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Authors

Sallman, David

Al Malki, Monzr

Asch, Adam

et al.

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Magrolimab in Combination With Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes: Final Results of a Phase Ib Study

David A. Sallman, MD[1]; Monzr M. Al Malki, MD[2]; Adam S. Asch, MD[3]; Eunice S. Wang, MD[4]; Joseph G. Jurcic, MD[5]; Terrence J. Bradley, MD[6]; Ian W. Flinn, MD[7]; Daniel A. Pollyea, MD, MS[8]; Suman Kambhampati, MD[9]; Tiffany N. Tanaka, MD[10]; Joshua F. Zeidner, MD[11]; Guillermo Garcia-Manero, MD[12]; Deepa Jeyakumar, MD[13]; Rami Komrokji, MD[1]; Jeffrey Lancet, MD[1]; Hagop M. Kantarjian, MD[12]; Lin Gu, MS[14]; Yajia Zhang, PhD[14]; Anderson Tan, PharmD, RPh[14]; Mark Chao, MD, PhD[14]; Carol O'Hear, MD, PhD[14]; Giridharan Ramsingh, MD[14]; Indu Lal, MD[14]; Paresh Vyas, MD, PhD[15]; and Naval G. Daver, MD[12]

abstract

PURPOSE Magrolimab is a monoclonal antibody that blocks cluster of differentiation 47, a don't-eat-me signal overexpressed on cancer cells. Cluster of differentiation 47 blockade by magrolimab promotes macrophage-mediated phagocytosis of tumor cells and is synergistic with azacitidine, which increases expression of eat-me signals. We report final phase Ib data in patients with untreated higher-risk myelodysplastic syndromes (MDS) treated with magrolimab and azacitidine (ClinicalTrials.gov identifier: NCT03248479).

PATIENTS AND METHODS Patients with previously untreated Revised International Prognostic Scoring System intermediate-/high-/very high-risk MDS received magrolimab intravenously as a priming dose (1 mg/kg) followed by ramp-up to a 30 mg/kg once-weekly or once-every-2-week maintenance dose. Azacitidine 75 mg/m^2 was administered intravenously/subcutaneously once daily on days 1-7 of each 28-day cycle. Primary end points were safety/tolerability and complete remission (CR) rate.

RESULTS Ninety-five patients were treated. Revised International Prognostic Scoring System risk was intermediate/high/very high in 27%, 52%, and 21%, respectively. Fifty-nine (62%) had poor-risk cytogenetics and 25 (26%) had *TP53* mutation. The most common treatment-emergent adverse effects included constipation (68%), thrombocytopenia (55%), and anemia (52%). Median hemoglobin change from baseline to first postdose assessment was −0.7 g/dL (range, −3.1 to +2.4). CR rate and overall response rate were 33% and 75%, respectively. Median time to response, duration of CR, duration of overall response, and progression-free survival were 1.9, 11.1, 9.8, and 11.6 months, respectively. Median overall survival (OS) was not reached with 17.1-month follow-up. In *TP53*-mutant patients, 40% achieved CR with median OS of 16.3 months. Thirty-four patients (36%) had allogeneic stem-cell transplant with 77% 2-year OS.

CONCLUSION Magrolimab + azacitidine was well tolerated with promising efficacy in patients with untreated higher-risk MDS, including those with *TP53* mutations. A phase III trial of magrolimab/placebo + azacitidine is ongoing (ClinicalTrials.gov identifier: NCT04313881 [ENHANCE]).

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Patients with higher-risk myelodysplastic syndromes (HR-MDS) as classified by Revised International Prognostic Scoring System (IPSS-R; including intermediate-, high-, and very high-risk patients) have poor prognosis and high risk of progression to acute myeloid leukemia (AML).[1] Patients with HR-MDS receive hypomethylating agents (HMAs), including azacitidine and decitabine, as the most common frontline therapy with intensive chemotherapy or targeted therapies in selected patients (eg, young patients with excess blasts and available donors, those with AML-defining mutations). The only potentially curative therapy is allogeneic hematopoietic stem-cell transplant (allo-HSCT) in a minority of patients, which is associated with improved overall survival (OS) in patients up to age 75 years.[2-4] However, complete remission (CR) rates are low with single-agent HMAs in pivotal trials and a large meta-analysis (7%-17%),[5-12] with few exceptions.[13-15] Although median OS with azacitidine was 24.5 months in the AZA-001 trial,[6] almost all subsequent published data sets have demonstrated

CONTEXT

Key Objective

Is the first-in-class anti–cluster of differentiation 47 monoclonal antibody magrolimab safe, well tolerated, and efficacious when combined with azacitidine in untreated patients with higher-risk myelodysplastic syndromes, a population with high unmet need?

Knowledge Generated

In the overall population and in the subset of patients with *TP53* mutations, magrolimab + azacitidine produced encouraging overall and complete remission rate, duration of overall and complete remission, and overall survival; over one third of patients were able to receive allogeneic stem-cell transplant, the only potentially curative treatment for higher-risk myelodysplastic syndromes. Magrolimab plus azacitidine was generally well tolerated, with manageable expected on-target anemia with hemoglobin improvement and reduced transfusion requirement over time on treatment.

Relevance *(C.F. Craddock)*

Magrolimab uses a novel mechanism of action in myelodysplasia and in combination with azacitidine is well tolerated and demonstrates promising clinical activity. The combination is currently undergoing evaluation in a randomized phase III trial.*

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

median OS ranging from 10 to 19 months.[10-14,16] Notably, multiple completed trials combining investigational agents with HMAs have failed to meet primary end points.[17-22] Thus, there is a high unmet need to improve outcomes in newly diagnosed HR-MDS.

Cluster of differentiation 47 (CD47), a cell surface molecule, functions as a phagocyte immune checkpoint when bound to its receptor, phagocyte cell surface signal-regulatory protein alpha, impeding phagocytosis and serving as a don't-eat-me signal (Data Supplement, online only).[23,24] CD47 is overexpressed on most cancer cells including blasts in MDS.[25]

Magrolimab is a first-in-class humanized immunoglobulin G4 anti-CD47 antibody that blocks CD47 binding to signal-regulatory protein alpha and enhances the phagocytosis of tumor cells.[26] Magrolimab has promising activity in relapsed/refractory non-Hodgkin lymphoma in combination with rituximab.[27] Synergy with anti-CD47 therapies occurs with therapeutics that increase prophagocytic signals on tumor cells. Preclinical data demonstrated that azacitidine robustly upregulated a cell surface prophagocytic marker, calreticulin, on malignant myeloid cells.[28] Furthermore, magrolimab + azacitidine increased phagocytosis in vitro and in vivo in myeloid models, providing strong mechanistic rationale for investigating the combination in patients.[28-30] This report describes final results of the phase Ib combination study (5F9005) of magrolimab + azacitidine in patients with untreated HR-MDS (ClinicalTrials.gov identifier: NCT03248479).

PATIENTS AND METHODS

Eligibility Criteria

Adults with untreated MDS by WHO classification and an IPSS-R risk category of intermediate, high, or very high risk were eligible. Patients could not have received prior treatment with HMAs but could have received lower-risk MDS therapies, including growth factors, transfusions, lenalidomide, and/or hydroxyurea. Patients had an Eastern Cooperative Oncology Group performance status of 0-2, AST/ALT $\leq 5\times$ the upper limit of normal, and a glomerular filtration rate of $\geq$ 40 mL/min/1.73 m^2. No baseline hemoglobin requirement was specified in the Protocol (online only). Full inclusion/exclusion criteria are available in the protocol (Data Supplement).

Study Oversight

All patients provided written informed consent before study participation. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Institutional review board approval was required at each site before study conduct.

