Title

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ABSTRACT

PURPOSE Magrolimab is a first-in-class humanized monoclonal antibody against cluster of differentiation 47, an antiphagocytic signal used by cancer cells to evade phagocytosis. Azacitidine upregulates prophagocytic signals on AML cells, further increasing phagocytosis when combined with magrolimab. We report final phase Ib data for magrolimab with azacitidine in patients with untreated AML ineligible for intensive chemotherapy (ClinicalTrials.gov identifier: NCT03248479).

PATIENTS AND METHODS Patients with previously untreated AML, including *TP53*-mutant AML, received magrolimab intravenously as an initial dose (1 mg/kg, days 1 and 4), followed by 15 mg/kg once on day 8 and 30 mg/kg once weekly or every 2 weeks as maintenance. Azacitidine 75 mg/m² was administered intravenously/subcutaneously once daily on days 1-7 of each 28-day cycle. Primary end points were safety/tolerability and proportion with complete remission (CR).

RESULTS Eighty-seven patients were enrolled and treated; 72 (82.8%) had *TP53* mutations with a median variant allele frequency of 61% (range, 9.8-98.7). Fifty-seven (79.2%) of *TP53*-mutant patients had European LeukemiaNet 2017 adverse-risk cytogenetics. Patients received a median of 4 (range, 1-39) cycles of treatment. The most common treatment-emergent adverse events included constipation (49.4%), nausea (49.4%), and diarrhea (48.3%). Thirty (34.5%) experienced anemia, and the median hemoglobin change from baseline to first postdose assessment was −0.9 g/dL (range, −3.6 to 2.5 g/dL). Twenty-eight (32.2%) patients achieved CR, including 23 (31.9%) patients with *TP53* mutations. The median overall survival in *TP53*-mutant and wild-type patients were 9.8 months and 18.9 months, respectively.

CONCLUSION Magrolimab with azacitidine was relatively well tolerated with promising efficacy in patients with AML ineligible for intensive induction chemotherapy, including those with *TP53* mutations, warranting further evaluation of magrolimab with azacitidine in AML. The phase III randomized ENHANCE-2 (ClinicalTrials.gov identifier: NCT04778397) and ENHANCE-3 (ClinicalTrials.gov identifier: NCT05079230) studies are recruiting frontline patients with AML.

INTRODUCTION

Older age, performance status, and genetic risk group are independent predictors of poor outcomes in AML.[1] Patients 65 years and older with AML have a 5-year overall survival (OS) of only 11% in recent SEER data,[2] because of intolerance to intensive chemotherapy (IC),[1,3] and a higher burden of poor-risk genetic abnormalities and genetic secondary AML.[4,5] Newly diagnosed patients with *TP53*-mutant AML treated with IC have a median OS of only 4-7 months and high induction mortality.[6-8] Lower-intensity treatments, including standard-of-care venetoclax-azacitidine for older/unfit

CONTEXT

Key Objective
Is the first-in-class anticluster of differentiation 47 monoclonal antibody magrolimab safe, well-tolerated, and efficacious when combined with azacitidine in patients with untreated AML unfit for intensive induction chemotherapy, particularly those with *TP53* mutations, a population with a very high unmet need?

Knowledge Generated
Efficacy data support the magrolimab-azacitidine synergy observed in preclinical studies, with encouraging complete remission (CR) rates, durations of CR, and overall survival in patients with AML regardless of *TP53* mutation status including a subset that bridged to allogeneic hematopoietic stem-cell transplantation. Magrolimab + azacitidine was generally well-tolerated, with manageable expected early anemia and hemoglobin improvement over time on treatment.

Relevance *(C.F. Craddock)*
It will be important to confirm this promising early-phase data relating to tolerability and efficacy of the novel magrolimab-azacitidine combination in adults with de novo AML deemed ineligible for intensive chemotherapy, and the results of ongoing randomized trials are awaited with interest.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

TP53-mutant AML, have a similarly poor median OS of 5.5-7.2 months.[8-10] Evidence suggests that outcomes may be even poorer in patients with *TP53*-mutant AML with concomitant adverse-risk cytogenetics, a *TP53* variant allele frequency (VAF) of >40%, or multihit *TP53*-mutant disease.[7,11-13] However, a recent study reported no association between any *TP53* molecular characteristics and survival (2-year OS, 12.8%) and suggested that *TP53* mutation represents a distinct disease entity.[14] These findings highlight a major unmet need for patients with *TP53*-mutant AML.

The cluster of differentiation 47 (CD47) is a widely expressed cell surface protein that binds signal-regulatory protein alpha (SIRPα) on phagocytic cells providing an antiphagocytic *don't eat me* signal. Its overexpression on cancer cells is postulated to overcome prophagocytic *eat me* signals to evade phagocytosis.[15,16] Magrolimab is a first-in-class humanized immunoglobulin G4 anti-CD47 monoclonal antibody that blocks CD47-SIRPα interaction, promoting cancer cell phagocytosis (Data Supplement, Fig S1 [online only]). Azacitidine upregulates *eat me* signals, such as calreticulin, on AML cell surfaces.[17,18] In preclinical studies, magrolimab promoted AML cell phagocytosis[19] and was synergistic with azacitidine in vitro and in vivo.[17,18]

Magrolimab monotherapy was well tolerated in two phase I clinical studies in solid tumors and lymphoma (ClinicalTrials.gov identifier: NCT02216409)[20] and in relapsed/refractory AML (ClinicalTrials.gov identifier: NCT02678338, CAMELLIA study).[21] We report results from a phase Ib trial (5F9005, ClinicalTrials.gov identifier: NCT03248479) of magrolimab + azacitidine in untreated patients with AML ineligible for IC.

PATIENTS AND METHODS

Study Design and Participants

This open-label, multicenter, multicohort, phase Ib trial had a screening period of ≤30 days, a 3 + 3 dose-evaluation phase, and an expansion phase (Data Supplement, Fig S2). Eligible patients were previously untreated adults (18 years and older) with histologically confirmed AML by WHO 2008 classification, who could not receive standard IC because of age, comorbidities, treating physicians' discretion, or who refused IC. After 25 patients were enrolled in the expansion, the study accrued only patients with *TP53* mutations on the basis of poor outcomes in this molecular subgroup with hypomethylating agent (HMA)-venetoclax combinations.[22,23] Patients had an Eastern Cooperative Oncology Group performance score of 0-2 and a WBC count of ≤20× 10³/μL before the first and each magrolimab dose in cycle 1. Hydroxyurea or oral etoposide was permitted for WBC count control. No minimum hemoglobin (Hb) value at baseline was required. Enrolled patients were required to have AST and ALT ≤5× upper limit of normal (ULN); bilirubin ≤1.5× or ≤3.0× ULN and primarily unconjugated if documented history of Gilbert's syndrome or genetic equivalent; and serum creatinine ≤1.5× ULN or calculated glomerular filtration rate ≥40 mL/min/1.73 m². Patients with acute promyelocytic leukemia or clinical suspicion of active CNS involvement by leukemia were excluded. Each patient was tested for *TP53* and prespecified somatic mutations using local next-generation sequencing (NGS) per each institutional standard. *TP53* VAF was available at screening in a subset of patients; another subset underwent baseline and longitudinal central whole-exome sequencing (WES) using customized processing pipelines combining

