and administration for repriming (Table 29).
b. Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.4.5.
c. Hemoglobin must be performed within 24 hours prior to magrolimab dosing on Days 1 and 4 to ensure hemoglobin is ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 magrolimab doses. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (see Section 5.8).
d. Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming. Premedications should include oral acetaminophen 650 to 1000 mg, oral or IV diphenhydramine 25 to 50 mg, and IV dexamethasone 4 to 20 mg or comparable regimen. For patients who do not experience an IRR with the first 2 doses of magrolimab, steroid pretreatment can be discontinued at investigators' discretion. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. (Sections 5.9 and 7.8.1.2).
e. Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion for priming, repriming/re-escalation, and maintenance doses during the first 4 weeks. For magrolimab dosing, refer to Table 2.

Table 28. Schedule of Assessments – Posttreatment, in the Event the Study Meets Futility, and the Sponsor Decides to Terminate the Study

	End of Treatment Visit	Safety Follow-up Visit/Call (Telephone)
	Within 7 Days After Last Dose or EOT Decision, Whichever Occurs Later	30 Days After Last Dose
Visit Window	**± 7 Days**	**± 7 Days**
Serum or Urine Pregnancy Test[a]	Q4W	
CBC with Differential, Platelet Count, Reticulocytes, Blasts	X	
Serum or Plasma Chemistry	X	
Bone Marrow Aspirate for Response Assessment[b, c]	X	
ECOG performance status	X	
Vital Signs	X	
Symptom-Directed Physical Examination	X	
Adverse Events[d, e]	X	X
Concomitant Medications	X	X

AE = adverse event; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRD = minimal residual disease; Q4W = every 4 weeks; SAE = serious adverse event; SCT = stem cell transplant; SOC = standard of care

a. Pregnancy tests should be taken at monthly intervals until end of contraception requirement (Appendix 5).
b. Response assessment at EOT may be performed locally at last dose or EOT decision (± 14 days). MRD testing will not be required nor performed by the central laboratory but may be done locally per SOC.
c. Conventional cytogenetic testing may be performed per SOC but is not required.
d. Report all AEs through the safety follow-up visit/call. SAEs that occur after the 30 days (± 7 days) posttreatment follow-up visit may be reported if deemed relevant to the use of study drug by the investigator. Adverse events and concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled. In the event the study meets futility and the sponsor decides to terminate the study, AEs and concomitant medications will be collected until 30 days (± 7 days) after last administration of study drug and reported on eCRFs as instructed. Post-study anti-AML therapy status will not be collected for patients discontinuing study treatment in the event of study termination due to futility.
e. If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site. In the event the study meets futility, and the sponsor decides to terminate the study, SAEs that occur after the 30 days (± 7 days) posttreatment follow-up visit may be reported if deemed relevant to the use of study drug by the investigator.

Table 29. Schedule of Assessments - Repriming/Re-escalation Cycle (Required after Magrolimab Delays of > 4 Weeks), in the Event the Study Meets Futility, and the Sponsor Decides to Terminate the Study

Visit Window (Days)[a]	None			± 3				
Day	1	2	4	8	11	15	22[b]	29, then every 2 weeks OR 57, then every 2 weeks[b]
Safety								
CBC with differential, platelets, reticulocytes[c,d]	X	X	X	X	X	X	X	
Chemistry[c]	X	X	X	X		X		
Vital signs[e]	X		X	X	X	X	X	X
Weight	X							
Symptom-directed physical examination[c]	X			X		X		
Adverse events[f]	→	→	→	→	→	→	→	→
Concomitant medications[f]	→	→	→	→	→	→	→	→
Magrolimab Administration								
Premedication[g]	X		X	X	X			
Magrolimab[h]	X		X	X	X	X	X	X

CBC = complete blood count; Q2W = every 2 weeks; WBC = white blood cell

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

b. In case the repriming occurs during the first 4 weeks of magrolimab treatment, patient should receive magrolimab 30 mg/kg weekly × 5 after receiving Day 15 dose. All Day 22 safety assessments should be completed weekly × 5. One week after the 5th weekly dose, dosing of magrolimab will be 30 mg/kg Q2W.