Study Design

Study 5F9005 was an open-label, single-arm, multicenter phase Ib trial (Data Supplement) to evaluate the safety/tolerability (primary objective) and efficacy (secondary objective) of magrolimab + azacitidine in patients with untreated HR-MDS. A safety run-in cohort with standard 3 + 3 design was conducted in patients with MDS to evaluate dose-limiting toxicities and confirm the dose and schedule for the expansion phase. In the expansion phase, magrolimab was administered intravenously at the selected expansion dose with a priming dose of 1 mg/kg on days 1 and 4, 15 mg/kg on day 8, and 30 mg/kg on days 11, 15, and 22, then 30 mg/kg once weekly in the initial expansion cohort (planned enrollment 36 patients), or with maintenance dose interval increased to once daily every 2 weeks beginning cycle 3 day 1 in the additional expansion cohort

(planned enrollment 58 patients). Azacitidine was administered subcutaneously or intravenously at 75 mg/m^2 once daily on days 1-7 of each 28-day cycle in all cohorts. Treatment was continued until unacceptable toxicity, progression, or death. A study design schema is provided (Data Supplement).

Primary end points were adverse events (AEs) and serious AEs per Common Terminology Criteria for AEs Version 4.03, and efficacy per investigator-assessed rate of CR by International Working Group 2006 MDS response criteria.[31] Secondary and exploratory end points are listed in the Data Supplement. Treatment-emergent AEs (TEAEs) were assessed from first dose until 30 days after last dose of study drugs. Bone marrow evaluations for response assessment were conducted at screening and every two cycles beginning on cycle 3 day 1 and then every three cycles beginning on cycle 7 day 1 (Data Supplement). Overall response rate was a secondary end point defined per protocol as CR + marrow CR (mCR) + partial remission + stable disease with any hematologic improvement (HI). Minimal residual disease (MRD) negativity was centrally assessed using multiparameter flow cytometry (Hematologics, Inc, Seattle, WA) with a 0.02% lower limit of detection. Cytogenetics were evaluated locally using IPSS-R criteria.[1,32] *TP53* and other prespecified mutations were identified using next-generation sequencing (NGS) conducted locally per each institution's standard practice.

Statistical Analysis

Statistical analyses were based on all patients who received at least one dose of magrolimab. Descriptive statistics were calculated for continuous variables; frequency and percentage were determined for categorical variables with 95% CIs using the Clopper and Pearson method for primary and secondary efficacy end points. Formal hypothesis testing of the CR rate used the chi-square test at a two-sided significance level of 0.05 (see the Data Supplement for details of sample size and power assumptions). Time-to-event variables were assessed by Kaplan-Meier estimates and corresponding two-sided 95% CIs for the median. Durations of response include response maintained in the post-transplant settings of patients who received allo-HSCT. Data cutoff was December 1, 2021.

RESULTS

Patients

This study enrolled 95 patients between July 10, 2018, and August 4, 2020, including one patient from the safety run-in cohort who received the same regimen as the expansion cohort. Median age was 69 (range, 28-91) years, and 69.5% had Eastern Cooperative Oncology Group performance status 1/2 (Table 1). A total of 62.1% had poorer-risk cytogenetics (ie, poor/very poor by IPSS-R criteria[1,32]) and 27.4% had complex cytogenetics (≥ 3 cytogenetic abnormalities); 22.1% had therapy-related MDS (Table 1).

TABLE 1. Baseline Demographics and Characteristics (N = 95)

Characteristic	Magrolimab + Azacitidine
Age, years, median (range)	69 (28-91)
Male/female, No. (%)	62 (65.3)/33 (34.7)
Race, No. (%)	
American Indian or Alaska Native	1 (1.1)
Asian	2 (2.1)
Black or African American	3 (3.2)
White	85 (89.5)
Not reported/missing	4 (4.2)
ECOG performance status, No. (%)	
0	29 (30.5)
1	60 (63.2)
2	6 (6.3)
MDS risk category by IPSS-R, No. (%)	
Intermediate	26 (27.4)
High	49 (51.6)
Very high	20 (21.1)
WHO classification, No. (%)	
MDS-RS	2 (2.1)
MDS-RS with single lineage dysplasia	2 (2.1)
MDS-RS with multilineage dysplasia	6 (6.3)
MDS with multilineage dysplasia	12 (12.6)
MDS with excess blasts	64 (67.4)
MDS with isolated del(5q)	1 (1.1)
MDS, unclassifiable	8 (8.4)
Cytogenetic risk category, No. (%)	
Favorable	12 (12.6)
Intermediate	17 (17.9)
Poor	59 (62.1)
Unknown/missing	7 (7.4)
Complex cytogenetics, No. (%)	26 (27.4)
Therapy-related MDS, No. (%)	21 (22.1)
Mutations at baseline, No. (%)[a]	
TP53	25 (26.3)
TET2	17 (17.9)
IDH1/IDH2	5 (5.3)
DNMT3A	5 (5.3)
FLT3	1 (1.1)
NPM1	1 (1.1)
TP53 VAF %, median (range)[b]	41.3 (29.8-64.7)
RBC transfusion-dependent, No. (%)[c]	37 (38.9)
Hemoglobin, g/dL, median (range)	8.6 (6.5-13.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MDS-RS, MDS with ring sideroblasts; NGS, next-generation sequencing; VAF, variant allele frequency.

[a]Baseline mutation status unknown for nine patients (9.5%); percentages are based on N = 86 as denominator.

[b]Data from five patients who had *TP53* mutations at baseline and VAF data available by NGS conducted locally.

[c]Defined as transfusion within 4 weeks before the first study treatment.

TABLE 2. TEAEs Occurring in ≥ 10% of Patients Regardless of Causality (N = 95)

TEAE	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation	65 (68.4)	50 (52.6)	15 (15.8)	—	—	—
Thrombocytopenia	52 (54.7)	1 (1.1)	7 (7.4)	9 (9.5)	35 (36.8)	—
Anemia	49 (51.6)	—	4 (4.2)	44 (46.3)	1 (1.1)	—
Neutropenia	45 (47.4)	—	1 (1.1)	4 (4.2)	40 (42.1)	—
Nausea	44 (46.3)	31 (32.6)	11 (11.6)	2 (2.1)	—	—
Diarrhea	41 (43.2)	33 (34.7)	7 (7.4)	1 (1.1)	—	—
Fatigue	33 (34.7)	9 (9.5)	22 (23.2)	2 (2.1)	—	—
Blood bilirubin increased	34 (35.8)	12 (12.6)	19 (20.0)	3 (3.2)	—	—
Dyspnea	33 (34.7)	16 (16.8)	14 (14.7)	3 (3.2)	—	—
Headache	31 (32.6)	22 (23.2)	8 (8.4)	1 (1.1)	—	—
Febrile neutropenia	29 (30.5)	2 (2.1)	—	26 (27.4)	1 (1.1)	—
Decreased appetite	29 (30.5)	18 (18.9)	11 (11.6)	—	—	—
WBC count decreased	28 (29.5)	—	—	4 (4.2)	24 (25.3)	—
Infusion-related reaction	24 (25.3)	7 (7.4)	11 (11.6)	6 (6.3)	—	—
Cough	24 (25.3)	20 (21.1)	4 (4.2)	—	—	—
Pyrexia	24 (25.3)	18 (18.9)	5 (5.3)	1 (1.1)	—	—
Hypokalemia	23 (24.2)	6 (6.3)	9 (9.5)	7 (7.4)	1 (1.1)	—
Vomiting	23 (24.2)	16 (16.8)	6 (6.3)	1 (1.1)	—	—
Dizziness	22 (23.2)	20 (21.1)	2 (2.1)	—	—	—
Peripheral edema	21 (22.1)	19 (20.0)	2 (2.1)	—	—	—
Chills	20 (21.1)	16 (16.8)	4 (4.2)	—	—	—
Pruritus	20 (21.1)	16 (16.8)	4 (4.2)	—	—	—
Abdominal pain	19 (20.0)	13 (13.7)	3 (3.2)	3 (3.2)	—	—
Hypophosphatemia	18 (18.9)	1 (1.1)	6 (6.3)	11 (11.6)	—	—
ALT increased	19 (20.0)	11 (11.6)	2 (2.1)	6 (6.3)	—	—
Fall	17 (17.9)	12 (12.6)	3 (3.2)	2 (2.1)	—	—
Arthralgia	16 (16.8)	11 (11.6)	4 (4.2)	1 (1.1)	—	—
AST increased	15 (15.8)	11 (11.6)	1 (1.1)	3 (3.2)	—	—
Back pain	14 (14.7)	3 (3.2)	10 (10.5)	1 (1.1)	—	—
Insomnia	14 (14.7)	11 (11.6)	3 (3.2)	—	—	—
Rash maculopapular	14 (14.7)	9 (9.5)	4 (4.2)	1 (1.1)	—	—
Weight decreased	14 (14.7)	6 (6.3)	8 (8.4)	—	—	—
Hypertension	13 (13.7)	3 (3.2)	5 (5.3)	5 (5.3)	—	—
Hyponatremia	13 (13.7)	10 (10.5)	1 (1.1)	2 (2.1)	—	—
Pneumonia	12 (12.6)	—	1 (1.1)	9 (9.5)	—	2 (2.1)
Blood creatinine increased	11 (11.6)	10 (10.5)	1 (1.1)	—	—	—
Urinary tract infection	11 (11.6)	—	4 (4.2)	7 (7.4)	—	—
Hypomagnesemia	11 (11.6)	10 (10.5)	1 (1.1)	—	—	—
Pain in extremity	11 (11.6)	7 (7.4)	4 (4.2)	—	—	—

NOTE. Data are expressed as No. (%).
Abbreviation: TEAE, treatment-emergent adverse event.

