Nature of Clinical Response and Depth of Molecular Response in Patients With *TP53*-Mutant Myelodysplastic Syndromes and Acute Myeloid Leukemia Treated With Magrolimab With Azacitidine

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MDS-345

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Conclusions

In this phase 1b study, magrolimab + azacitidine (AZA) demonstrated a reduction in the allele frequency of *TP53* mutations as early as cycle 3 in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML), particularly those who achieved complete remission (CR)

These results suggest that magrolimab + AZA potentially alters the disease course in patients with *TP53* mutations

A similar analysis is planned in bone marrow samples of patients with previously untreated *TP53*-mutant AML treated with magrolimab + AZA, venetoclax + AZA, or chemotherapy in the phase 3 ENHANCE-2 trial (NCT04778397)

Background

- Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal overexpressed on cancer cells, including myeloid blasts[1,2]
  - CD47 blockade by magrolimab induces macrophage-mediated phagocytosis of tumor cells and is synergistic with AZA via upregulation of "eat me" signals, such as calreticulin[3]
- In patients with AML or MDS, response to therapy and overall survival (OS) are heavily influenced by the underlying molecular architecture and loss of detection of mutations with treatment (ie, molecular negativity)[4,5]
  - In particular, molecular negativity has been associated with improved OS in patients with *TP53*-mutated MDS and AML
- Here, we report on the analysis of the somatic mutational landscape of a subset of patients with previously untreated AML or HR MDS who received magrolimab + AZA performed to identify genetic mutations prognostic of response and OS
  - Longitudinal analysis of the most frequent mutations during treatment was also performed

References: **1.** Chao MP, et al. *Front Oncol*. 2020;9:1380. **2.** Liu J, et al. *PLoS One*. 2015;10(9):e0137345. **3.** Feng D, et al. *Blood*. 2018;132(suppl 1). Abstract 2729. **4.** Hunter AM, et al. *Blood Adv*. 2021;5(4):1017-1028. **5.** Yun S, et al. *Leukemia*. 2021;35(4):1145-1155.

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Methods

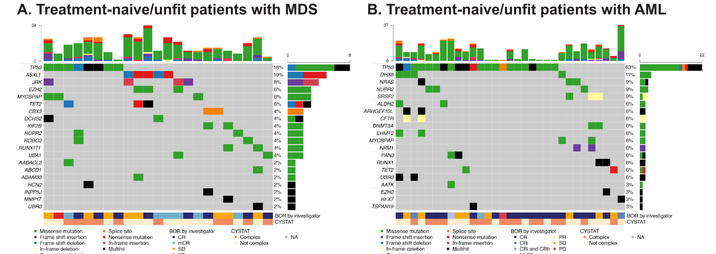
- Data from an open-label, multicenter, phase 1b study of magrolimab + AZA (NCT03248479) were analyzed
- Patients had either previously untreated AML ineligible for standard induction chemotherapy or previously untreated, confirmed MDS by World Health Organization classification with intermediate, high, or very high risk by the Revised International Prognostic Scoring System
- Magrolimab was administered intravenously (IV) in an escalating dose from 1 to 30 mg/kg for the first 2 weeks then at a maintenance dose of 30 mg/kg weekly or once every 2 weeks from cycle 3 onward
- AZA 75 mg/m^2 was administered subcutaneously or IV on days 1 to 7 of each 28-day cycle
- Whole-exome sequencing (WES) was performed on available samples from screening and posttreatment bone marrow aspirates
  - Customized WES processing pipelines combining published algorithms with novel filtering, curation, and quality-control steps were developed using a variant allele frequency (VAF) cutoff of 0.07

Results

- In the treatment-naive/unfit expansion cohorts, 51 patients with MDS and 35 patients with AML had information available on both WES and best overall response (BOR) by investigator
- The top 20 genes harboring somatic mutations at the time of screening are presented in **Figure 1**
  - *TP53* was the most common variant observed in patients with MDS (8/51 [15.7%]) and AML (22/35 [62.9%])
    - Among the 22 patients with AML with somatic *TP53* mutations, 13 had a "complex" cytogenetic status
  - *TP53* biallelic loss, defined as 2 *TP53* mutations, 1 *TP53* mutation plus "complex cytogenetics", or *TP53* VAF >0.5, was observed in 5 patients with MDS and 17 with AML
- The CR/marrow CR (mCR) rate was 62.7% in patients with MDS and the CR/CR with incomplete hematologic recovery (CRi)/CR with partial hematologic recovery (CRh) rate was 62.9% in patients with AML (**Table 1**)
  - Among patients with *TP53* mutations or *TP53* biallelic loss, CR rates were 37.5% or 60.0%, respectively, in patients with MDS and 59.1% or 58.8%, respectively, in patients with AML
- Similar response rates (CR range, 0%-50% in MDS and 0%-100% in AML) were observed in patients with mutations other than *TP53* in this subset of patients (**Figure 2**)
- The VAF over time in patients with *TP53* mutations, as measured from bone marrow aspirate over time, is presented in **Figure 3**
  - Median *TP53* VAF at screening was 0.38 (range, 0.14-0.86) (data not shown) in patients with *TP53*-mutated MDS; among the 3 patients with CR, 3 (100%) had a *TP53* VAF <0.07 by cycle 5 day 1
    - 1 of 1 patient with mCR had a VAF of 0.1 at cycle 3 day 1
  - In patients with *TP53*-mutated AML, median *TP53* VAF at screening was 0.37 (range, <0.07-0.88) (data not shown); among the 13 patients with CR, 9 (69.2%) had a *TP53* VAF of <0.07 by cycle 5 day 1
- Longitudinal assessment of *TET2*, *EZH2*, and *RUNX1* did not demonstrate decreases of <0.07 over time in patients with MDS (**Figure 4**)
  - One patient with an *ASXL1* mutation who achieved a mCR had a VAF of <0.07 by cycle 3 day 1
- In patients with AML, a VAF of <0.07 was observed in patients with *NRAS* (2/3 [66%]) and *RUNX1* (2/2 [100%]) mutations, but patients with *DNMT3A* or *EZH2* mutations had a VAF of >0.10 at all time points (**Figure 5**)

