Magrolimab Alters the Tumor Microenvironment to Improve Bone Marrow Functions in Patients With Acute Myeloid Leukemia and Higher-Risk Myelodysplastic Syndromes

MDS-488

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Key Findings

- Indicators of innate and adaptive immunity were present in the bone marrow of patients with acute myeloid leukemia (AML) and higher-risk myelodysplastic syndromes (HR MDS) receiving magrolimab and azacitidine (AZA)
- A trend towards a reduction in inflammatory pathways such as interleukin (IL)-6 and complement was observed as well, suggesting an overall improvement in the bone marrow environment of patients with AML and MDS following magrolimab and AZA treatment

Conclusions

This initial study of a subset of 5F9005 patients treated with magrolimab + AZA demonstrated a shift in the bone marrow environment that is dominated by a phagocytic response shown by increased detection of proteins associated with macrophages including LYVE1 and LRP11. Anti-tumor proteins, such as RANTES, were increased following magrolimab

As suggested by the mechanism of action, adaptive immunity was triggered via innate checkpoint inhibition, including an increase in CD8+ T cells in patients with objective responses

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)

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Introduction

- Magrolimab (Hu5F9-G4) is a monoclonal antibody that blocks CD47, an antiphagocytic signal overexpressed on tumor cells[1,2]
- CD47 is a negative regulator of innate immunity; therapeutic blockade of CD47 has the potential to trigger both innate and adaptive antitumor activity[3]
- The combination of AZA, a hypomethylating agent that can deliver a pro-phagocytic signal to tumor cells in combination with magrolimab, tips the balance in favor of phagocytosis of tumor cells[1]

Objective

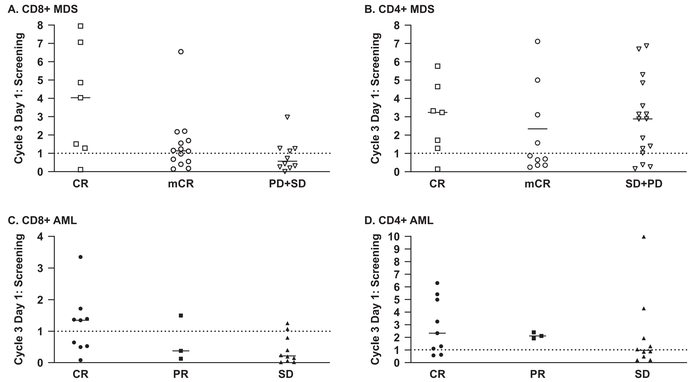
- To report the pharmacodynamic and immune effects of magrolimab + AZA on the tumor microenvironment in patients with untreated HR MDS or AML in a phase 1b trial (NCT03248479)[4,5]

Methods

- **Dosing:** Patients with untreated HR MDS or AML received magrolimab intravenously (IV) as a priming dose (1 mg/kg) on days 1 and 4, followed by a ramp-up to a 30-mg/kg weekly or biweekly maintenance dose. AZA 75 mg/m^2 was administered IV or subcutaneously on days 1 to 7 of each 28-day cycle
- Bone marrow aspirate and biopsies were obtained prior to the priming dose and at cycle 3 day 1 (C3D1)
- Stand-alone and integrated deep learning approaches using genomic, proteomic cell surface, transcriptomic, and histopathologic data were used to gain comprehensive insight into the pharmacodynamic effects of magrolimab + AZA
- **Multimodal data:** Multimodal integration learning can help to overcome the complexity and heterogenous nature of the tumor microenvironment by combining data from multiple sources: immunohistochemistry (IHC), RNAseq, and soluble proteomic parameters were measured using slow off-rate modified aptamer (SOMAmer)–based technology. Quartile normalization was used to learn the differences in the distribution of the expression-based multimodal data to make them comparable across different modalities[6]