TABLE 1. Baseline Characteristics

Characteristic	TP53-Mutant (n = 72)	TP53 Wild-Type (n = 15)	All Patients (N = 87)
Age, years, median (range)	73 (31-89)	75 (62-83)	73 (31-89)
Male/female, No. (%)	41 (56.9)/31 (43.1)	9 (60.0)/6 (40.0)	50 (57.5)/37 (42.5)
Race, No. (%)			
Asian	4 (5.6)	0 (0)	4 (4.6)
Black or African American	3 (4.2)	0 (0)	3 (3.4)
White	60 (83.3)	15 (100)	75 (86.2)
Not reported/missing	5 (6.9)	0 (0)	5 (5.7)
ECOG performance status, No. (%)			
0	10 (13.9)	3 (20.0)	13 (14.9)
1	51 (70.8)	11 (73.3)	62 (71.3)
2	11 (15.3)	1 (6.7)	12 (13.8)
Bone marrow blast, median, % (range)	32.5 (3.0-92.0)	37.0 (21.0-90.8)	35.0 (3.0-92.0)
Blasts 20%-50%, No. (%)	45 (62.5)	9 (60.0)	54 (62.1)
Blasts >50%, No. (%)	17 (23.6)	6 (40.0)	23 (26.4)
WHO classification, No. (%)			
AML with recurrent genetic abnormalities	10 (13.9)	1 (6.7)	11 (12.6)
AML with myelodysplasia-related changes	34 (47.2)	10 (66.7)	44 (50.6)
AML related to previous chemotherapy or radiation	15 (20.8)	1 (6.7)	16 (18.4)
AML not otherwise specified	13 (18.1)	3 (20.0)	16 (18.4)
Cytogenetic risk category, No. (%)			
Favorable	1 (1.4)	2 (13.3)	3 (3.4)
Intermediate	2 (2.8)	4 (26.7)	6 (6.9)
Adverse	57 (79.2)	3 (20.0)	60 (69.0)
Unknown	12 (16.7)	6 (40.0)	18 (20.7)
Baseline cytogenetics, No. (%)	n = 61	NA	NA
Add5q/del5q/del5	33 (54.1)	NA	NA
Del7q	3 (4.9)	NA	NA
Del7	13 (21.3)	NA	NA
Del17p	1 (1.6)	NA	NA
Del17	10 (16.4)	NA	NA
Complex karyotype	47 (77.0)	NA	NA
Monosomal karyotype	28 (45.9)	NA	NA
Trisomy 8	7 (11.5)	NA	NA
t(9;22)	1 (1.6)	NA	NA
Normal karyotype	1 (1.6)	NA	NA
Mutations at baseline, No. (%)			
TP53	72 (100.0)	0 (0)	72 (82.8)
TET2	11 (15.3)	2 (13.3)	13 (14.9)
DNMT3a	7 (9.7)	4 (26.7)	11 (12.6)
IDH1/IDH2	4 (5.6)	2 (13.3)	6 (6.9)
FLT3	0 (0)	2 (13.3)	2 (2.3)
NPM1	0 (0)	1 (6.7)	1 (1.1)
RBC transfusion−dependent, No. (%)[a]	37 (51.4)	6 (40.0)	43 (49.4)
Platelet transfusion−dependent, No. (%)[b]	24 (33.3)	1 (6.7)	25 (28.7)
TP53 VAF (n = 39), median (range)[c,d]	61.0 (9.8-98.7)	NA	NA
WBC counts (10⁹/L), median (range)	2.10 (0.50-22.91)	2.40 (0.71-14.94)	2.12 (0.50-22.91)

TABLE 1. Baseline Characteristics (continued)

Characteristic	TP53-Mutant (n = 72)	TP53 Wild-Type (n = 15)	All Patients (N = 87)
Hemoglobin, g/dL, median (range)	8.6 (6.3-13.0)	8.8 (6.0-11.0)	8.6 (6.0-13.0)
<9, No. (%)	44 (61.1)	8 (53.3)	52 (59.8)
≥9, No. (%)	28 (38.9)	7 (46.7)	35 (40.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available; NGS, next-generation sequencing; VAF, variant allele frequency.
[a]Baseline RBC transfusion dependence is defined as transfusion within 4 weeks before the first study treatment.
[b]Baseline platelet transfusion dependence is defined as transfusion within 4 weeks before the first study treatment.
[c]Patients with TP53 mutations had at least one TP53 gene mutation locally assessed by NGS per each institution's standard practice.
[d]Thirty-three (45.8%) patients were missing baseline TP53 VAF data.

published algorithms with novel filtering, curation, and quality control steps that were developed using a VAF cutoff of 0.07. Full inclusion/exclusion criteria are given in the Protocol (online only) and sample size description is given in the Data Supplement (Methods).

All patients provided written informed consent before study participation. The study was conducted according to International Conference on Harmonisation Good Clinical Practice guidelines, Declaration of Helsinki, and local Institutional Review Board requirements.

Procedures

RBC phenotyping or genotyping, type and screen (ABO/Rh), and direct antiglobulin test were performed at screening to select appropriate RBC products for transfusion because magrolimab can interfere with pretransfusion test results and crossmatching (Data Supplement, Methods). The initial cohort evaluated dose-limiting toxicities in eight patients (seven AML and one myelodysplastic syndrome [MDS]) during the first 28 days before expansion (Protocol). In expansion, magrolimab was administered intravenously at 1 mg/kg once each on days 1 and 4; 15 mg/kg once on day 8; and 30 mg/kg once each on days 11, 15, and 22. Beginning in cycle 2, 30 mg/kg was administered once weekly, followed by 30-mg/kg maintenance once weekly or biweekly from cycle 3. Azacitidine 75 mg/m² was administered subcutaneously/intravenously once daily on days 1-7 of each 28-day cycle. Treatment was continued until unacceptable drug-related toxicity, disease progression, or death. Dose modifications and delays were allowed per protocol. Magrolimab and azacitidine were delayed together until a protocol amendment (August 2021, implemented after enrollment completion) decoupled treatments and recommended magrolimab to be continued per schedule if azacitidine was delayed because of adverse events (AEs) not considered related to magrolimab. AEs and serious AEs occurring after the first dose through 30 days after the last dose of study drugs were assessed according to Common Terminology Criteria for Adverse Events version 4.03 or the customized protocol-defined AE severity grading system for RBC agglutination. Bone marrow (BM) response assessments were conducted at screening and on day 1 of cycles 3, 5, 7, and every three cycles thereafter. Measurable residual disease (MRD) was assessed on BM aspirates obtained at BM biopsy time points by a central laboratory (Hematologics, Inc, Seattle, WA) using multiparameter flow cytometry for AML with a sensitivity of 0.02%. RBC and platelet transfusion independence were defined as ≥8 consecutive weeks without transfusion for patients who were transfusion-dependent at baseline (ie, requiring transfusion [s] within 4 weeks before first study treatment). Additional details are provided in the Protocol.

