AML-464

Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine in Patients With Frontline *TP53*m AML: Phase 1b Results

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Background

- Patients with newly diagnosed acute myeloid leukemia (AML) harboring a *TP53* mutation (*TP53*m) have a particularly poor prognosis; their disease is refractory to available therapies[1,2]
- Magrolimab is a monoclonal antibody that blocks cluster of differentiation 47 (CD47), a "don't eat me" signal overexpressed on AML cells[3]
- CD47 blockades induce macrophage-mediated phagocytosis of tumor cells and are synergistic with azacitidine (AZA) via upregulation of "eat me" signals such as calreticulin[4]
- Here we report data from a phase 1b trial of magrolimab + AZA in patients with untreated *TP53*m AML who were ineligible for cytarabine and anthracycline induction regimen or who refused such therapy (NCT03248479)

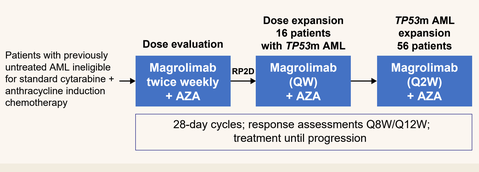
Objectives

- **Primary objectives:** assess safety, tolerability, and efficacy of magrolimab with AZA as measured by complete remission (CR) rate
- **Secondary objectives:** assess magrolimab concentration vs time and immunogenicity and efficacy as measured by objective response rate (ORR), CR with partial hematologic recovery (CRh), duration of CR (DCR), duration of response (DOR), progression-free survival (PFS), event-free survival, overall survival (OS), and level of minimal residual disease negativity (MRD−)
- **Exploratory objectives:** assess CD47 receptor occupancy, biomarkers of immune cell efficacy and bone marrow penetration of magrolimab, and efficacy in molecular subtypes of AML

Methods

- Open-label, multicenter, phase 1b trial with a 30-day screening period and dose-evaluation, dose-expansion, and *TP53*m AML expansion cohorts (**Figure 1**)
- Eligible patients had previously untreated AML and were ineligible for standard induction chemotherapy
- Patients received magrolimab intravenously (IV) as a 1-mg/kg priming dose on days 1 and 4, then ramped up to the maintenance dose of 30 mg/kg once weekly (QW) or every 2 weeks (Q2W). AZA 75 mg/m^2 was administered subcutaneously or IV on days 1 to 7 of each cycle
- Statistical analyses were based on all patients who received ≥1 dose of magrolimab

Figure 1. Study Design



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

Results

Patients

- 72 previously untreated patients with *TP53*m and a median age of 73 years were enrolled; 79% had adverse cytogenetics (**Table 1**)

Table 1. Baseline Characteristics

Characteristic	*TP53*m N=72
Age, median (range), years	73 (31-89)
Age ≥65, n (%)	57 (79.2)
Male/female, n (%)	41 (56.9)/31 (43.1)
ECOG performance status, n (%)	
0	10 (13.9)
1	51 (70.8)
2	11 (15.3)
Bone marrow blast, median (range), %	32.5 (3-92)
WHO classification, n (%)	
AML with recurrent genetic abnormalities	10 (13.9)
AML with myelodysplasia-related changes	34 (47.2)
AML related to prior chemotherapy or radiation	15 (20.8)
AML not otherwise specified	13 (18.1)
Cytogenetic risk category, n (%)[a]	
Favorable	1 (1.4)
Intermediate	2 (2.8)
Adverse	57 (79.2)
Unknown	12 (16.7)
Mutations at baseline, n (%)	
TP53	72 (100)
IDH1/IDH2	4 (5.6)
FLT3	0
NPM1	0
DNMT3A	7 (9.7)
TET2	11 (15.3)
TP53 VAF (n=13), median (range), %	38 (13-88)
RBC transfusion dependent, n (%)[b]	37 (51.4)
Platelet transfusion dependent, n (%)[b]	24 (33.3)

ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; RBC, red blood cell; VAF, variant allele frequency; WHO, World Health Organization.
[a] By ELN criteria. [b] Defined as transfusion within 4 weeks prior to the first study treatment.