c. Pretreatment assessments for the initial dose may be collected up to 72 hours before administration of any study treatment. Pretreatment laboratory assessments are to be collected within 24 hours prior to any intravenous or subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.

d. 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 dose during first 4 weeks of repriming. In the case of repriming, before the administration of the 2 first doses of magrolimab, hemoglobin should be ≥ 9 g/dL. Transfusions are allowed to meet this hemoglobin level.

e. Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.4.5.

f. Adverse events and concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled. In the event the study meets futility, and the sponsor decides to terminate the study, AEs and concomitant medications will be collected until 30 days (± 7 days) after last administration of study drug and reported on eCRFs as instructed. Post-study anti-AML therapy status will not be collected for patients discontinuing study treatment in the event of study termination due to futility.
g. Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment in case of reintroduction with repriming. Premedications should include oral acetaminophen 650 to 1000 mg, oral or IV diphenhydramine 25 to 50 mg, and IV dexamethasone 4 to 20 mg or comparable regimen. For patients who do not experience an IRR with the first 2 doses of magrolimab, steroid pretreatment can be discontinued at investigators' discretion. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequence doses at the investigator's discretion (Sections 5.9 and 7.8.1.2).
h. Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion, during first 4 weeks for repriming. For magrolimab dosing, please refer to Table 2.

Appendix 3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study.

These potential risks and mitigation plans can be summarized as follows:

1) Schedule of assessments:

    a) Physical examination:

        i) For all assessments where a physical examination is indicated, this portion of the visit can be conducted virtually; however, when samples need to be collected or dosing performed, these activities must occur in the clinic.

        ii) If a virtual visit is conducted for the physical examination assessment portion, in order to limit a patient's time in the clinic, vital signs may be omitted.

    b) Dosing:

        i) For Cycle 2 and repriming cycles, magrolimab can be administered on Day 7 with azacitidine, with collection of Day 8 assessments (ie, laboratory assessments, PK) on Day 7 in order to minimize an extra patient visit.

        ii) Dosing delays with magrolimab:

            (1) For patients who may have travel restrictions, the 4-week period of magrolimab dose delay for repriming can be extended to 6 weeks in order to minimize the need for repriming for patients in this scenario. Medical monitor approval is needed for this specific situation. Magrolimab every-2-week dosing should be encouraged as dosing intervals longer than this will lead to suboptimal efficacy.

        iii) Dosing with azacitidine:

            (1) If needed under specific circumstances, sites can allow for administration of azacitidine locally nearer to patient's residence, with proper documentation (eg, name of site, name of physician overseeing transfusion, name of laboratory used, including accreditation certificate). Administration of azacitidine outside the center should be reserved only in cases where patients will not be able to get azacitidine dosing otherwise.

            (2) If treatment administration is given locally, then the patient should be evaluated by a local hematologist on Day 1 of that treatment cycle and have all laboratory assessments required on the Day 1 treatment cycle performed as per the protocol. The site should procure the clinical notes and laboratory reports for the principal investigator (PI) review and signature. The site is to ensure that all of these documents are filed in the patient's source records.

(3) The treating physician at the study site should speak to the local hematologist and review protocol guidelines/dosing of azacitidine/reporting of reactions and document this information in the medical records.

c) Sample collection:

i) While it is preferred to collect all protocol-specified laboratory samples, if resources are limited, PK/ADA samples may be collected and stored (frozen) and not shipped in real-time if staff are not available to do so.

ii) MRD testing should be collected and shipped in real-time.

iii) For correlative peripheral blood or bone marrow aspirate samples, if they cannot be shipped according to their corresponding standard procedures same day, or refrigerated overnight for shipment the next day, please isolate the mononuclear cells (eg, by Ficoll gradient) and cryopreserve according to local best practices. If it is not possible to either ship samples or preserve and store according to the guidance above, then collection of these samples may be omitted until normal operations can resume.

d) General patient selection guidance:

i) To minimize patients receiving RBC transfusions given the current transfusion product shortage, we recommend selecting patients with higher hemoglobin thresholds at baseline and use IV iron and/or erythropoietin where clinically indicated.