Outcomes

Primary end points were safety and tolerability measured by AEs and efficacy measured by investigator-assessed European LeukemiaNet (ELN) 2017[3] complete remission (CR) rate. Secondary and exploratory end points are listed in the Data Supplement (Methods).

Statistical Analysis

Intent-to-treat (ITT) analysis was conducted on patients who received ≥1 dose of magrolimab. Objective response rate (ORR) was defined as CR, CR with incomplete blood count recovery (CRi), CR with partial hematologic recovery, partial response, and morphologic leukemia-free state. Event-free survival (EFS) was defined as the time from the date of study treatment initiation until the date of documented disease progression, death from any cause, or failure to achieve CR/CRi by cycle 5 day 1.[24] OS was measured from the date of study treatment initiation until the date of death from any cause. Patients who did not die during the trial active period were censored at their last known alive date from survival follow-up. Durations of responses and survival outcomes were not censored for allogeneic hematopoietic stem-cell transplant (allo-HSCT).

RESULTS

Eighty-seven patients were enrolled between February 13, 2018, and May 21, 2021; 72 had TP53 mutations (Table 1; Data Supplement, Fig S3). The median age of patients with TP53 mutations was 73 years (range, 31-89); 57 (79.2%) were

TABLE 2. TEAEs (≥10%) Overall and by Grade

TEAE	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation	43 (49.4)	25 (28.7)	18 (20.7)	—	—	—
Nausea	43 (49.4)	24 (27.6)	19 (21.8)	—	—	—
Diarrhea	42 (48.3)	25 (28.7)	16 (18.4)	1 (1.1)	—	—
Febrile neutropenia	37 (42.5)	4 (4.6)	3 (3.4)	29 (33.3)	—	1 (1.1)
Fatigue	35 (40.2)	9 (10.3)	19 (21.8)	7 (8.0)	—	—
Thrombocytopenia[a]	35 (40.2)	1 (1.1)	1 (1.1)	8 (9.2)	25 (28.7)	—
Anemia	30 (34.5)	—	—	28 (32.2)	2 (2.3)	—
Decreased appetite	29 (33.3)	16 (18.4)	10 (11.5)	3 (3.4)	—	—
Cough	28 (32.2)	21 (24.1)	7 (8.0)	—	—	—
Peripheral edema	26 (29.9)	20 (23.0)	6 (6.9)	—	—	—
Pyrexia	26 (29.9)	19 (21.8)	7 (8.0)	—	—	—
Dizziness	24 (27.6)	20 (23.0)	4 (4.6)	—	—	—
Neutropenia[b]	23 (26.4)	—	—	3 (3.4)	20 (23.0)	—
Dyspnea	23 (26.4)	10 (11.5)	10 (11.5)	2 (2.3)	1 (1.1)	—
Fall	23 (26.4)	14 (16.1)	5 (5.7)	4 (4.6)	—	—
Hypokalemia	23 (26.4)	6 (6.9)	13 (14.9)	2 (2.3)	2 (2.3)	—
Hypophosphatemia	22 (25.3)	6 (6.9)	4 (4.6)	12 (13.8)	—	—
Vomiting	22 (25.3)	19 (21.8)	3 (3.4)	—	—	—
Abdominal pain	21 (24.1)	14 (16.1)	6 (6.9)	1 (1.1)	—	—
Blood bilirubin increased	21 (24.1)	7 (8.0)	10 (11.5)	4 (4.6)	—	—
Headache	21 (24.1)	13 (14.9)	8 (9.2)	—	—	—
Infusion-related reaction	20 (23.0)	5 (5.7)	13 (14.9)	2 (2.3)	—	—
Chills	19 (21.8)	14 (16.1)	5 (5.7)	—	—	—
Epistaxis	18 (20.7)	12 (13.8)	4 (4.6)	2 (2.3)	—	—
Pneumonia	18 (20.7)	—	—	15 (17.2)	—	3 (3.4)
Alanine aminotransferase increased	17 (19.5)	8 (9.2)	4 (4.6)	5 (5.7)	—	—
Hyponatremia	17 (19.5)	6 (6.9)	3 (3.4)	8 (9.2)	—	—
Hypotension	17 (19.5)	3 (3.4)	8 (9.2)	6 (6.9)	—	—
Confusional state	16 (18.4)	6 (6.9)	5 (5.7)	4 (4.6)	1 (1.1)	—
Muscular weakness	15 (17.2)	2 (2.3)	7 (8.0)	6 (6.9)	—	—
Arthralgia	14 (16.1)	9 (10.3)	5 (5.7)	—	—	—
Insomnia	14 (16.1)	10 (11.5)	4 (4.6)	—	—	—
WBC count decreased	14 (16.1)	1 (1.1)	—	1 (1.1)	12 (13.8)	—
Aspartate aminotransferase increased	13 (14.9)	7 (8.0)	3 (3.4)	3 (3.4)	—	—
Pain in extremity	13 (14.9)	6 (6.9)	7 (8.0)	—	—	—
Weight decreased	13 (14.9)	8 (9.2)	5 (5.7)	—	—	—
Acute kidney injury	12 (13.8)	5 (5.7)	2 (2.3)	1 (1.1)	4 (4.6)	—
Back pain	12 (13.8)	3 (3.4)	8 (9.2)	1 (1.1)	—	—
Hypoxia	12 (13.8)	1 (1.1)	5 (5.7)	5 (5.7)	—	1 (1.1)
Dyspepsia	11 (12.6)	6 (6.9)	5 (5.7)	—	—	—
Pleural effusion	11 (12.6)	5 (5.7)	4 (4.6)	1 (1.1)	—	1 (1.1)
Anxiety	10 (11.5)	8 (9.2)	2 (2.3)	—	—	—
Fluid overload	10 (11.5)	1 (1.1)	8 (9.2)	1 (1.1)	—	—
Rash maculopapular	10 (11.5)	8 (9.2)	2 (2.3)	—	—	—
Asthenia	9 (10.3)	3 (3.4)	4 (4.6)	2 (2.3)	—	—
Contusion	9 (10.3)	7 (8.0)	2 (2.3)	—	—	—
Hypomagnesemia	9 (10.3)	7 (8.0)	2 (2.3)	—	—	—
Nasal congestion	9 (10.3)	8 (9.2)	1 (1.1)	—	—	—

(continued on following page)

TABLE 2. TEAEs (≥10%) Overall and by Grade (continued)

TEAE	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oropharyngeal pain	9 (10.3)	7 (8.0)	2 (2.3)	—	—	—
Pruritus	9 (10.3)	7 (8.0)	2 (2.3)	—	—	—
Urinary tract infection	9 (10.3)	1 (1.1)	5 (5.7)	3 (3.4)	—	—

NOTE. Data expressed as No. (%).
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.
[a]Thrombocytopenia includes MedDRA-preferred terms thrombocytopenia and platelet count decreased.
[b]Neutropenia includes MedDRA-preferred terms neutropenia and neutrophil count decreased.

