MDS-445

Magrolimab in Combination With Azacitidine for Untreated Higher-Risk Myelodysplastic Syndromes (HR-MDS): 5F9005 Phase 1b Study Results

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

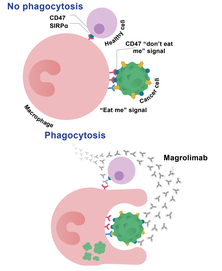
[1]Moffitt Cancer Center, Tampa, FL; [2]City of Hope National Medical Center, Duarte, CA; [3]Stephenson Cancer Center, Oklahoma University Health, Oklahoma City, OK; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [5]Columbia University Medical Center, New York, NY; [6]Sylvester Comprehensive 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 Research 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]Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK

An online version of this poster can be found through this QR code.

Background

- Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal overexpressed on cancer cells (**Figure 1**)[1,2]
- CD47 blockade by magrolimab induces macrophage-mediated phagocytosis of tumor cells and is synergistic with azacitidine (AZA) via upregulation of "eat me" signals[3]
- A high unmet need exists for new therapies that increase efficacy beyond standard of care while maintaining a tolerable safety profile[4,5]
- Here we report final phase 1b data in patients with untreated HR-MDS (NCT03248479)

Figure 1. MOA[2]



MOA, mechanism of action; SIRPα, signal regulator protein alpha.

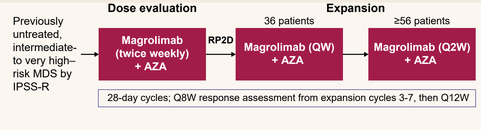
Objectives

- **Primary objectives:** assess safety, tolerability, and efficacy of magrolimab with AZA by complete remission (CR) rate
- **Secondary objectives:** assess magrolimab concentration vs time and immunogenicity and efficacy of magrolimab + AZA by objective response rate (ORR), duration of complete response (DCR), duration of response (DOR), hemoglobin increase on treatment, progression-free survival (PFS), relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), and red blood cell (RBC) transfusion independence
- **Exploratory objectives:** assess CD47 receptor occupancy, biomarkers, and efficacy in molecular subtypes

Methods

- Open-label, multicenter phase 1b trial with a 30-day screening period, dose-evaluation, and dose-expansion cohort (**Figure 2**)
- Eligible patients were previously untreated, aged ≥18 years, with confirmed MDS by World Health Organization (WHO) classification with intermediate, high, or very high risk by the Revised International Prognostic Scoring System (IPSS-R), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2
- Patients received magrolimab intravenously (IV) as a 1-mg/kg priming dose on days 1 and 4, then ramped up to 30 mg/kg once-weekly (QW) or every-2-week (Q2W) maintenance. AZA dose was administered subcutaneously or IV 75 mg/m^2 on days 1 to 7 of each cycle
- Statistical analyses were based on all patients who received ≥1 dose of magrolimab; data from the expansion cohort are presented

Figure 2. Study Design



Q8W, every 8 weeks; Q12W, every 12 weeks; RP2D, recommended phase 2 dose.

Results

- Patients (N=95[a]) received a median of 6 (range, 1-27) treatment cycles
- Main reasons for treatment discontinuation were hematopoietic stem cell transplant (HSCT; 31.6%[b]), progressive disease (30.5%), adverse events (AEs; magrolimab, 6.3%; AZA, 7.4%)
- 35 patients (36.8%[b]) received HSCT (4 *TP53*-mutated [mut], 30 *TP53*-wild type [wt], 1 *TP53* status missing), and 14.7% experienced progression to acute myeloid leukemia
- Patient baseline characteristics are presented in **Table 1**

[a] Includes 1 patient from the dose evaluation cohort who received the same regimen as the expansion cohort.
[b] Not all patients who received HSCT had HSCT recorded as a reason for treatment discontinuation.