IPSS-R risk was intermediate, high, or very high in 27.4%, 51.6%, and 21.1% of patients, respectively; 26.3% (n = 25) had a *TP53* mutation. Median exposure was six cycles (range, 1-27 cycles), and as of data cutoff, four patients were ongoing on treatment and 40 remained in follow-up. Primary reasons for treatment discontinuation

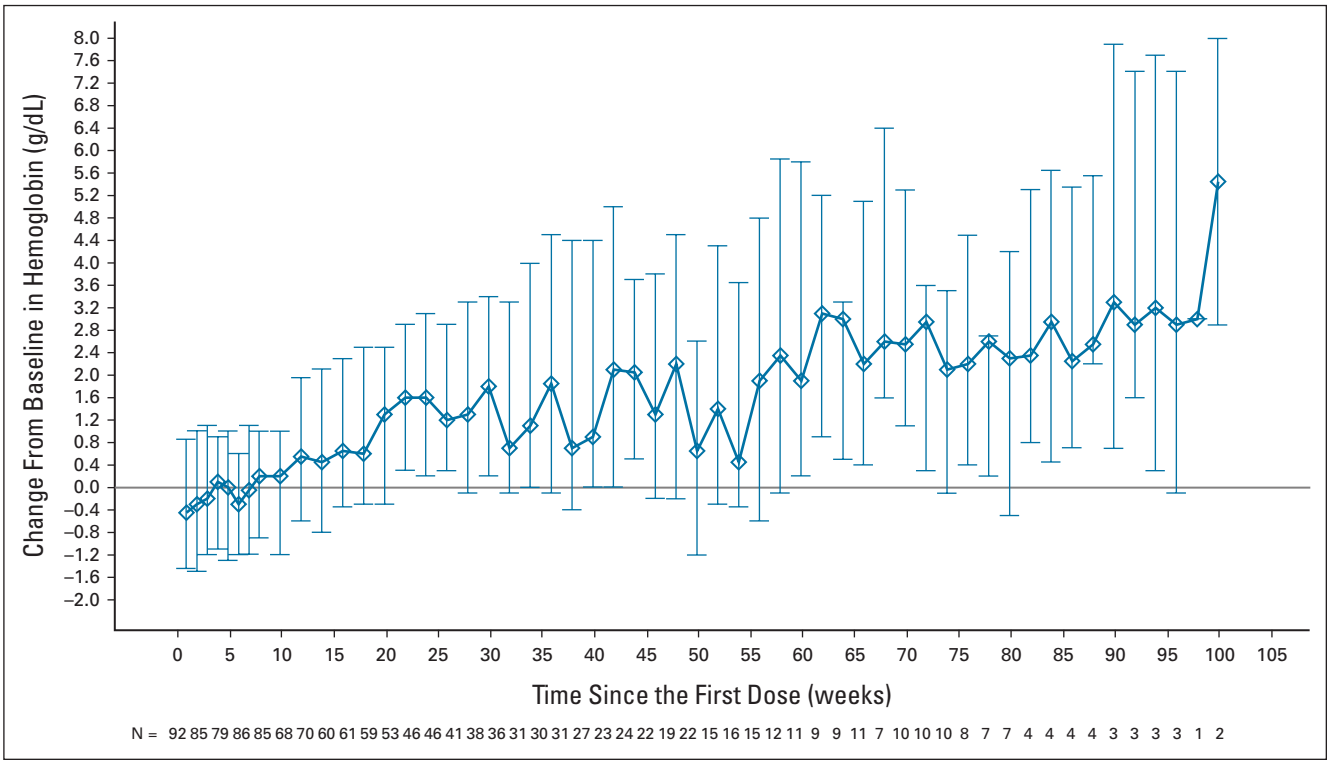

FIG 1. Hemoglobin changes from baseline over time on treatment with magrolimab + azacitidine in patients with HR-MDS (N = 95). Data shown are median (Q1, Q3) change in blood samples drawn before each magrolimab dose. Analysis includes all patients who received at least one dose of magrolimab. HR-MDS, higher-risk myelodysplastic syndrome; Q1, first quartile; Q3, third quartile.

in 91 who discontinued included progressive disease (30.5%), AE (6.3% for magrolimab, 7.4% for azacitidine), patient decision, physician decision, lack of efficacy (5.3% each), and consent withdrawn (4.2%); 34 patients (35.8%) discontinued and received allo-HSCT; of these, five received alternative MDS-directed therapy before allo-HSCT and were censored for CR (or objective response [OR]) duration at the last response assessment before new MDS-directed therapy.

Safety

The most common all-grade TEAEs regardless of attribution were constipation (68.4%), thrombocytopenia (54.7%), anemia (51.6%), neutropenia (47.4%), nausea (46.3%), and diarrhea (43.2%; Table 2). The most common grade 3/4 TEAEs regardless of attribution were anemia (47.4%), neutropenia (46.3%), and thrombocytopenia (46.3%; Data Supplement). Serious TEAEs documented in ≥ 5% of patients were febrile neutropenia (24.2%), pneumonia (9.5%), anemia (8.4%), bacteremia (6.3%), pyrexia (5.3%), and infusion-related reaction (IRR; 5.3%; Data Supplement).

Immune-related reactions possibly/probably related to magrolimab were infrequent (2.1%; one grade 2 pneumonitis and one grade 3 pneumonitis). Treatment-related TEAEs occurring in ≥ 10% of patients by grade are shown in the Data Supplement. Magrolimab-related TEAEs were anemia in 37.9% of patients (3.2% grade 2, 34.7% grade 3, no grade 4/5). Of the patients with magrolimab-related anemia, 33.3% had grade 1, 50.0% had grade 2, and 13.9% had grade 3 anemia at baseline. In cycle 1, median (range) hemoglobin change from baseline to the first post–magrolimab infusion sample was −0.7 g/dL (−3.1 to +2.4 g/dL), and median maximum drop was −1.1 g/dL (−5.6 to +2.0 g/dL) between the first and second magrolimab doses and −0.5 g/dL (−4.9 to +5.4 g/dL) between the second and third magrolimab doses. A total of 27.2% of patients had a ≥ 2 g/dL drop and 10.9% had a ≥ 3 g/dL drop from baseline between magrolimab doses 1 and 3. Hemoglobin change from baseline over time on treatment is shown in Figure 1 and the number of RBC/whole blood units transfused over time in the Data Supplement.