65 years and older, and 27 (37.5%) were 75 years and older. The median percentage of BM blasts was 35.0% (range, 3.0%-92.0%). Fifty-seven (79.2%) patients with *TP53* mutation had adverse cytogenetic risk per ELN 2017 criteria (specific abnormalities in Table 1). Sixteen (18.4%) patients had therapy-related AML, and 44 (50.6%) had AML with myelodysplasia-related changes. One patient received previous HMA for MDS and was technically ineligible per protocol but was enrolled and included in the analysis. *TP53* was the most common mutation detected at screening with central WES (Data Supplement, Table S1). *TP53* mutations identified by local NGS had 91% sequence concordance with central WES in the WES subset, and all were documented as pathogenic with low transcriptional activity.

The median duration of treatment for all patients was 3.48 (range, 0.03-38.21) months for magrolimab and 3.02 (range, 0.03-37.85) months for azacitidine. Patients received a median of 4 (range, 1-39) cycles of treatment (10 [3-39] cycles in patients who achieved CR but did not receive allo-HSCT). Eighty-six (98.9%) patients discontinued treatment as of data cutoff; primary reasons were progressive disease (PD; 32.2%), AE (17.2%), lack of efficacy (11.5%), stem-cell transplant (10.3%), death (9.2%), patient decision (8.0%), and physician decision (8.0%).

Nineteen (21.8%) patients had grade 3 anemia at baseline, and 60 (69.0%) had grade 3/4 neutropenia. The most common treatment-emergent AEs (TEAEs) regardless of causality were constipation (49.4%), nausea (49.4%), diarrhea (48.3%), febrile neutropenia (42.5%), and fatigue (40.2%; Table 2; Data Supplement, Table S2). The most common grade ≥3 TEAEs were thrombocytopenia (37.9%), anemia (34.5%), febrile neutropenia (34.5%), neutropenia (26.4%), and pneumonia (20.7%; Data Supplement, Table S3); serious AEs occurring in >1 patient included febrile neutropenia (24.1%), pneumonia (12.6%), and infusion-related reactions (IRRs; 6.9%; Data Supplement, Table S4).

The most common TEAEs considered related to magrolimab included anemia (28.7%; including one grade 4 occurring on cycle 1 day 1), IRRs (23.0%; most grade 1/2, only 2.3% grade 3), and fatigue (21.8%; Data Supplement, Table S5); possible immune-related reactions related to magrolimab were rare (one grade 2 enterocolitis infection, one grade 3 ulcerative colitis). The most common TEAEs considered related to azacitidine included thrombocytopenia (33.3%), nausea (28.7%), and anemia (27.6%; all grade ≤3; Data Supplement, Table S5).

Dose reductions were uncommon; few TEAEs led to dose reductions (1 [1.1%] for magrolimab, 9 [10.3%] for azacitidine). Dose delays were common (40 [46.0%] for magrolimab, 32 [36.8%] for azacitidine; Data Supplement, Table S6). TEAEs (regardless of attribution) led to discontinuation of magrolimab in 26 (29.9%) and azacitidine in 25 (28.7%) patients; the most common TEAEs for both were pneumonia (4.6%), acute respiratory failure, sepsis, and septic shock (2.3% each). One patient discontinued treatment because of a grade 2 IRR. Hemolysis occurred in two patients: one grade 1 and one grade 3 refractory to RBC transfusion and eventually resolved with Hb improvement after 2 weeks in whom treatment was discontinued per patient/investigator decision.

Fifty-two (59.8%) patients had a Hb level of <9 g/dL at baseline. The median Hb change from baseline to first assessment postmagrolimab dose in cycle 1 was −0.9 g/dL (range, −3.6 to 2.5 g/dL). The median maximum Hb decrease between first and third doses (ie, over the first 7 days of therapy) among 82 patients with data was −1.3 g/dL (range, −6.2 to 1.4 g/dL). Only one patient had a 6.2 g/dL Hb decrease. Importantly, 24 (29.3%) patients had a ≥2 g/dL decrease and 5 (6.1%) had a ≥3 g/dL decrease in Hb between magrolimab doses 1 and 3. Decreases in Hb in the first 24 hours after magrolimab dose 1 among 72 patients with data were <1 g/dL in 27 (37.5%), 1-2 g/dL in 27 (37.5%), and >2 g/dL in 8 (11.1%); 10 (13.9%) had no Hb decrease in the first 24 hours. Despite initial decreases, Hb levels improved over time (Fig 1A) and the median number of packed RBC/whole blood units transfused decreased over time on treatment (Fig 1B). Forty-three patients (49.4%) were RBC transfusion–dependent at baseline, 14 (32.6%) of whom became transfusion-independent. Twenty-five (28.7%) were platelet transfusion–dependent at baseline, and 12 (48.0%) became transfusion-independent.