Exposure and Disposition

- The median exposure was 4 cycles (range, 1-17 cycles)
- Primary reasons for magrolimab discontinuation included progressive disease in 21 patients (29.2%), adverse events (AEs) in 13 (18.1%), death in 8 (11.1%), stem cell transplant (SCT) in 8 (11.1%), and lack of efficacy in 6 (8.3%)

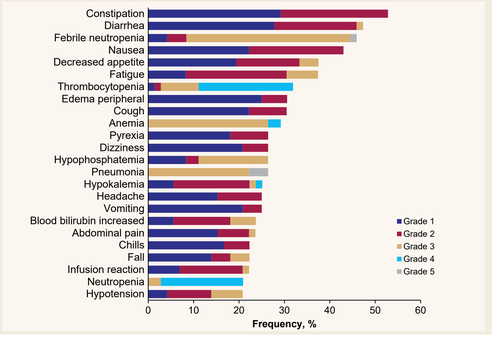
Safety

- The most common treatment-emergent adverse events (TEAEs) were gastrointestinal disorders (**Figure 2**)
- 13 patients (18.1%) died within 60 days of first study drug dose
- Magrolimab-related grade ≥3 TEAEs occurred in 43.1% of patients (**Table 2**)
- 19 patients (26.4%) had grade 3 anemia, and 2 (2.8%) had grade 4 anemia. No patient had fatal anemia
- TEAEs led to discontinuation of magrolimab in 22 (30.6%) and of AZA in 21 patients (29.2%); none discontinued for magrolimab-related anemia
- TEAEs led to deaths in 21 patients; none were magrolimab related

Table 2. TEAEs

TEAEs, n (%)	N=72
Any TEAE	72 (100)
Grade ≥3 TEAEs	68 (94.4)
Magrolimab related	31 (43.1)
AZA related	34 (47.2)
Serious TEAEs	53 (73.6)
Magrolimab related	13 (18.1)
AZA related	8 (11.1)
TEAEs of interest (in ≥10% of patients regardless of causality), n (%)	**N=72**
Febrile neutropenia	33 (45.8)
Thrombocytopenia	23 (31.9)
Anemia	21 (29.2)
Pneumonia	19 (26.4)
Blood bilirubin increase	17 (23.6)
Neutropenia	15 (20.8)
Dyspnea	14 (19.4)
Hypoxia	10 (13.9)
Urinary tract infection	8 (11.1)

Figure 2. Common TEAEs (≥20%)



Efficacy

- CR was achieved by 33.3% of patients (**Table 3**), with half of patients achieving CR being MRD−. Thirty patients (41.7%) achieved CR/CRi
- 29.7% of patients converted to RBC transfusion independence; 45.8% converted to platelet transfusion independence

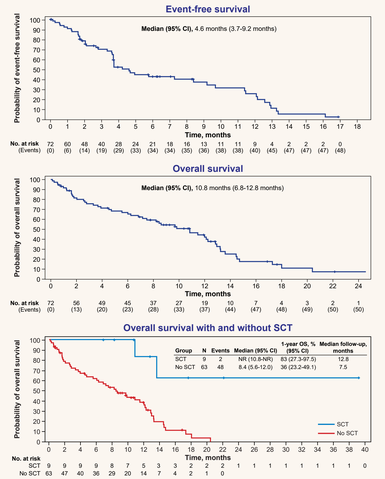
Table 3. Efficacy Endpoints (Intent-to-Treat Analysis)

Outcome	N=72
ORR (95% CI), %	48.6 (36.7-60.7)
CR (95% CI), % MRD− CR	(n=24/72) 33.3 (22.7-45.4) (n=12/24) 50.0 (29.1-70.9)
CRi/CRh, n (%)	6 (8.3)
PR, n (%)	4 (5.6)
MLFS, n (%)	1 (1.4)
SD, n (%)	12 (16.7)
DOR, median (95% CI), months	8.7 (6.5-10.4)
DCR, median (95% CI), months	7.7 (4.7-10.9)
Duration of CR/CRi, median (95% CI), months	8.7 (5.3-10.9)
PFS, median (95% CI), months	7.3 (3.7-9.7)

CRi, complete remission with incomplete blood count recovery; MLFS, morphologic leukemia-free state; PR, partial remission; SD, stable disease.

- Overall survival curves are shown in **Figure 3**
- Median (Q1-Q3) survival follow-up was 8.3 months (2.6-12.2 months)

Figure 3. Kaplan-Meier Survival Curves



NR, not reached.

TP53 VAF

- Thirteen patients with *TP53*m disease had whole exome sequencing (WES) and best overall response data available[a]
- Seven of 9 responders achieved *TP53* VAF <0.07 by cycle 5 day 1

[a] A mutation limit of detection at VAF of 0.07 was used to identify somatic mutation from WES.

Conclusions

- Magrolimab + AZA has an acceptable safety/tolerability profile
- Magrolimab + AZA demonstrates promising efficacy in patients with *TP53*m AML consistent with magrolimab + AZA synergy observed in preclinical studies[4]
- Magrolimab + AZA is being studied in patients with previously untreated *TP53*m AML in the phase 3 ENHANCE-2 trial (currently recruiting; NCT04778397)

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Disclosures

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