Antidrug antibodies were detected in 2.2% of patients treated with magrolimab; these were transient, not neutralizing, and without clinical sequelae. TEAEs led to magrolimab and azacitidine dose delays in 52.6% and 49.5% (the most common reason for magrolimab and azacitidine dose delays was neutropenia: 14.7% and 12.6%, respectively), and dose reduction in 0% and 17.9%, respectively (most commonly because of neutropenia: 11.6%; Data Supplement). TEAEs led to treatment discontinuation in 10 patients (10.5%; Data Supplement). Mortality was 2.1% at 60 days from treatment

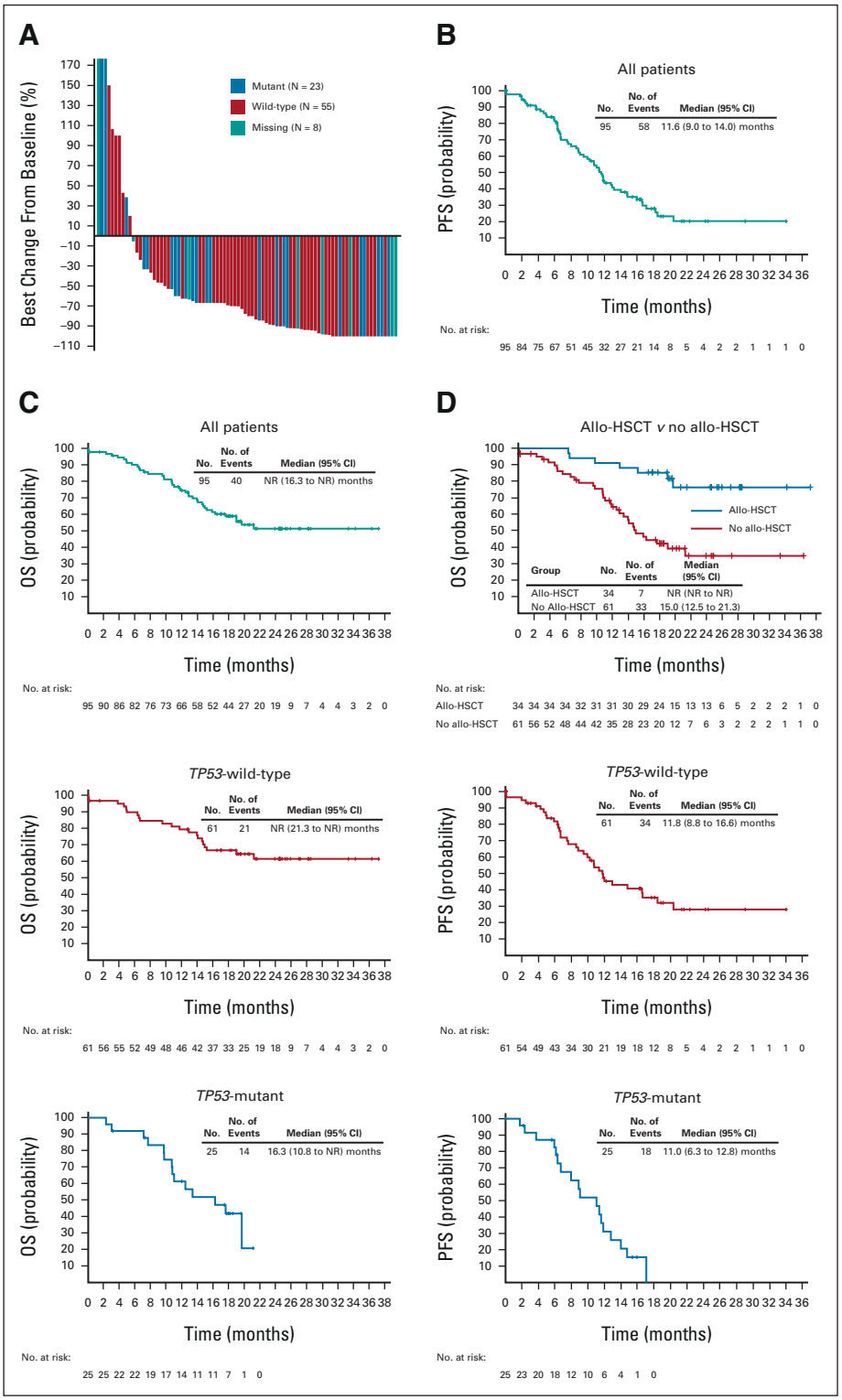

FIG 2. Efficacy of magrolimab + azacitidine in patients with HR-MDS (N = 95). Assessments of efficacy were based on bone marrow aspirate and trephine bone marrow biopsy collected every two cycles starting with cycle 3 day 1, then every three cycles starting with cycle 7 day 1. Analyses include all patients who received at least one dose of magrolimab. (A) Best change from baseline in percent of bone marrow blasts for each patient. Bars are labeled by *TP53* mutation status; those labeled as missing represent patients with *TP53* mutation status unknown. (B) KM curves of PFS for the overall population and by *TP53* mutation status. (C) KM curve of OS for the overall population and by (continued on following page)

FIG 2. (Continued). *TP53* mutation status. (D) KM curve of OS for patients who did and did not undergo allo-HSCT after magrolimab + azacitidine treatment. allo-HSCT, allogeneic hematopoietic stem-cell transplantation; HR-MDS, higher-risk myelodysplastic syndrome; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PFS, progression-free survival.

initiation. During the TEAE assessment period, most patients died because of progressive disease (20.0%) or AE (8.4%; Data Supplement).

Efficacy

The primary efficacy end point of CR with magrolimab + azacitidine was achieved by 32.6% (95% CI, 23.4 to 43.0) of the overall population by intention-to-treat analysis, with an overall response rate of 74.7% (95% CI, 64.8 to 83.1; Fig 2A; Table 3). Median (range) time to first response was 1.9 months (0.7-10.9) and median time to CR was 3.7 months (1.7-7.2). Median CR duration was 11.1 months (95% CI, 7.6 to 13.4) and median OR duration was 9.8 months (95% CI, 8.8 to 12.9). Among patients who achieved a CR, four patients had responses that deepened to CR between 6 and 8 months of therapy (Fig 3). Of those who achieved CR, 41.9% were flow cytometric MRD-negative. An mCR with or without HI was achieved by 16.8% and 14.8%, respectively. Of 65 patients with abnormal cytogenetics at baseline, a complete cytogenic response was achieved in 19 of 47 (40.4%) evaluable patients. Among 20 patients with abnormal cytogenetics who achieved CR, the complete cytogenic response rate was 50.0%. Of 26 patients with complex cytogenetics, 12 (46.2%) achieved CR. Any HI was achieved in 58.9% (HI in neutrophils, 22 [23.2%]; platelets, 38 [40.0%]; and erythroid, 36 [37.9%]). Overall, 37 patients (38.9%) were RBC transfusion-dependent at baseline, defined as transfusion within 4 weeks before first study treatment; 13 of these patients (35.1%) converted to RBC transfusion independence, defined as no transfusions for at least 8 consecutive weeks. Median duration of transfusion independence was 5.2 months (range, 1.9-18.0) as of data cut-off.

With median (Q1, Q3) duration of follow-up for survival of 17.1 months (10.8, 21.2), median progression-free survival was 11.6 months (95% CI, 9.0 to 14.0) and median OS was not reached (NR; 95% CI, 16.3 to NR; Figs 2B and 2C). Survival rates at 1 and 2 years were 74.6% and 51.6%, respectively. Median OS was NR in MRD-negative or MRD-positive patients with separation of survival curves favoring achievement of MRD negativity (Data Supplement). Fourteen patients (14.7%) progressed to AML in a median of 26.0 months (95% CI, 26.0 to NR).

Efficacy of magrolimab + azacitidine was assessed in patients with and without a detectable *TP53* mutation at trial entry (Table 3). In the 25 *TP53*-mutant patients, 10 (40.0%) achieved CR, with a median CR duration of 7.6 months (95% CI, 3.1 to 13.4), a median OR duration of 9.2 months (95% CI, 5.0 to 12.2), and a median OS of 16.3 months (95% CI, 10.8 to NR); 1-year survival rate was 61.5% with a median follow-up of 12.5 months (Fig 2C). In *TP53*-wild-type patients, 19 (31.1%) achieved CR, with a median (95% CI) CR duration of 12.9 months (95% CI, 8.0 to NR), a median OR duration of 9.8 months (95% CI, 8.5 to 18.5), and a median OS NR (95% CI, 21.3 to NR); 1-year survival rate was 79.4% with a median follow-up of 19.0 months (Fig 2C).