The 30-day mortality was 6.9%, and the 60-day mortality was 16.1% (14 patients total); all patients with early deaths had *TP53* mutations (12 because of AEs unrelated to treatment before first response assessment, one because of PD, and one because of other cause; details are provided in
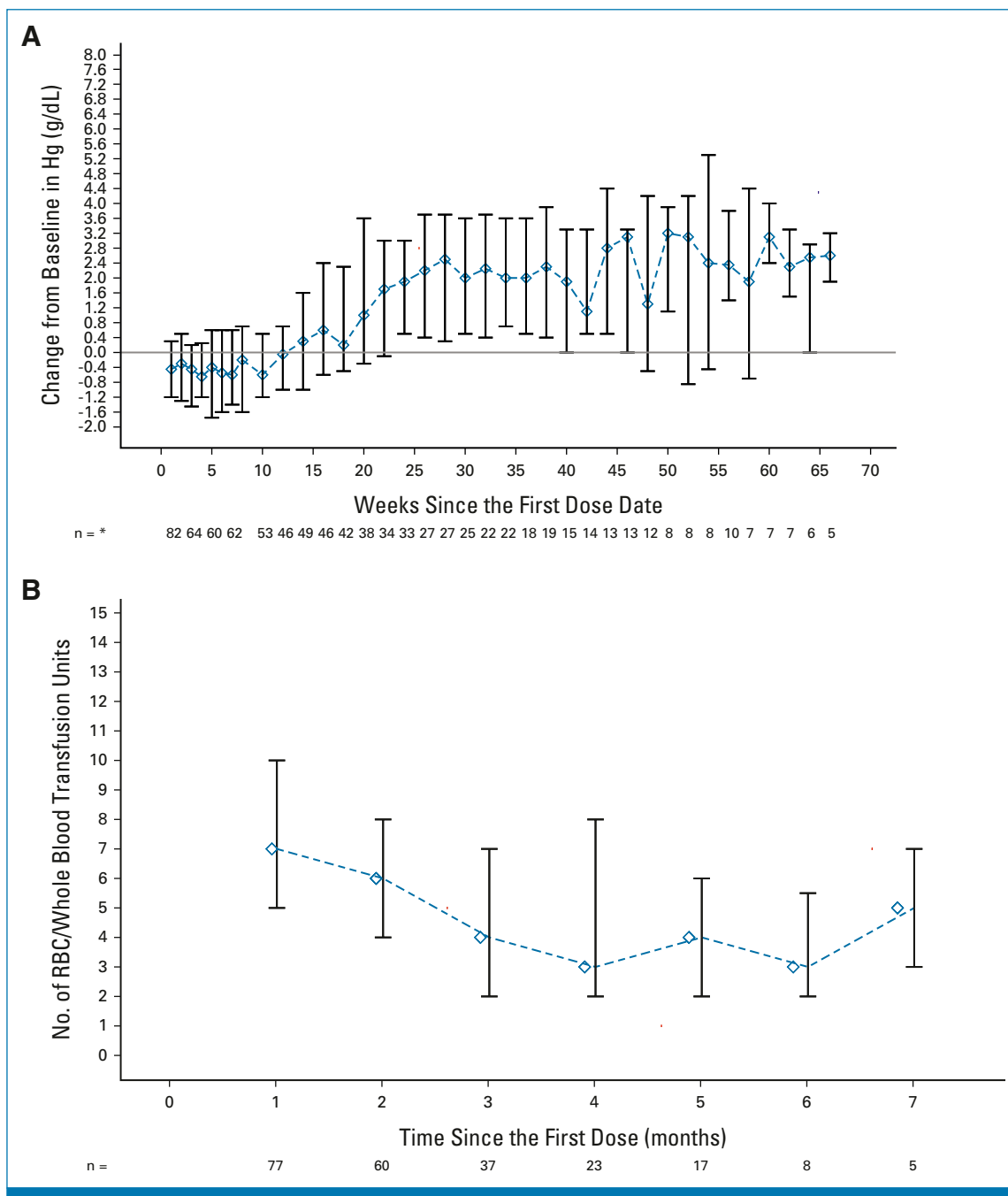
FIG 1. Hb change from baseline and RBC/whole blood transfusion over time. (A) Hb (g/dL) change from baseline over time. Median (IQR) shown for all patients (n = 87). Numbers below the graph indicate the number of patients with Hb assessment at that time point. (B) RBC/whole blood units transfused over time in patients remaining on treatment from the overall study population (n = 87); median (IQR). Numbers below the graph indicate the number of patients who received a transfusion at that time point. *Time points with at least five patients. Hb, hemoglobin.

the Data Supplement, Table S7). Overall, 66 patients (75.9%) died during the study, 39 (44.8%) from PD and 18 (20.7%) from AEs (none treatment-related; Data Supplement, Table S7).

Efficacy data for all 87 patients are shown in Table 3. Twenty-eight patients achieved CR (32.2% [95% CI, 22.6 to 43.1]). Among 63 response-evaluable patients, 58 (92%) had

a reduction in BM blasts from baseline (Fig 2A). Among TP53-mutant patients, responses were as follows: CR, 31.9% (95% CI, 21.4 to 44.0); CR/CRi, 40.3% (28.9 to 52.5); partial remission (PR), 5.6%; and ORR, 47.2% (35.3 to 59.3). The median time to first objective response was 2.0 (range, 1.0-5.6) months, and to CR was 3.7 (1.8-9.6) months. In patients with TP53 mutations, the median duration of CR was 7.6 (95% CI, 4.7 to 9.7) months (Fig 2B) and the median

TABLE 3. Efficacy End Points

Outcome	TP53-Mutant (n = 72)	TP53 Wild-Type (n = 15)	All Patients (ITT; N = 87)
ORR,[a] % (95% CI)	47.2 (35.3 to 59.3)	46.7 (21.3 to 73.4)	47.1 (36.3 to 58.1)
CR, % (95% CI)	31.9 (21.4 to 44.0)	33.3 (11.8 to 61.6)	32.2 (22.6 to 43.1)
MRD−CR[b]	n = 12/23	n = 4/5	n = 16/28
% (95% CI)	52.2 (30.6 to 73.2)	80.0 (28.4 to 99.5)	57.1 (37.2 to 75.5)
CRh, No. (%)	1 (1.4)	0	1 (1.1)
CRi, No. (%)	5 (6.9)	0	5 (5.7)
CR or CRh, No. (%)	24 (33.3)	5 (33.3)	29 (33.3)
CR or CRi or CRh, No. (%)	29 (40.3)	5 (33.3)	34 (39.1)
PR, No. (%)	4 (5.6)	1 (6.7)	5 (5.7)
MLFS, No. (%)	1 (1.4)	1 (6.7)	2 (2.3)
SD, No. (%)	13 (18.1)	5 (33.3)	18 (20.7)
DOR, months, median (95% CI)	7.7 (6.5 to 10.1)	18.7 (5.7 to NR)	8.7 (7.4 to 10.9)
DCR, months, median (95% CI)	7.6 (4.7 to 9.7)	31.3 (18.7 to 31.3)	9.6 (5.1 to 10.9)
Duration of CR/CRi, months, median (95% CI)	7.7 (5.3 to 10.4)	31.3 (18.7 to 31.3)	9.6 (7.5 to 11.5)
EFS, months, median (95% CI)	3.7 (2.0 to 9.2)	2.9 (0.0 to 20.4)	3.7 (2.1 to 7.3)
OS, months, median (95% CI)	9.8 (6.8 to 12.3)	18.9 (4.3 to NR)	10.8 (7.2 to 12.8)
Received allo-HSCT, No. (%)	8 (11.1)	2 (13.3)	10 (11.5)

Abbreviations: allo-HSCT, allogeneic hematopoietic stem-cell transplant; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; DCR, duration of complete remission; DOR, duration of response; EFS, event-free survival; ELN, European LeukemiaNet; ITT, intent-to-treat; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; SD, stable disease.

[a]Objective response defined as CR, CRi, CRh, PR, and MLFS on the basis of ELN 2017 recommendations per evaluation by the investigator.

[b]No. = number of patients with CR by group. MRD was assessed in bone marrow samples by a central laboratory using multiparameter flow cytometry with a sensitivity of 0.02%.

duration of response (DOR) was 7.7 (95% CI, 6.5 to 10.1) months (Data Supplement, Fig S4A). In patients with TP53 mutations who achieved CR (n = 23), 26% occurred after 4 months on therapy (range, 1.8-9.6 months; Data Supplement, Fig S5); and 52.2% (12 of 23) demonstrated MRD negativity (Table 3).