2) Study drug supplies to patients and sites:

a) Patients may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

Mitigation plan: If permitted by local EC/IRB/Regulatory authority as applicable and with sponsor's approval, study drug supplies may be provided to the patient from the site without a clinic visit. It must be confirmed that the patient may safely continue on study drug as determined by the PI. A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study patients, and a qualified vendor may be utilized to perform infusions in the patients' local vicinity.

b) Shipments of study drug from the sponsor to the investigational site could be delayed because of transportation issues. Without study drug, the patient would not be able to stay on the study drug as planned per protocol.

Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered, as necessary.

3) Patient safety monitoring and follow-up:

   a) Patients may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

      Mitigation plan: For patients who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the patient within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

      i) Confirm if patient has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs

      ii) Review current list of concomitant medications and document any new concomitant medications

      iii) If applicable, confirm patient's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (2)

      iv) If applicable, confirm that electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

      v) If applicable, remind patient to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit

   b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence, samples may not be sent for central lab analyses.

      Mitigation plan: Accredited local laboratory may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Alternative sample handling and storage may be possible for samples routinely sent to the central laboratory; sites should refer to the study laboratory manual and discuss with the sponsor for further guidance.

c) Patients may be unable or unwilling to attend the study visit to sign an updated ICF version if there is an update.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if it has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) The safety of study participants is important and testing of COVID-19 infection will be based on local clinical guidelines for testing based on signs/symptoms and or suspected exposure to COVID-19.

Mitigation plan: If patient has a diagnosis of COVID-19 while on this clinical study, study drugs may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general magrolimab/azacitidine dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in a clinical study will have this event documented as an adverse event in the clinical database.

4) Protocol and monitoring compliance:

a) Protocol deviations may occur if scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on site, must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

   a) There may be an increased amount of missing data due to patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of the study drugs in study patients remains unchanged. In the event that these potential risks cannot be mitigated due to the escalation of a pandemic, randomization of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 4. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

There are no adequate and well-controlled studies of magrolimab in pregnant women. Magrolimab when dosed to pregnant monkeys was not teratogenic, but high-dose magrolimab resulted in stillbirth and neonate deaths, secondary to fetal anemia. Based on these data, magrolimab should not administered to pregnant women. Advise females with reproductive potential to avoid pregnancy during treatment with magrolimab and for at least 3 months after treatment.

For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the MOA and findings in animals, azacitidine may cause fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid pregnancy during treatment with azacitidine. Duration of required contraception for female patients in this clinical study should start from screening visit until 6 months after the last dose of the latest administered study drug. Studies in vitro have demonstrated that CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Based on its MOA and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid pregnancy during treatment with venetoclax. Duration of required contraception for female patients in this clinical study should start from screening visit until 6 months after the last dose of the latest administered study drug.It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives.

Cytarabine can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.

Daunorubicin crosses the placenta and experiments in animals have shown it to be mutagenic, carcinogenic, and teratogenic. Women of childbearing potential should be advised to avoid becoming pregnant. For women who want to become pregnant after completing daunorubicin treatment, genetic counselling is also recommended.

The embryotoxic potential of idarubicin has been demonstrated in both in vitro and in vivo studies. There is no conclusive information about idarubicin adversely affecting human fertility or causing teratogenesis. The patient should be informed of the potential hazard to the fetus. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling first if appropriate and available.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information for information on the potential risks of treatment with azacitidine, venetoclax, cytarabine, daunorubicin, or idarubicin.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. Pregnancy tests will be performed at the beginning of each cycle thereafter (described in the protocol) until the end of contraception requirement.

Duration of required contraception for female patients in this clinical study should start from screening visit until 6 months after the last dose of the latest administered study drug.

Female patients must agree to one of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Non-hormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)

- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows, where local standard of care practices allow:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone*
  - Transdermal contraceptive patch*
  - Contraceptive vaginal ring*
  - Subdermal contraceptive implant*
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)*
  - Diaphragm with spermicide*
  - Cervical cap with spermicide*
  - Sponge with spermicide*

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

3) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 6 months after last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive method should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Patients will be instructed to notify the investigator immediately if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months post last study drug dose. Study drug must be discontinued immediately.

Patients whose partner has become pregnant or suspects she is pregnant from start of study to 6 months post last study drug dose must also report the information to the investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. 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 ELN 2017 recommendations for AML with modifications {Dohner 2017} (Table 30). 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)

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

The date of the bone marrow assessment should be used as the date of response assessment. The complete blood count (CBC) 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 disease progression 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.