Overall, 34/95 patients received allo-HSCT. Most patients were in CR or mCR at the last assessment before transplant (Data Supplement). Median OS was NR (95% CI, NR to NR), and 1-year survival was 91.2% (95% CI, 75.1 to 97.1) in allografted patients, compared with 15.0 months (95% CI, 12.5 to 21.3) and 1-year survival of 64.7% (95% CI, 50.7 to 75.6) in those without allo-HSCT (Fig 2D; Data Supplement). Four patients with *TP53* mutation received allo-HSCT (Data Supplement). Median OS in these patients was 19.7 months (95% CI, 9.8 to 19.7) versus 13.4 months (95% CI, 9.8 to NR) in patients without allo-HSCT. Seven of 34 patients were MRD-negative at the assessment before allo-HSCT; median (95% CI) OS was NR (19.7 months to NR) in these patients and NR (NR to NR) in MRD-positive patients (Data Supplement).

The proportion of patients who achieved CR or mCR was consistent across NGS-identified driver mutations at screening (Data Supplement).

DISCUSSION

Although immunotherapy has shifted the paradigm in solid tumors and Hodgkin lymphoma, targeting traditional immune checkpoints in patients with MDS or AML (eg, with anti-programmed cell death protein 1, anti-programmed death-ligand 1, or cytotoxic T-cell lymphocyte-4 therapy) with or without azacitidine has shown significant immune-related toxicities and no clear evidence of synergy, possibly because of a functionally abrogated T-cell response.[22,33-35] Magrolimab offers a dual mechanistic approach not only to augment the innate immune response by macrophage-mediated phagocytosis but also to eradicate the underlying leukemia stem cell and augment adaptive immunity.[36,37] Importantly, in preclinical models, the combination with azacitidine is synergistic, mediated via upregulation of pro-phagocytic signals such as calreticulin.[28]

Magrolimab + azacitidine was well tolerated in this study, and although dose delays of both treatments occurred in about 50% of patients, no patients had magrolimab dose reductions and few (6.3%) discontinued magrolimab treatment because of TEAEs. Magrolimab and azacitidine dosing are decoupled in more recent ongoing trials to avoid potential loss of efficacy and receptor saturation that may be associated with magrolimab dose delays beyond a 3-week

TABLE 3. Efficacy Outcomes

Outcome	All (N = 95[a])	*TP53*-wt MDS (N = 61)	*TP53*-mut MDS (N = 25)
OR rate, %[b]	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0
Converted to RBC transfusion independence, %[c]	35.1	26.1	46.2
PFS, months, median (95% CI)	11.6 (9.0 to 14.0)	11.8 (8.8 to 16.6)	11.0 (6.3 to 12.8)
OS, months, median (95% CI)	NR (16.3 to NR)	NR (21.3 to NR)	16.3 (10.8 to NR)

Abbreviations: CR, complete remission; HI, hematologic improvement; mCR, marrow CR; MDS, myelodysplastic syndrome; mut, mutation; NR, not reached; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial remission; SD, stable disease; wt, wild-type.

[a]Nine patients included in all patients had missing *TP53* status.

[b]Defined as CR + PR + mCR + SD with HI in all patients who received at least one dose of magrolimab.

[c]On the basis of the number in each group who were transfusion-dependent at baseline (all, n = 37; *TP53*-wt, n = 23; *TP53*-mut, n = 13).

interdose interval. Importantly, only one significant immune-related reaction was noted with magrolimab treatment (a grade 3 pneumonitis), which is consistent with no or very few immune-related AEs noted in prior magrolimab studies.[27,38] IRRs to the first doses were observed, which were well managed with acetaminophen and diphenhydramine premedication (with corticosteroid for grade 3 IRR) in the subsequent three to four doses with no need for continued premedication in subsequent doses.

Anemia is a known on-target side effect of anti-CD47 treatment.[26,39] Red cells express CD47 and are naturally removed from the circulation by macrophages as they lose CD47 expression and express higher levels of prophagocytic signals with increasing red cell age.[24,40] The priming dose removes older RBCs that express higher levels of eat-me signals with compensatory reticulocytosis,[26,38] which allows consistent delivery of higher maintenance doses without subsequent anemia. In this study, anemia related to magrolimab was reported in 37.9% (3.2% grade 2, 34.7% grade 3) of patients, 97.2% of whom had grade 1-3 anemia at baseline; however, grade 4 events were rare (1 anemia and 2 hemolytic anemia) and these were not considered magrolimab related. A drop in hemoglobin $\geq$ 2 g/dL between the first and third doses of magrolimab was seen in 27.2% of patients, and 10.9% had a $\geq$ 3 g/dL drop. This highlights the importance of close hemoglobin monitoring during the initiation of magrolimab treatment (Data Supplement). Anemia events because of magrolimab in later treatment cycles are uncommon. Importantly, 35.1% of patients who were transfusion-dependent at baseline converted to transfusion independence on treatment, and the overall need for RBC/whole blood unit transfusions decreased during the study.

Azacitidine is currently standard of care for HR-MDS,[41] yet CR rates were < 20% in pivotal studies,[5,6] with most responders relapsing within 2 years and an OS of approximately 17-19 months.[11-14,16] In this context, the CR rate of 32.6% is encouraging. More importantly, the median OS was NR with a 17.1-month median follow-up, which is encouraging since 62.1% of patients had poor/very poor cytogenetic risk and 26% had *TP53* mutations, populations that tend to have a worse prognosis.[1,12]

Mutations in *TP53* are observed in 10%-28% of patients with MDS,[42] and are associated with short response durations to currently available therapies.[43] In this phase Ib study, magrolimab + azacitidine demonstrated promising efficacy overall and in *TP53*-mutated MDS. CR rate was 32.6% overall, with CR rates of 40.0% in *TP53*-mutated and 31.1% in *TP53*-wild-type patients. HI was achieved in 56.0% and 60.7% in *TP53*-mutated and *TP53*-wild-type subgroups, respectively, compared with 23%-36% of azacitidine-treated patients with MDS as published in Cancer and Leukemia Group B studies.[8] Clinical outcomes are dismal in patients with *TP53*-mutated MDS, with a median OS of 5-10 months in *TP53*-mutated patients on any available therapies.[43-46] In this study, we see an encouraging median OS of 16.3 months. Notably, the high prevalence of *TP53* mutation in this study (26.3%) makes the median OS of the entire cohort more promising (NR with a median follow-up of 17.1 months), with > 60% of *TP53*-wild-type patients alive at data cutoff. Of course, the efficacy of this combination needs confirmation in the ongoing registration study, given the single-arm phase Ib design of this study.

Historically, the proportion of patients with MDS who proceed to allo-HSCT is < 10%.[47] Limited data support improved outcomes with HMA treatment before allo-HSCT in