With a median follow-up for survival of 8.9 (IQR, 2.3-12.9) months in patients with TP53 mutations, the median protocol-defined EFS was 3.7 (95% CI, 2.0 to 9.2) months (Data Supplement, Fig S4B) and the OS was 9.8 (6.8 to 12.3) months (Fig 3A). The OS in patients with TP53 mutations with poor-risk ELN cytogenetics (n = 55) was 10.8 (95% CI, 7.2 to 12.8) months.

Thirty-nine patients with TP53 mutations had VAF assessed at screening; the median TP53 VAF was 61.0% (range, 9.8-98.7). MRD was assessed longitudinally by central multiparametric flow cytometry in all 72 TP53-mutant patients. Among 23 patients who achieved CR, 52.2% (12 of 23) demonstrated MRD negativity.

The median OS for 14 patients with TP53 mutations who achieved CR, CRi, or CR with partial hematologic recovery and flow MRD negativity was 14.5 (95% CI, 12.1 to 21.7) months versus 7.5 (4.5 to 10.8) months in the 53 patients who remained MRD-positive, regardless of response (Data Supplement, Fig S6).

Among TP53-wildtype patients (n = 15), the CR rate was 33.3% (95% CI, 11.8 to 61.6) and the median CR duration was 31.3 (95% CI, 18.7 to 31.3) months (Table 3; Fig 2B); the median OS was 18.9 (95% CI, 4.3 to not reached [NR]) months (Fig 3A). Of five patients who achieved CR, 80.0% (4 of 5) demonstrated MRD negativity (Table 3). The PR rate and ORR were 6.7% and 46.7% (95% CI, 21.3 to 73.4), respectively; no patient achieved CRi. A subset of 13 patients who had a baseline TP53 mutation detected by WES and achieved CR had TP53 clearance (Data Supplement, Fig S7).

Additional efficacy data of the ITT population are shown in Table 3, Figure 3, and the Data Supplement (Fig S4).

Ten (11.5%) patients proceeded to allo-HSCT (Table 3) after a median of 6.1 (range, 4.2-11.5) months, including eight TP53-mutant and two TP53 wild-type patients. In the landmark analysis at 10 months after treatment initiation, among patients who had TP53 mutations, the median (95% CI) OS was NR (0.8 months to NR) in those with allo-HSCT and 3.2 (2.3 to 4.5) months in those without (Fig 3B). In TP53-mutant patients, the 1-year survival estimate from the landmark time point was 87.5% with allo-HSCT and 0.0% without allo-HSCT.

DISCUSSION

This study reports the use of magrolimab + azacitidine in patients with untreated AML who were not candidates for IC.
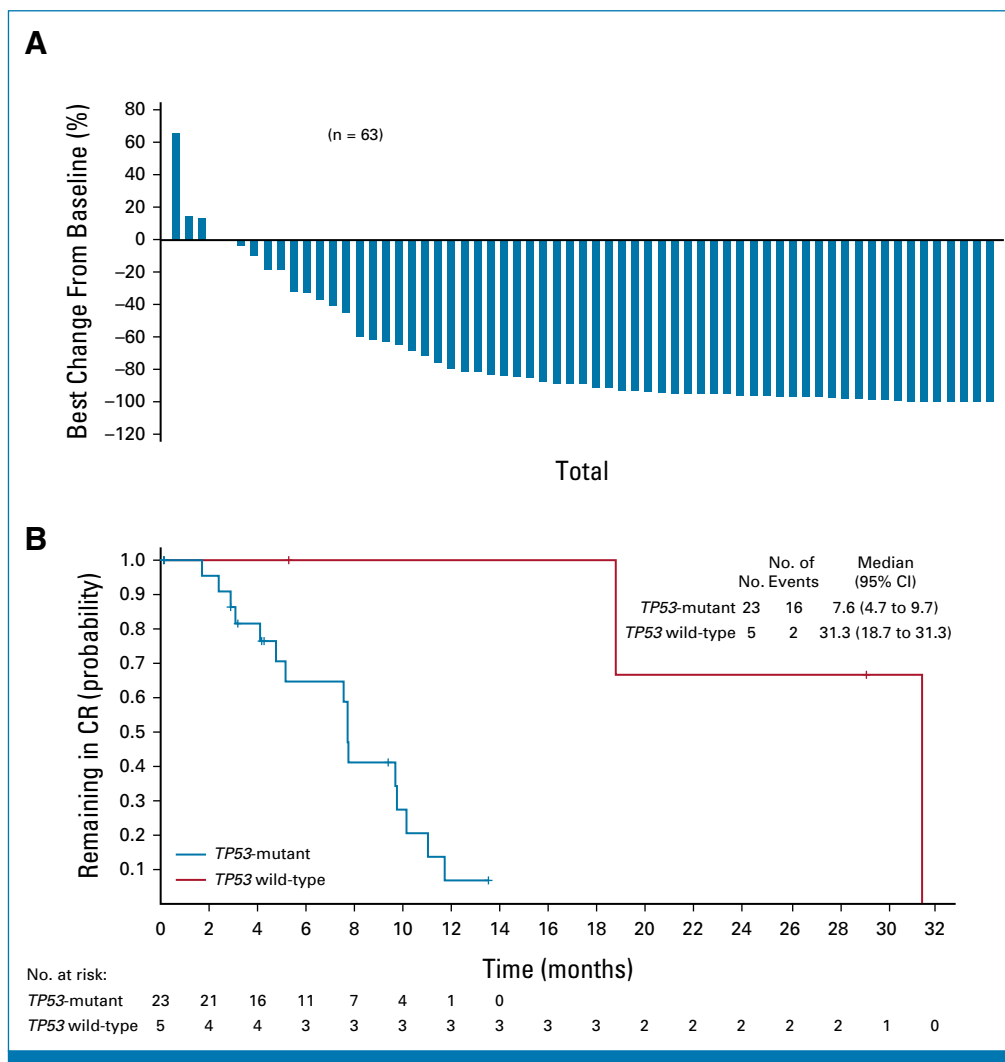
FIG 2. Responses to magrolimab + azacitidine in patients with untreated AML who were unfit for intensive chemotherapy. (A) Waterfall plot of best change from baseline in percent of bone marrow blasts in evaluable patients. (B) Kaplan-Meier curve of the duration of complete remission by *TP53* mutation status. Censored patients are represented by vertical tick marks in the Kaplan-Meier curve. CR, complete remission.

Magrolimab + azacitidine was well tolerated and, in patients with *TP53*-mutant AML, demonstrated promising preliminary efficacy (true CR rate of 31.9%) and OS (9.8 months). Notably, median OS was NR in patients bridged to allo–HSCT.