Results (continued)

Figure 1. Top 20 genes harboring somatic mutations at the time of screening



MLFS, morphologic leukemia-free state; NA, not available; PD, progressive disease; PR, partial remission; SD, stable disease.

Table 1. BOR by investigator

	MDS				AML			
	All patients N=51	*TP53* WT n=43	*TP53* mutated n=8	*TP53* biallelic loss n=5	All patients N=35	*TP53* WT n=13	*TP53* mutated n=22	*TP53* biallelic loss n=17
CR, n (%)	16 (31.4)	13 (30.2)	3 (37.5)	3 (60.0)	19 (54.3)	6 (46.2)	13 (59.1)	10 (58.8)
mCR, n (%)	16 (31.4)	15 (34.9)	1 (12.5)	1 (20.0)	–	–	–	–
CRi or CRh, n (%)	–	–	–	–	3 (8.6)	1 (7.7)	2 (9.1)	2 (11.8)
MLFS, n (%)	–	–	–	–	1 (2.9)	0	1 (4.5)	0
PR, n (%)	–	–	–	–	1 (2.9)	1 (7.7)	0	0
SD, n (%)	16 (31.4)	13 (30.2)	3 (37.5)	1 (20.0)	10 (28.6)	5 (38.5)	5 (22.7)	4 (23.5)
PD, n (%)	3 (5.9)	2 (4.7)	1 (12.5)	0	1 (2.9)	0	1 (4.5)	1 (5.9)

WT, wild type.

Figure 2. BOR by investigator across the mutational spectrum

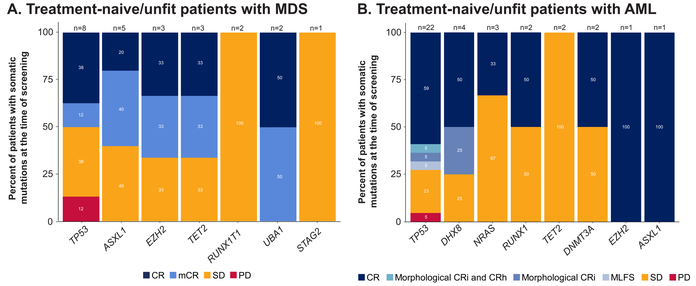
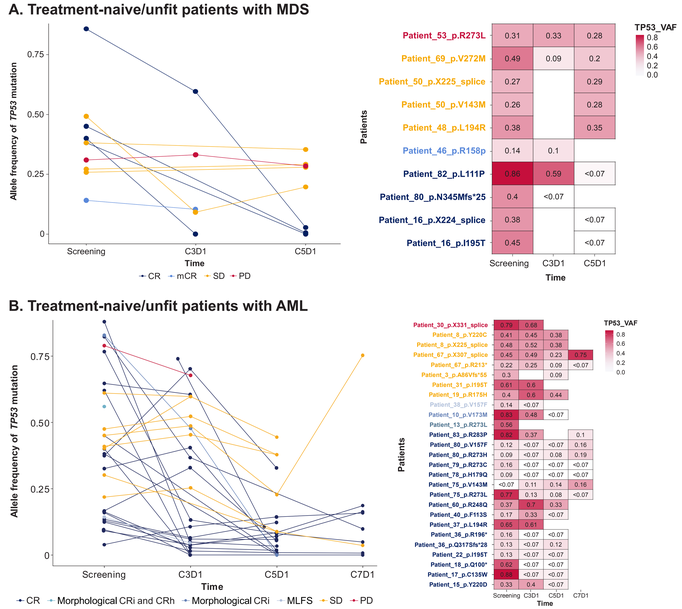


Figure 3. VAF over time in patients with *TP53* mutations



Left panels: *TP53* VAF by BOR; right panels: heatmaps of *TP53* VAF at each time point.
C, cycle; D, day.

Figure 4. VAF for *ASXL1*, *TET2*, *EZH2*, and *RUNX1* in patients with MDS

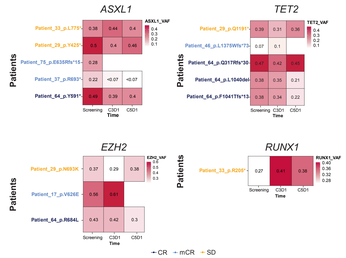


Figure 5. VAF for *NRAS*, *RUNX1*, *DNMT3A*, and *EZH2* in patients with AML