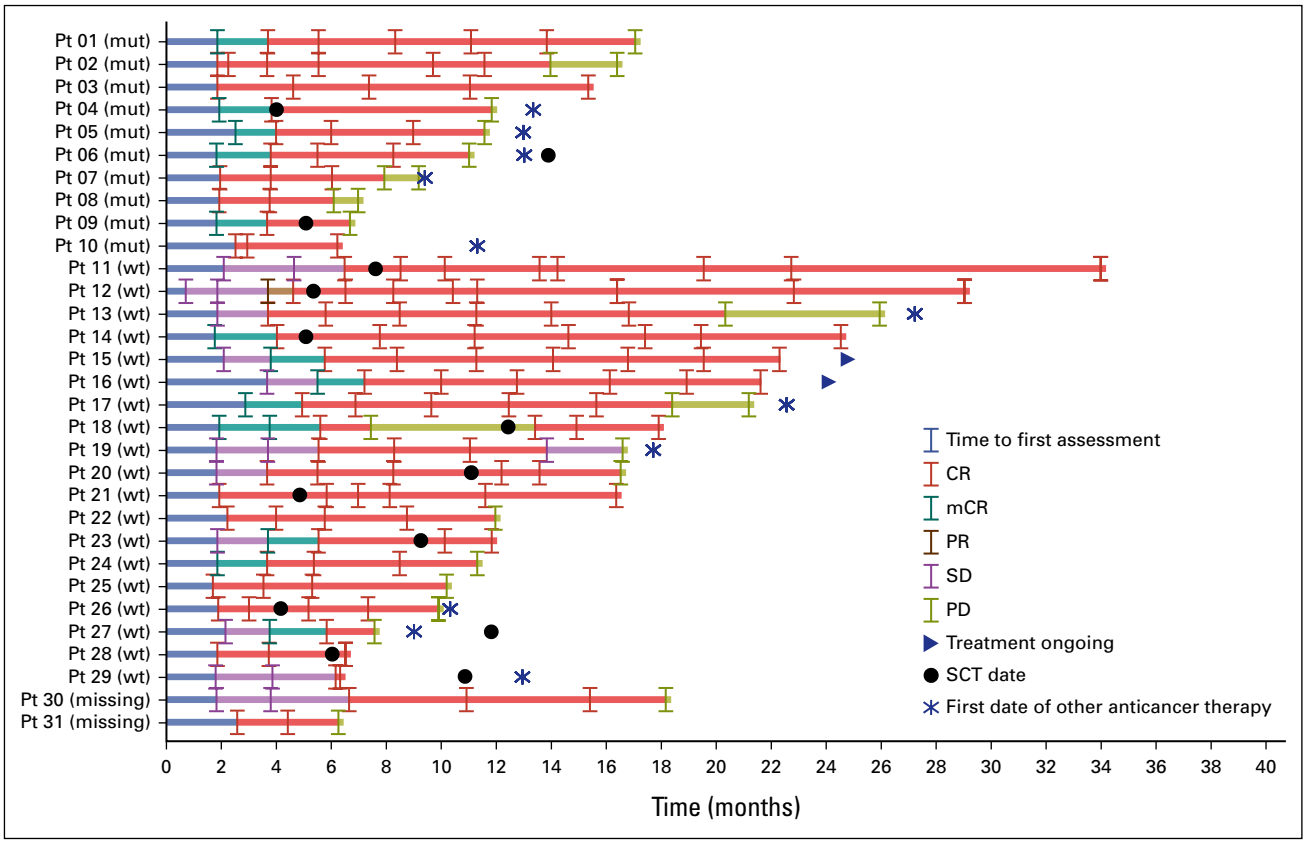

FIG 3. Swimmer plot of response over time, treatment duration, and next treatment initiation for individual patients treated with magrolimab + azacitidine who achieved a CR. *Y*-axis indicates *TP53*-mut status for each patient. Time of first response assessment and results of subsequent response assessments are indicated by vertical lines. Stem-cell transplant is shown by black dots. Blue stars indicate time of next treatment initiation, and blue arrows show patients who were ongoing on magrolimab treatment at the time of data cutoff. CR, complete remission; mCR, marrow CR; mut, mutation; PD, progressive disease; PR, partial remission; Pt, patient; SCT, stem-cell transplantation; SD, stable disease; wt, wild-type.

patients with HR-MDS,[3,48,49] although ideally, improving depth of response as defined by MRD negativity will improve OS after allo-HSCT.[50] Among the 34 patients (35.8%) who proceeded to allo-HSCT in our study, the median OS and 95% CI were NR. Four patients (16.0%) with *TP53* mutations had allo-HSCT, and the median OS of 19.7 months (95% CI, 9.8 to 19.7) is highly encouraging albeit with very small numbers precluding any definitive conclusions or recommendations. With the generally poor outcomes in HR-MDS, heightened further in patients with *TP53* mutations,[42,46,51] the potential that magrolimab + azacitidine treatment may enable more patients to proceed with allo-HSCT could be highly desirable and requires further study in the ongoing registration study. Adding venetoclax to magrolimab + azacitidine may further increase both CR and CR/CR with incomplete blood count recovery rates in AML on the basis of early data from single-arm studies,[52] potentially allowing more patients to be bridged to allo-HSCT; this strategy is under investigation in the ENHANCE-3 AML trial (ClinicalTrials.gov identifier: NCT05079230) and planned for HR-MDS, especially patients with excess blasts.

Limitations of this study include being a single-arm, nonrandomized study done at larger academic centers consistent with the phase Ib design, lack of centralized NGS assessment to annotate molecular responses, and lack of sufficient numbers to definitively delineate efficacy and outcomes in individual molecular subgroups.

To our knowledge, this phase Ib study represents the largest, most comprehensive data set for magrolimab with azacitidine in myeloid malignancies. On the basis of the interim results from this phase Ib trial, the combinations of magrolimab + azacitidine and placebo + azacitidine are being evaluated in patients with HR-MDS in the multinational, randomized phase 3 ENHANCE trial, which is recruiting as of this report (ClinicalTrials.gov identifier: NCT04313881). If successful, this combination could be an important addition for patients with HR-MDS, a population of significant unmet need.

AFFILIATIONS

[1]Moffitt Cancer Center, Tampa, FL
[2]City of Hope National Medical Center, Duarte, CA
[3]Stephenson Cancer Center-University of Oklahoma Health Sciences Center, Oklahoma City, OK
[4]Roswell Park Comprehensive Cancer Center, Buffalo, NY
[5]Columbia University Medical Center, New York, NY
[6]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL
[7]Tennessee Oncology, Nashville, TN
[8]University of Colorado School of Medicine, Denver, CO
[9]Sarah Cannon Cancer Institute, Kansas City, MO
[10]University of California San Diego Moores Cancer Center, San Diego, CA
[11]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[12]The University of Texas MD Anderson Cancer Center, Houston, TX
[13]University of California Irvine, Orange, CA
[14]Gilead Sciences, Inc, Foster City, CA
[15]MRC Molecular Haematology Unit, Oxford BRC, Department of Hematology, Weatherall Institute of Molecular Medicine, University of Oxford and Oxford University Hospitals NHS Trust, Oxford, United Kingdom

CORRESPONDING AUTHOR

David A. Sallman, MD, Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33612; e-mail: David.Sallman@moffitt.org.

EQUAL CONTRIBUTION

D.A.S. and N.G.D. contributed equally to this work.

PRIOR PRESENTATION

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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 on the basis of 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.

AUTHOR CONTRIBUTIONS

Conception and design: David A. Sallman, Mark Chao, Paresh Vyas, Naval G. Daver
Administrative support: Anderson Tan
Provision of study materials or patients: David A. Sallman, Monzr M. Al Malki, Adam S. Asch, Eunice S. Wang, Joseph G. Jurcic, Terrence J. Bradley, Ian W. Finn, Daniel A. Pollyea, Suman Kambhampati, Tiffany N. Tanaka, Joshua F. Zeidner, Guillermo Garcia-Manero, Deepa Jeyakumar, Rami Komorokji, Jeffrey Lancet, Hagop M. Katarjian, Paresh Vyas, Naval G. Daver
Collection and assembly of data: Anderson Tan, Mark Chao, Carol O'Hear, Giridharan Ramsingh, Indu Lal
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Greenberg PL, Tuechler H, Schanz J, et al: Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood 120:2454-2465, 2012
2. Aubrey BJ, Brunner AM: SOHO state of the art and next questions: Treatment of higher-risk myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk 22:P869-P877, 2022
3. Jain AG, Elmariah H: BMT for myelodysplastic syndrome: When and where and how. Front Oncol 11:771614, 2022
4. Nakamura R, Saber W, Martens MJ, et al: Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. J Clin Oncol 39:3328-3339, 2021
5. Silverman LR, Demakos EP, Peterson BL, et al: Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and Leukemia Group B. J Clin Oncol 20:2429-2440, 2002
6. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al: Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. Lancet Oncol 10:223-232, 2009
7. Garcia JS, Swords RT, Roboz GJ, et al: A systematic review of higher-risk myelodysplastic syndromes clinical trials to determine the benchmark of azacitidine and explore alternative endpoints for overall survival. Leuk Res 104:106555, 2021
8. Silverman LR, McKenzie DR, Peterson BL, et al: Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 24:3895-3903, 2006
9. Kantarjian H, Issa JP, Rosenfeld CS, et al: Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomized study. Cancer 106:1794-1803, 2006
10. Lubbert M, Suciu S, Baila L, et al: Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 29:1987-1996, 2011
11. Hasegawa KW, Wei AH, Garcia-Manero G, et al: Clinical outcomes associated with azacitidine monotherapy for treatment-naive patients with higher-risk myelodysplastic syndrome (HR MDS): A systematic literature review and meta-analysis. Presented at the European Hematology Association, Vienna, Austria, June 9-17, 2022