Anemia is a known side effect of magrolimab on the basis of its mechanism of action (MOA). The mechanism of anemia is not fully understood and is under investigation. This could potentially be an acute extravascular drug-related anemia because of removal of aged RBCs by phagocytic cells of the reticuloendothelial system[25] and possible hemagglutination. The proportion of patients with anemia in this study was consistent with observations in previous magrolimab studies.[20,25,26] Aged RBCs exhibit increased expression of *eat me* signals in parallel with a gradual decrease in CD47 expression, leading to a natural removal by splenic and hepatic macrophages.[27-29] Transient anemia and corresponding reticulocytosis were observed with magrolimab treatment in nonhuman primates and mitigated with a low initial dose.[19] Anemia related to magrolimab was common (reported in 28.7% of patients), but with a single grade 4 event occurring at treatment initiation. In this study, 59.8% of patients had a Hb level of <9 g/dL at baseline and Hb decreases were observed most commonly after the first one to two doses, with a ≥3 g/dL drop reported in 5.7% of patients. A requirement for adequate pretreatment Hb value and a repeat Hb check after initial infusions of magrolimab have been incorporated into current magrolimab trials to help mitigate observed initial drops in Hb (Data Supplement, Methods). Notably, anemia in later cycles was uncommon, with Hb increasing and need for RBC/whole blood transfusions decreasing over time on treatment (Fig 1).

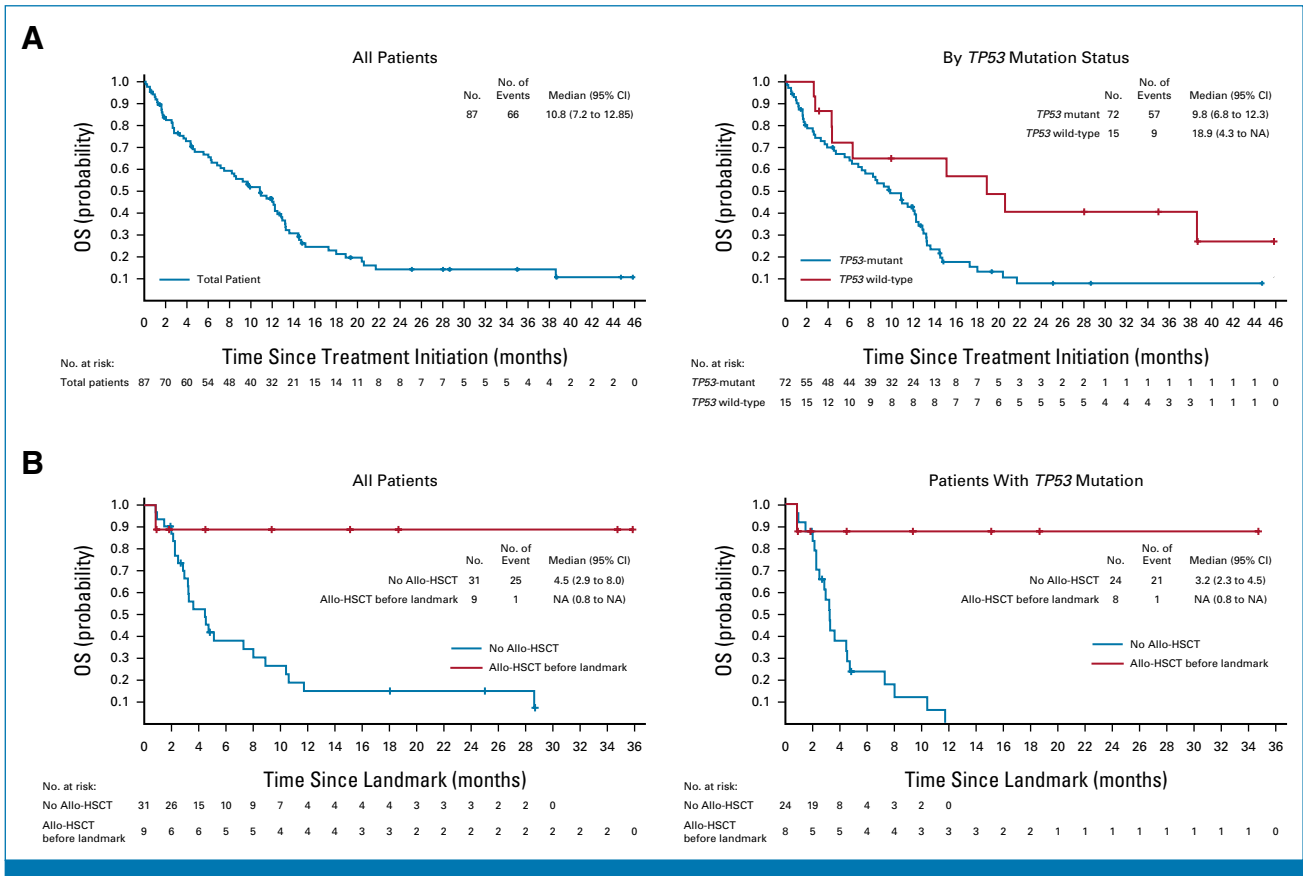Tolerability of azacitidine alone has varied widely across trials. Here, proportions of grade 3/4 TEAEs, including

FIG 3. Kaplan-Meier curves. (A) OS of all patients (left) and by *TP53* mutation status (right); (B) OS of patients who received allo-HSCT and patients who did not, including all patients (left), and patients with *TP53* mutations (right) using landmark analysis to control for lead-time bias, with 10 months as the landmark time point to include all patients with *TP53* mutations who received allo-HSCT. Patients who discontinued or were lost to follow-up before the landmark time point were excluded from the analyses. The allo-HSCT group includes all patients who had allo-HSCT by the landmark time point. The no allo-HSCT group includes all patients who did not receive allo-HSCT or received allo-HSCT after the landmark time point (n = 1). Among patients bridged to allo-HSCT, the median (range) age was 68 (51-73) years, and ECOG performance status at screening was 0 in 3 of 10 (30%), 1 in 5 of 10 (50%), and 2 in 2 of 10 (20%). Eight patients had adverse-risk cytogenetics, one had intermediate-I risk, and one had unknown risk; three had AML related to previous chemotherapy or radiation; and seven were RBC transfusion-independent at baseline. Allo-HSCT was entirely at the discretion of the investigator, and patients took off-trial treatment before conditioning, so no additional information is available. Censored patients are represented by vertical tick marks in the Kaplan-Meier curve. Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; NA, not available; OS, overall survival.

neutropenia and thrombocytopenia, were comparable with those noted in the frontline prospective randomized trial of azacitidine in patients with AML (febrile neutropenia was most frequent at 28%)[30] and lower than the 90.6% thrombocytopenia and 94.3% neutropenia rates reported in the AZA-001 study.[31] Overall, tolerability of magrolimab + azacitidine was consistent with the known profiles of the individual treatments[20,21,30,31] and no new safety signals were identified. The 16.1% 60-day mortality is comparable with 22% to 26% in *TP53*-mutant patients treated with venetoclax + azacitidine in other published studies.[8,23] The safety and tolerability profile of azacitidine + magrolimab appears to be distinct from that of azacitidine and venetoclax, where prolonged myelosuppression (especially neutropenia) and infections are common, leading to significant cycle delays and dose reductions. In our study, dose reductions occurred in 1.1% for magrolimab and in 10.3% of patients for

azacitidine, suggesting that the regimen may be easier to deliver in continuous cycles without need for frequent dose/duration modifications. Efficacy data from this phase Ib study support the magrolimab/azacitidine synergy observed in preclinical studies. Magrolimab + azacitidine showed encouraging efficacy in *TP53*-mutant AML and preliminary activity in a small subset of patients with *TP53* wild-type AML who were enrolled during the initial study period. Importantly, 52.2% of *TP53*-mutant patients with CR also achieved MRD negativity, and responses deepened over time with 26.1% of *TP53*-mutant patients without initial CR ultimately achieving CR beyond 4 months on therapy, suggesting that patients who do not achieve initial CR could still benefit over time and potentially proceed to allo-HSCT.