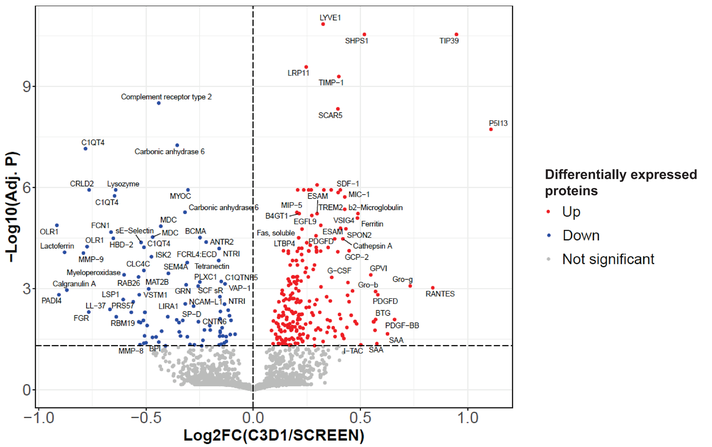
Results

Figure 1. Fold change of CD8+ and CD4+ T cells in bone marrow biopsies by immunofluorescence



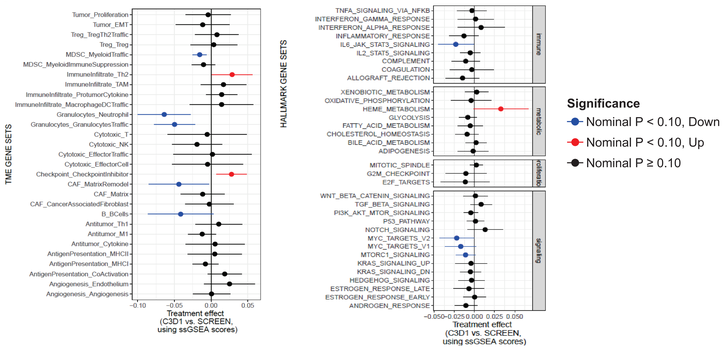
Bone marrow biopsies were taken from patients at screening and cycle 3 day 1 and evaluated for the percentage of CD8+ or CD4+ by immunofluorescence.
CR, complete response; mCR, marrow-complete response; PD, progressive disease; SD, stable disease.

Figure 2. Differential abundance in bone marrow plasma proteins suggests increased macrophage activity and decreased inflammation post treatment



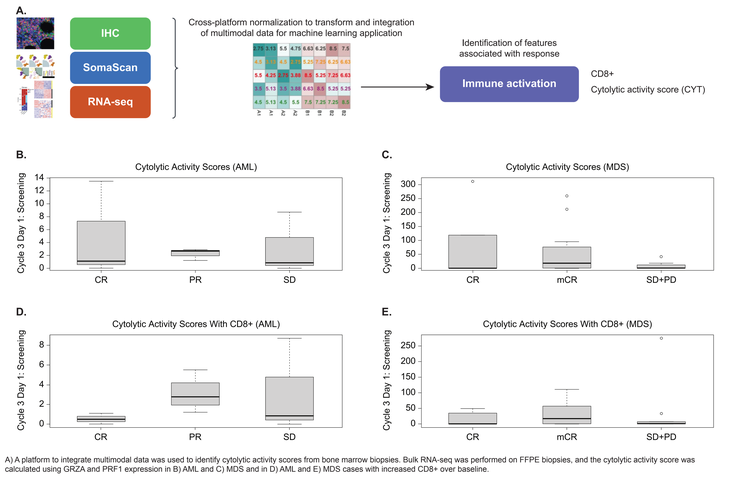
Bone marrow aspirates were collected at screening (N = 94) and cycle 3 day 1 (N = 92) from patients with AML (N = 28) and MDS (N = 66). Proteomic analysis of 7260 analytes using the SomaScan hybridization microarray platform identified 232 proteins that were increased and 94 that were decreased at cycle 3 day 1 compared to screening.

Figure 3. Trends towards increased immune infiltrate and decreased IL-6 signaling post treatment



RNA-seq was performed on MDS biopsies at screening (N = 14) and cycle 3 day 1 (N = 22) and A) TME and B) hallmark gene enrichment scores were calculated for each sample using age, sex, baseline platelet counts, and World Health Organization MDS classification as covariates. ssGSEA, single-sample Gene Set Enrichment Analysis; TME, tumor microenvironment.

Figure 4. Immune cytolytic activity profiles of patients with increased CD8+ T cells in bone marrow at cycle 3 day 1 using integrative analysis of IHC, RNAseq, and SomaScan[7,8]



A) A platform to integrate multimodal data was used to identify cytolytic activity scores from bone marrow biopsies. Bulk RNA-seq was performed on FFPE biopsies, and the cytolytic activity score was calculated using GRZA and PRF1 expression in B) AML and C) MDS and in D) AML and E) MDS cases with increased CD8+ over baseline.

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