12. Rajakumaraswamy N, Gandhi M, Wei AH, et al: Effectiveness of azacitidine in frontline higher-risk myelodysplastic syndrome (HR MDS): A retrospective cohort study of 382 patients. Presented at the European Hematology Association, Vienna, Austria, June 9-17, 2022
13. Garcia-Manero G, Montalban-Bravo G, Berdeja JG, et al: Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated, higher-risk myelodysplastic syndromes. Cancer 123:994-1002, 2017
14. Sekeres MA, Watts J, Radinoff A, et al: Randomized phase 2 trial of pevonedistat plus azacitidine versus azacitidine for higher-risk MDS/CMML or low-blast AML. Leukemia 35:2119-2124, 2021
15. Ades L, Girshova L, Doronin VA, et al: Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. Blood Adv 6:5132-5145, 2022
16. Zeidan AM, Davidoff AJ, Long JB, et al: Comparative clinical effectiveness of azacitidine versus decitabine in older patients with myelodysplastic syndromes. Br J Haematol 175:829-840, 2016
17. Sekeres MA, Girshova L, Doronin VA, et al: Pevonedistat (PEV) + azacitidine (AZA) versus AZA alone as first-line treatment for patients with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML) with 20–30% marrow blasts: The Randomized Phase 3 PANTHER Trial (NCT03268954). Presented at the ASH Annual Meeting & Exposition, Orlando, FL, December 11, 2021
18. Takada: Takeda Provides Update on Phase 3 PANTHER (Pevonedistat-3001) Trial. 2021. https://www.takeda.com/newsroom/newsreleases/2021/takeda-provides-update-on-phase-3-panther-pevonedistat-3001-trial
19. Aprea Therapeutics: Aprea Therapeutics Announces Results of Primary Endpoint From Phase 3 Trial of Eprenetapopt in TP53 Mutant Myelodysplastic Syndromes (MDS). 2020. https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3
20. Onconova Therapeutics: Onconova Therapeutics Announces Topline Results From the Pivotal Phase 3 INSPIRE Trial. 2020. https://investor.onconova.com/news-releases/news-release-details/onconova-therapeutics-announces-topline-results-pivotal-phase-3
21. Sekeres MA, Othus M, List AF, et al: Randomized phase II study of azacitidine alone or in combination with lenalidomide or with Vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol 35:2745-2753, 2017
22. Zeidan AM, Boss I, Beach CL, et al: A randomized phase 2 trial of azacitidine with or without durvalumab as first-line therapy for higher-risk myelodysplastic syndromes. Blood Adv 6:2207-2218, 2022
23. Chao MP, Weissman IL, Majeti R: The CD47-SIRPalpha pathway in cancer immune evasion and potential therapeutic implications. Curr Opin Immunol 24: 225-232, 2012
24. Oldenborg PA, Zheleznyak A, Fang YF, et al: Role of CD47 as a marker of self on red blood cells. Science 288:2051-2054, 2000
25. Pang WW, Pluvinage JV, Price EA, et al: Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. Proc Natl Acad Sci U S A 110: 3011-3016, 2013
26. Liu J, Wang L, Zhao F, et al: Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One 10:e0137345, 2015
27. Advani R, Flinn I, Popplewell L, et al: CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med 379:1711-1721, 2018
28. Feng D, Gip P, McKenna KM, et al: Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia. Blood 132: 2729, 2018
29. Jia Y, Zhang Q, Weng C, et al: Combined blockade of CD47-Sirpa interaction by 5F9 (magrolimab) and azacitidine/venetoclax therapy facilitates macrophage-mediated anti-leukemia efficacy in AML pre-clinical models. Blood 138:510, 2021
30. Chao MP, Takimoto CH, Feng DD, et al: Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. Front Oncol 9:1380, 2020
31. Cheson BD, Greenberg PL, Bennett JM, et al: Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 108:419-425, 2006
32. Schanz J, Tuchler H, Sole F, et al: New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 30:820-829, 2012
33. Garcia-Manero G, Sasaki K, Montalban-Bravo G, et al: A phase II study of nivolumab or ipilimumab with or without azacitidine for patients with myelodysplastic syndrome (MDS). Blood 132:465, 2018
34. Daver N, Garcia-Manero G, Basu S, et al: Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: A nonrandomized, open-label, phase II study. Cancer Discov 9:370-383, 2019
35. Chien KS, Kim K, Nogueras-Gonzalez GM, et al: Phase II study of azacitidine with pembrolizumab in patients with intermediate-1 or higher-risk myelodysplastic syndrome. Br J Haematol 195:378-387, 2021
36. Majeti R, Chao MP, Alizadeh AA, et al: CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 138:286-299, 2009
37. Tseng D, Volkmer JP, Willingham SB, et al: Anti-CD47 antibody-mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response. Proc Natl Acad Sci U S A 110:11103-11108, 2013
38. Sikic BI, Lakhani N, Patnaik A, et al: First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. J Clin Oncol 37:946-953, 2019
39. Maute R, Xu J, Weissman IL: CD47–SIRPα-targeted therapeutics: Status and prospects. Immunooncol Technol 13:100070, 2022
40. Khandelwal S, van Rooijen N, Saxena RK: Reduced expression of CD47 during murine red blood cell (RBC) senescence and its role in RBC clearance from the circulation. Transfusion 47:1725-1732, 2007
41. Montalban-Bravo G, Garcia-Manero G: Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. Am J Hematol 93:129-147, 2018
42. Montalban-Bravo G, Kanagal-Shamanna R, Benton CB, et al: Genomic context and TP53 allele frequency define clinical outcomes in TP53-mutated myelodysplastic syndromes. Blood Adv 4:482-495, 2020
43. Takahashi K, Patel K, Bueso-Ramos C, et al: Clinical implications of TP53 mutations in myelodysplastic syndromes treated with hypomethylating agents. Oncotarget 7:14172-14187, 2016
44. Hunter AM, Komrokji RS, Yun S, et al: Baseline and serial molecular profiling predicts outcomes with hypomethylating agents in myelodysplastic syndromes. Blood Adv 5:1017-1028, 2021
45. Montalban-Bravo G, Takahashi K, Patel K, et al: Impact of the number of mutations in survival and response outcomes to hypomethylating agents in patients with myelodysplastic syndromes or myelodysplastic/myeloproliferative neoplasms. Oncotarget 9:9714-9727, 2018
46. Sallman DA, Komrokji R, Vaupel C, et al: Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia 30:666-673, 2016

47. Sekeres MA, Schoonen WM, Kantarjian H, et al: Characteristics of US patients with myelodysplastic syndromes: Results of six cross-sectional physician surveys. J Natl Cancer Inst 100:1542-1551, 2008
48. Della Porta MG, Jackson CH, Alessandrino EP, et al: Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the Revised International Prognostic Scoring System. Leukemia 31:2449-2457, 2017
49. Gerds AT, Gooley TA, Estey EH, et al: Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. Biol Blood Marrow Transpl 18:1211-1218, 2012
50. Festuccia M, Deeg HJ, Gooley TA, et al: Minimal identifiable disease and the role of conditioning intensity in hematopoietic cell transplantation for myelodysplastic syndrome and acute myelogenous leukemia evolving from myelodysplastic syndrome. Biol Blood Marrow Transpl 22:1227-1233, 2016
51. Bernard E, Nannya Y, Hasserjian RP, et al: Author correction: Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat Med 27:927, 2021
52. Daver N, Konopleva M, Maiti A, et al: Phase I/II study of azacitidine (AZA) with venetoclax (VEN) and magrolimab (Magro) in patients (pts) with newly diagnosed older/unfit or high-risk acute myeloid leukemia (AML) and relapsed/refractory (R/R) AML. Blood 138:371-374, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Magrolimab in Combination With Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes: Final Results of a Phase Ib Study

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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
Speakers' Bureau: Incyte, Bristol Myers Squibb, Servier
Research Funding: Jazz Pharmaceuticals, Aprea Therapeutics (Inst)

Monzr M. Al Malki
Consulting or Advisory Role: Gilead/Forty Seven, Incyte, NexImmune, CareDX
Research Funding: NexImmune, Gilead/Forty Seven, Incyte, Stemline Therapeutics