The median OS of 9.8 months in patients with *TP53* mutations compares favorably with published outcomes with

HMA alone (median OS, 4.9-7.2 months),[10,32] venetoclax + HMA combinations (median OS, 5.2-7.2 months),[22,23] and IC (median OS, 4.1-6.8 months).[1,6,7,9] In a retrospective study, median OS in patients with newly diagnosed *TP53*-mutant AML was similar to that in patients treated with venetoclax-based regimens (5.7 months) versus nonvenetoclax regimens (6.6 months), suggesting that venetoclax may not improve survival outcomes in *TP53*-mutant patients.[8] Median DORs with magrolimab + azacitidine in patients with *TP53* mutations (DOR, 7.7 months; CR/CRi duration, 7.7 months) also compare favorably with those with venetoclax + HMA in *TP53*-mutant patients (median DOR, 3.5 months in a phase II trial[23]; median CR/CRi duration, 5.6 months in a phase Ib study).[22] Other agents such as eprenetapopt (APR-246) are being evaluated for frontline *TP53*-mutant MDS/AML treatment[33] and maintenance after allo-HSCT,[34] engaging divergent MOAs such as restoration of *TP53* wild-type function, but at this time, none has shown clear benefit in frontline *TP53*-mutant myeloid malignancies.

Median OS was longer in patients who achieved a flow-based MRD-negative response on treatment than those who did not. Median OS in *TP53*-mutant patients who received allo-HSCT was also longer than that in those who did not, suggesting that magrolimab + azacitidine could be an effective and tolerable bridge to allo-HSCT.

Limitations to this study are that it is a single-arm, non-randomized study conducted at larger academic centers consistent with the phase Ib design; lack of centralized serial *TP53* NGS assessments; insufficient numbers to definitively delineate efficacy and impact in individual molecular/cytogenetic subgroups; and enrollment of a predominately White population (86.2%), a shortcoming that continues to be noted across a majority of clinical trials conducted in the United States, and conclusions may not at this time be generalizable to other populations.

In conclusion, magrolimab + azacitidine has an acceptable safety profile with promising efficacy in patients with *TP53*-mutant AML unfit for standard induction chemotherapy. On the basis of the results presented here, two phase III trials of magrolimab and azacitidine have been initiated in patients with newly diagnosed *TP53*-mutant AML (ENHANCE-2; ClinicalTrials.gov identifier: NCT04778397) and in patients with newly diagnosed AML ineligible for IC (ENHANCE-3; ClinicalTrials.gov identifier: NCT05079230). Future clinical and translational investigations are also focused on evaluating potential differential activity in molecular subsets, including patients with *TP53* mutations in AML and their mechanisms. The ongoing and future larger trials will help determine whether magrolimab combinations can address the urgent unmet need for new treatments for these patients.

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DATA SHARING STATEMENT

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting nonconflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tolerability and Efficacy of the Anticluster of Differentiation 47 Antibody Magrolimab Combined With Azacitidine in Patients With Previously Untreated AML: Phase Ib Results

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Consulting or Advisory Role: AbbVie
Research Funding: Amgen (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), AbbVie (Inst), Immunogen (Inst), Jazz Pharmaceuticals (Inst), Ascentage Pharma (Inst), Daiichi Sankyo/Lilly (Inst)

Guillermo Garcia-Manero
Honoraria: Astex Pharmaceuticals, Acceleron Pharma, AbbVie, Novartis, Gilead Sciences, Curis, Genentech, Bristol Myers Squibb/Celgene
Consulting or Advisory Role: Astex Pharmaceuticals, Acceleron Pharma, Bristol Myers Squibb
Research Funding: Astex Pharmaceuticals, Novartis, AbbVie, Bristol Myers Squibb, Genentech, Aprea Therapeutics, Curis, Gilead Sciences

Rami Komrokji
Stock and Other Ownership Interests: AbbVie
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Jazz Pharmaceuticals, AbbVie, Geron, CTI BioPharma Corp, Pharmaessentia, Taiho Oncology, Takeda, Gilead/Forty Seven
Speakers' Bureau: Jazz Pharmaceuticals, Servier, AbbVie, Pharmaessentia, CTI BioPharma Corp
Research Funding: Bristol Myers Squibb/Celgene (Inst)
Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Bristol Myers Squibb, Pharmaessentia

Guan Xing
Employment: Gilead Sciences
Stock and Other Ownership Interests: Gilead Sciences

Giridharan Ramsingh
Employment: Gilead Sciences, Obsidian Therapeutics
Stock and Other Ownership Interests: Gilead Sciences, Genentech/Roche, Obsidian Therapeutics

Camille Renard
Employment: Gilead Sciences, Alphabet
Stock and Other Ownership Interests: Gilead Sciences, Alphabet

Joshua F. Zeidner
Consulting or Advisory Role: AbbVie, Takeda, Genentech, Bristol Myers Squibb/Celgene, Shattuck Labs, Servier, Gilead Sciences, Immunogen, Daiichi Sankyo/Lilly, Foghorn Therapeutics
Research Funding: Takeda (Inst), Merck (Inst), Gilead Sciences (Inst), Arog (Inst), Astex Pharmaceuticals (Inst), Sumitomo Dainippon Pharma Oncology (Inst), AbbVie (Inst), Stemline Therapeutics (Inst), Shattuck Labs (Inst)

David A. Sallman
Consulting or Advisory Role: AbbVie, Bristol Myers Squibb, Gilead Sciences, Intellia Therapeutics, Kite, a Gilead company, Novartis, Syndax, Bluebird Bio, Janssen, Servier, Shattuck Labs, Syros Pharmaceuticals, Takeda, Magenta Therapeutics, Molecular Partners, Jasper Therapeutics, Nkarta, Affimed Therapeutics, Intellisphere, Precigen, Zentalis, AvenCell
Speakers' Bureau: Incyte
Research Funding: Jazz Pharmaceuticals, Aprea Therapeutics (Inst)

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