Table 30. 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) non-transfused); or • ≥ 50% increase in peripheral blasts (WBC x% 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 count recovery; CR_{MRD} = complete remission without minimal residual disease; 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}

Table 31. 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 months of treatment with magrolimab + azacitidine or venetoclax + azacitidine, or up to 2 months of treatment with 7 + 3 chemotherapy			

cCR = cytogenetic complete remission; CR = complete remission; IWG = International Working Group
a. Treatment failure defined for this protocol.
Source: {Cheson 2003}

Table 32. 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 $\geq 30 \times 10^9$/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 Hematologic 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}

Appendix 7. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 8. 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

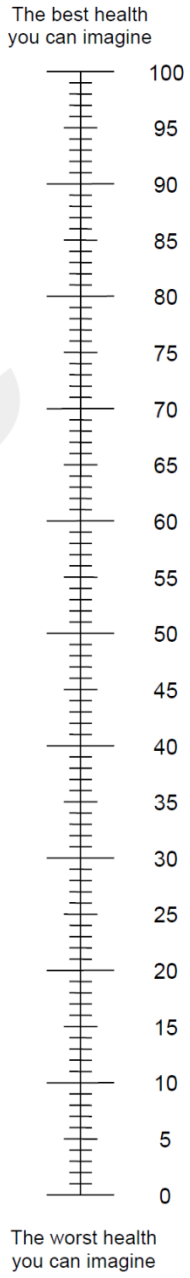
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 9. Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

HEALTH-RELATED QUALITY OF LIFE

PGIS: Please choose the response below that best describes your health-related quality of life (physical, social and psychological wellbeing) during the past week

- Excellent
- Good
- Moderate
- Poor
- Very Poor

PGIC: All things considered, how did your health-related quality of life (physical, social and psychological wellbeing) change since you started taking the study medication?

- Much improved
- A little improved
- No change
- A little worsened
- Much worsened

PHYSICAL FUNCTION

PGIS: Please choose the response below that best describes your physical function (the ability to carry out physical activities in your daily life) during the past week:

- Excellent
- Good
- Moderate
- Poor
- Very Poor

PGIC: All things considered, how did your physical function (the ability to carry out physical activities in your daily life) change since you started taking the study medication?

- Much improved
- A little improved
- No change
- A little worsened
- Much worsened

Appendix 10. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Scale of Performance Status

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Available online: http://ecog-acrin.org/resources/ecog-performance-status. Accessed 18 February 2020.

Appendix 11. Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided in the table below. The formula appropriate to the units in which serum creatinine was measured and the subject's gender should be used.

Serum Creatinine Units	Gender	Formula
mg/dL	Males	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1}{72 \times \text{subject serum creatinine [mg/dL]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dL]}}$
µM/dL	Males	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.23}{\text{Subject serum creatinine [mg/dL]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.04}{\text{Subject serum creatinine [mg/dL]}}$

Abbreviation: eCcr = estimated creatinine clearance
Source: {Cockcroft 1976}

Appendix 12. World Health Organization (WHO) Classification of AML

AML with recurrent genetic abnormalities (gene or chromosome changes)

- AML with a translocation between chromosomes 8 and 21 [t(8;21)]
- AML with a translocation or inversion in chromosome 16 [t(16;16) or inv(16)]
- APL with the *PML-RARA* fusion gene
- AML with a translocation between chromosomes 9 and 11 [t(9;11)]
- AML with a translocation between chromosomes 6 and 9 [t(6;9)]
- AML with a translocation or inversion in chromosome 3 [t(3;3) or inv(3)]
- AML (megakaryoblastic) with a translocation between chromosomes 1 and 22 [t(1;22)]
- AML with the *BCR-ABL1* (*BCR-ABL*) fusion gene
- AML with mutated *NPM1* gene
- AML with biallelic mutations of the *CEBPA* gene (that is, mutations in both copies of the gene)
- AML with mutated *RUNX1* gene

AML with myelodysplasia-related changes

AML related to previous chemotherapy or radiation

AML not otherwise specified (This includes cases of AML that do not fall into one of the above groups.)