Adam S. Asch
Research Funding: Forty Seven (Inst), MEI Pharma (Inst), Astellas Pharma (Inst), Juno Therapeutics (Inst), Gilead Sciences (Inst)
Patents, Royalties, Other Intellectual Property: Provisional patent submitted

Eunice S. Wang
Consulting or Advisory Role: AbbVie, Pfizer, Jazz Pharmaceuticals, Astellas Pharma, Stemline Therapeutics, Kite/Gilead, PTC Therapeutics, Celgene/Bristol Myers Squibb, GlaxoSmithKline, Novartis, Genentech, Takeda, Gilead Sciences, Pharmaessentia
Speakers' Bureau: Stemline Therapeutics, Pfizer, Dava Oncology, Kite, a Gilead company, Astellas Pharma

Joseph G. Jurcic
Consulting or Advisory Role: Novartis, Bristol Myers Squibb/Celgene, Jazz Pharmaceuticals, Syros Pharmaceuticals, Rigel
Research Funding: Astellas Pharma (Inst), FORMA Therapeutics (Inst), AbbVie (Inst), Arog (Inst), PTC Therapeutics (Inst), Bristol Myers Squibb/Celgene (Inst), Gilead/Forty Seven (Inst), Celularity (Inst), Blueprint Medicines (Inst)

Terrence J. Bradley
Consulting or Advisory Role: AbbVie, Novartis, Gilead Sciences
Speakers' Bureau: Novartis, AbbVie

Ian W. Flinn
Consulting or Advisory Role: AbbVie (Inst), Seattle Genetics (Inst), TG Therapeutics (Inst), Verastem (Inst), Roche (Inst), Gilead Sciences (Inst), Kite, a Gilead company (Inst), Janssen (Inst), BeiGene (Inst), Takeda (Inst), AstraZeneca (Inst), Juno Therapeutics (Inst), Unum Therapeutics (Inst), MorphoSys (Inst), Nurix (Inst), Shanghai Yingli Pharmaceuticals (Inst), Genentech (Inst), Great Point Partners (Inst), Iksuda Therapeutics (Inst), Novartis (Inst), Pharmacyclics (Inst), Century Therapeutics (Inst), Hutchison MediPharma (Inst), Servier (Inst), Vincerx Pharma (Inst), Genmab (Inst), Innocare (Inst)
Research Funding: Acerta Pharma (Inst), Agios (Inst), Celgene (Inst), Constellation Pharmaceuticals (Inst), Genentech (Inst), Gilead Sciences (Inst), Incyte (Inst), Infinity Pharmaceuticals (Inst), Janssen (Inst), Kite, a Gilead company (Inst), Novartis (Inst), Pharmacyclics (Inst), Portola Pharmaceuticals (Inst), Roche (Inst), TG Therapeutics (Inst), Trillium Therapeutics (Inst), AbbVie (Inst), ArQule (Inst), BeiGene (Inst), Curis (Inst), FORMA Therapeutics (Inst), Forty Seven (Inst), Merck (Inst), Pfizer (Inst), Verastem (Inst), AstraZeneca (Inst), Unum Therapeutics (Inst), MorphoSys (Inst), Seattle Genetics (Inst), IGM Biosciences (Inst), Loxo (Inst), Rhizen Pharmaceuticals (Inst), Triact Therapeutics (Inst), Bristol Myers Squibb (Inst), CALGB (Inst), CTI (Inst), Fate Therapeutics (Inst), Millennium (Inst), TCR2 Therapeutics (Inst), Tessa Therapeutics (Inst), City of Hope (Inst), CALIBR (Inst), Bio-Path Holdings, Inc (Inst), Nurix (Inst), Innocare (Inst), Myeloid Therapeutics (Inst)

Daniel A. Pollyea
Consulting or Advisory Role: Celgene, AbbVie, Agios, Takeda, Glycomimetics, Gilead Sciences, Astellas Pharma, Janssen, Forty Seven, Amgen, Genentech, Novartis, Karyopharm Therapeutics, Syndax, Syros Pharmaceuticals, Kiadis Pharma, Bristol Myers Squibb, Foghorn Therapeutics, Aprea Therapeutics, BerGenBio, BeiGene, Jazz Pharmaceuticals
Research Funding: AbbVie (Inst), Karyopharm Therapeutics (Inst), Teva (Inst), Bristol Myers Squibb/Celgene (Inst)

Tiffany N. Tanaka
Honoraria: CTI BioPharma Corp
Research Funding: Function Oncology

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)
Travel, Accommodations, Expenses: Dava Oncology

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

Deepa Jeyakumar
Research Funding: Pfizer, Jazz Pharmaceuticals

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

Jeffrey Lancet
Stock and Other Ownership Interests: Arvinas
Consulting or Advisory Role: AbbVie, BerGenBio, Daiichi Sankyo, ElevateBio, Bristol Myers Squibb/Celgene, Millennium, Novartis, Jazz Pharmaceuticals, Servier/Pfizer, The Dedham Group, RW Baird, Medtalks, Boxer Capital

Hagop M. Kantarjian
Honoraria: AbbVie, Amgen, Pfizer, Ascentage Pharma Group, Astellas Pharma, AstraZeneca/MedImmune, Ipsen, KAHR Medical, Novartis, Precision Biosciences, Shenzhen Target Rx, Taiho Pharmaceutical, Daiichih-Sankyo (Inst), Immunogen (Inst), Jazz Pharmaceuticals (Inst)
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)

Lin Gu
Employment: Gilead Sciences
Leadership: Gilead Sciences
Stock and Other Ownership Interests: Gilead Sciences
Travel, Accommodations, Expenses: Gilead Sciences

Yajia Zhang
Employment: Gilead Sciences
Stock and Other Ownership Interests: Gilead Sciences

Anderson Tan
Employment: Gilead Sciences
Stock and Other Ownership Interests: Gilead Sciences, Inc
Travel, Accommodations, Expenses: Gilead Sciences

Mark Chao
Employment: Forty Seven, Gilead Sciences, TenSixteen Bio
Leadership: Forty Seven, TenSixteen Bio
Stock and Other Ownership Interests: Forty Seven, Hepatx, Gilead Sciences, TenSixteen Bio, TigaTx, Chimera Bioengineering, IconOVir Bio
Honoraria: D2G Oncology
Consulting or Advisory Role: Chimera Bioengineering, Gilead Sciences
Patents, Royalties, Other Intellectual Property: I am an inventor on several patents from Stanford University that have been licensed to Forty Seven, Inc, I

am also an inventor on patents generated from Forty Seven, Inc, I am an inventor on patents licensed to Hepatx Inc
Travel, Accommodations, Expenses: Forty Seven, Gilead Sciences, TenSixteen Bio

Carol O'Hear
Employment: Genentech/Roche, Gilead Sciences
Stock and Other Ownership Interests: Genentech/Roche, Gilead Sciences
Patents, Royalties, Other Intellectual Property: Antibody buffering
Travel, Accommodations, Expenses: Genentech/Roche, Gilead Sciences

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

Indu Lal
Employment: Gilead Sciences, AbbVie/Pharmacyclics, The Permanente Medical Group NorCal
Stock and Other Ownership Interests: Gilead Sciences, AbbVie, Reviva Pharmaceuticals

Paresh Vyas
Honoraria: Celgene, Pfizer, Jazz Pharmaceuticals, AbbVie, Daiichi Sankyo, Astellas Pharma
Research Funding: Celgene
Patents, Royalties, Other Intellectual Property: Patent for flow cytometric detection of leukemic stem cells

Naval G. Daver
Consulting or Advisory Role: Celgene, Agios, Jazz Pharmaceuticals, Pfizer, AbbVie, Astellas Pharma, Daiichi Sankyo, Novartis, Bristol Myers Squibb, Amgen, Immunogen, Genentech, Servier, Syndax, Trillium Therapeutics, Gilead Sciences, Arog, Shattuck Labs
Research Funding: Bristol Myers Squibb, Pfizer, Immunogen, Genentech, AbbVie, Astellas Pharma, Servier, Daiichi Sankyo, Gilead Sciences, Amgen, Trillium Therapeutics, Hanmi, Trovagene, FATE Therapeutics, Novimmune, Glycomimetics

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