Table 1. Baseline Characteristics

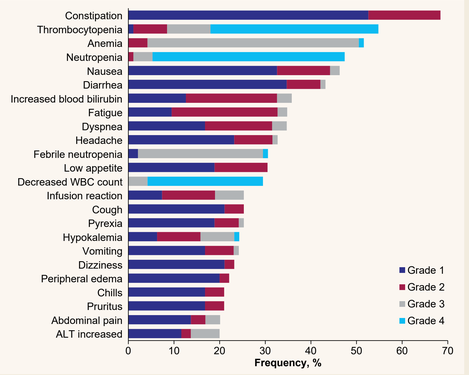
Characteristic	N=95[a]
Age, median (range), years	69 (28-91)
Male/female, n (%)	62 (65.3)/33 (43.7)
ECOG PS, n (%)	
0	29 (30.5)
1	60 (63.2)
2	6 (6.3)
MDS risk category by IPSS-R, n (%)	
Intermediate	26 (27.4)
High	49 (51.6)
Very high	20 (21.1)
WHO classification, n (%)	
MDS-RS	2 (2.1)
MDS-RS with single-lineage 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, unclassified	8 (8.4)
Cytogenetic risk category, n (%)	
Favorable	12 (12.6)
Intermediate	17 (17.9)
Poor	59 (62.1)
Unknown/missing	7 (7.4)
Therapy-related MDS, n (%)	21 (22.1)
Mutations at baseline, n (%)[b]	
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)
Complex cytogenetics, n (%)	26 (27.4)
RBC transfusion dependent, n (%)	37 (38.9)
Hemoglobin, median (range), g/dL	8.6 (6.5-13.0)

MDS-RS, MDS with ring sideroblasts.
[a] Includes 1 patient from the dose evaluation cohort who received the same regimen as the expansion cohort.
[b] Baseline mutation status was unknown for 9 patients (9.5%).

Safety and Tolerability

- Treatment-emergent AEs (TEAEs) reported in ≥20% of patients are shown in **Figure 3**

Figure 3. TEAEs by Grade (N=95)[a]



- Grade ≥3 TEAEs occurred in 90.5% of patients (magrolimab related, 60.0%; AZA related, 69.5%)
- Serious AEs were reported in 63.2% of patients
- TEAEs led to death in 8 patients: pneumonia in 2 patients[b]; COVID-19, intracranial hemorrhage, leukemia, myocardial ischemia, pulmonary embolism, and sepsis in 1 patient each
- Grade 4 anemia was not magrolimab related

ALT, alanine aminotransferase; WBC, white blood cell.
[a] Regardless of causality. Assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[b] One death from pneumonia was considered AZA related; no other deaths were considered treatment related.

- TEAEs leading to treatment discontinuation were anemia, hemolytic anemia, myocardial infarction, myocardial ischemia, asthenia, pneumonia, hemophagocytic lymphohistiocytosis, pneumonitis, and pulmonary embolism
- 30-day mortality was 2%, with no additional deaths at 60 days
- 2.2% of magrolimab-treated patients developed transient antidrug antibodies
- Median (range) hemoglobin change from baseline was −0.7 g/dL (−3.1 to 2.4) at first posttreatment visit, with maximum of −1.1 g/dL (−5.6 to 2.0) between doses 1 and 2, −0.5 g/dL (−4.9 to 5.4) between doses 2 and 3, and −1.2 g/dL (−5.6 to 1.8) between doses 1 and 3
- Anemia was managed with a low priming dose, intrapatient dose escalation, and supportive care with RBC transfusions

Efficacy

- The CR rate was 32.6% (95% CI, 23.4%-43.0%), and the ORR was 74.7%, with response rates similar in *TP53*-mut and *TP53*-wt (**Table 2**)
- Median PFS was 11.6 months, and median OS was not reached (NR) with a median 17.1 months of follow-up; in patients with vs without stem cell transplant (SCT), the median OS was NR vs 14.8 months (**Figures 4** and **5**)

Table 2. Efficacy Outcomes

Outcome	All (N=95)[a]	*TP53*-wt (n=61)	*TP53*-mut (n=25)
ORR, %[b]	74.7	78.7	68.0
CR (95% CI), %	32.6 (23.4-43.0)	31.1 (19.9-44.3)	40.0 (21.1-61.3)
Marrow CR, %	31.6	37.7	20.0
Any HI, %	58.9	60.7	56.0
Marrow CR with HI, %	16.8	19.7	12.0
SD with HI, %	10.5	9.8	8.0
DCR, median (95% CI), mo	11.1 (7.6-13.4)	12.9 (8.0-NR)	7.6 (3.1-13.4)
Time to CR, median (range), mo	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
DOR, median (95% CI), mo	9.8 (8.8-12.9)	9.8 (8.5-18.5)	9.2 (5.0-12.2)
Time to OR, median (range), mo	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
Conversion to RBC transfusion independence, n/N (%)[c]	13/37 (35.1)	6/23 (26.1)	6/13 (46.2)
PFS, median (95% CI), mo	11.6 (9.0-14.0)	11.8 (8.8-16.6)	11 (6.3-12.8)

HI, hematologic improvement; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.
[a] 9 patients included in the "All" category had missing *TP53* status. [b] Defined as CR + PR + marrow CR + HI without PD in all patients who received ≥1 magrolimab dose. [c] Based on patients who were RBC transfusion dependent at baseline.