Appendix 13. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the Amendment 4 to this amendment will be made available upon the publication of this protocol.

Amendment 5 (02 November 2023)

Rationale for Key Changes Included in Amendment 5	Affected Sections
Added the information that the current study met futility and sites were informed of the outcome and sponsor's decision in a communication in September 2023.	Synopsis, Section 3.2, Section 7.3.2
Clarified that, in the event the study meets futility and is terminated, discontinued patients will not be followed for response or survival. Specifics about follow-up were clarified.	Section 3.2, Section 3.5, Section 3.7, Section 6.10, Section 7.3.2, Section 7.3.3, Section 8.2.1, Section 8.2.3
Clarification of collection of study samples and adverse events in the event that the study meets futility.	Section 3.9, Section 3.9.1, Section 3.9.2, Section 6.1.2, Section 6.4, Section 6.5, Section 6.6, Section 6.7, Section 6.8, Section 6.9, Section 8.5.4
Clarification that if the study meets futility and the sponsor decides to terminate the study, no further patients will be enrolled.	Section 4.1
Addition of "anemia, neutropenia, thrombocytopenia, and infections are known adverse drug reactions associated with both azacitidine and magrolimab"	Section 1.7
Updates were made to the Management of Infusion Related Reactions information section to incorporate the use of corticosteroids as premedication during the first few infusions of magrolimab, and to incorporate guidance for discontinuation of magrolimab in certain cases.	Table 16
Moved language about the objective and endpoint of time to first deterioration on the global health status/quality of life and on the physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30) from secondary to CCI endpoints. Moved language on transfusion conversion rate from secondary to CCI endpoints. Changed endpoint and updated definition of TTD on the global health status/quality of life and on the physical functioning scales of the EORTC QLQ-C30.	Synopsis, Section 2

Rationale for Key Changes Included in Amendment 5	Affected Sections
Added language about the objective and endpoint comparing the efficacy of magrolimab + azacitidine versus physician's choice of venetoclax + azacitidine or 7 + 3 chemotherapy as measured by event-free survival (including CR, CRi, and CRh).	Synopsis, Section 2
Added language in the endpoint to clarify mean change from baseline on the EORTC QLQ-C30 domains, EQ visual analogue scale, and PGIS scale, as well as addition of descriptive summaries.	Section 2
Added language about the study meeting futility, study termination, and movement of patients to standard of care therapy, and provision of standard of care by the sponsor.	Synopsis, Section 3.2
Added information about post infusion monitory beginning after the infusion is complete.	Section 5.8
The update to Section 5.9 is to incorporate guidance for the use of corticosteroids as premedication for the first few infusions of magrolimab.	Section 5.9
Clarified SAE collection in the event that the study meets futility.	Section 7.3
Clarified that "significant drops (up to 3 g/dL or more) have also been observed in early doses."	Section 7.8.1.1
Guidelines for dose delay and discontinuation are provided in case of severe neutropenia, serious infections, and IRR.	Section 5.10.1.1, Section 7.8.1.2, Section 7.8.1.4, Section 7.8.1.5
Removal of time until meaningful definitive deterioration (TUDD) language for EORTC QLQ-C30 GHS/QoL scale and physical functioning scale in all patients.	Table 1, Section 8.2.1.2, Table 19, Section 8.8
Clarification that if the study meets futility and is terminated, the planned interim analysis is no longer required.	Section 8.2.1
Clarification that if the study meets futility and is terminated, the planned primary analysis is no longer required.	Section 8.2.2
Updating the timing of adverse event and laboratory event collection.	Section 8.6.2, 8.6.3
Addition of a schedule of assessments table to clarify the treatment period for azacitidine or venetoclax+azacitidine in the event that the study meets futility and is terminated.	Table 26
Addition of a schedule of assessments table to clarify the treatment period for magrolimab in the event that the study meets futility and is terminated.	Table 27
Addition of a schedule of assessments table to clarify the post treatment period in the event that the study meets futility and is terminated.	Table 29
Addition of a schedule of assessments for repriming/reescalation (required after magrolimab delays of > 4 weeks) table to clarify the post treatment period in the event that the study meets futility and is terminated.	Table 30

Prot GS-US-546-5857 amd-5

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	02-Nov-2023 20:14:05