Figure 4. Kaplan-Meier Overall Survival Curves

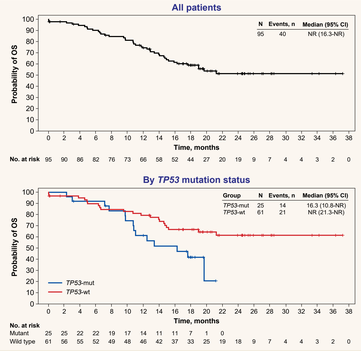
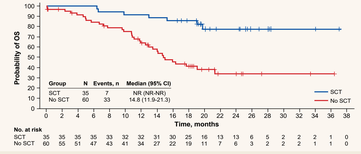
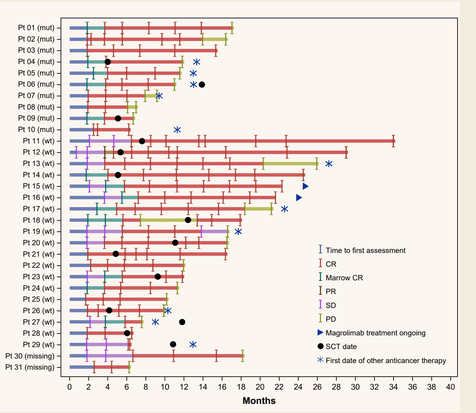


Figure 5. Kaplan-Meier Overall Survival Curves With and Without SCT (All Patients)



- In most patients who achieved CR, responses deepened over time from initial disease assessments (**Figure 6**)

Figure 6. Responses Over Time in Patients Achieving CR



Conclusions

- Magrolimab + AZA is well tolerated in patients with HR-MDS
  - Low rates of discontinuation due to AEs were shown
  - No significant immune-related reactions occurred
  - Expected on-target anemia was manageable with priming dose mitigation
- Promising efficacy was shown in both *TP53*-wt and *TP53*-mut patients
- Magrolimab + AZA is being studied in patients with HR-MDS in the phase 3 ENHANCE trial (currently recruiting; NCT04313881)

References

1. Liu J, et al. *PLoS One*. 2015;10(9):e0137345. 2. Chao MP, et al. *Front Oncol*. 2020;9:1380. 3. Feng D, et al. *Blood*. 2018;132(suppl 1). Abstract 2729. 4. Fenaux P, et al. *Lancet Oncol*. 2009;10(3):223-232. 5. Kantarjian H, et al. *Cancer*. 2006;106(6):1794-1803.

Acknowledgments

We extend our thanks to the patients, family, friends, caregivers, and study staff. This study was funded by Gilead Sciences, Inc. Medical writing support was provided by Jackie Stone, of SciMentum, Inc, a Nucleus Holdings Ltd company, Hamilton, NJ, and funded by Gilead Sciences, Inc.

Disclosures

DAS reports consulting fees from AbbVie, Affined GmbH, Intellisphere, Molecular Partners AG, Novartis, PGEN Therapeutics, Takeda, and Zentalis Pharmaceuticals; grants or contracts from Aprea and Jazz Pharmaceuticals; participation on data safety monitoring or advisory boards for AvenCell, bluebird bio, Bristol Myers Squibb, Intellia, Jasper Therapeutics, Kite, Novartis, Servier, and Shattuck Labs; payment for expert testimony from Kiernan Trebach LLP; and payments or honoraria from Bristol Myers Squibb, Incyte, and Servier.

Correspondence: David.Sallman@moffitt.org

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SOHO© or the author of this poster.

Presented at the Society of Hematologic Oncology 2022 Annual Meeting, September 28 to October 1, 2022; Houston, TX.

© 2022 Gilead Sciences, Inc. All rights reserved.