Molecular biomarker analyses for exploring the therapeutic mechanism of lemzoparlimab and azacitidine (AZA) in newly diagnosed higher risk myelodysplastic syndrome (HR-MDS)

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Poster #3974

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INTRODUCTION

- Lemzoparlimab is a differentiated antibody targeting a distinct CD47 epitope to spare red blood cell binding while retaining potent anti-tumor activity[1].
- Without requiring a priming dose, Lemzoparlimab is well tolerated in combination with AZA and exhibited clinically meaningful efficacy in newly diagnosed HR-MDS in an ongoing phase IIa trial (NCT04202003)[2].
- Here we conducted pharmacodynamics, pharmacogenetics, and molecular biomarker analyses to investigate the potential underlying mechanism of the therapeutic effect of lemzoparlimab and AZA treatment in HR-MDS.

METHODS

Analysis of correlation of clinical efficacy and biomarker data

- 53 patients with untreated IPSS-R intermediate or high-risk MDS were treated with lemzoparlimab at 30 mg/kg IV weekly and AZA at 75 mg/m2 SC on Days 1–7 in 28-day cycle.
- Clinical efficacy was assessed by IWG 2006 criteria per investigator. Patients achieved CR, PR, HI, or marrow-CR were defined as responders and those with SD without HI or PD were defined as non-responders.
- Biomarker expression between responders and non-responders was analyzed in patients who received with ≥ 3 cycles of treatment (n=28) using *Student's t-test.*

Immunophenotyping

- Bone marrow aspirates obtained at baseline and post treatment were subjected to immune profiling, including CD47 and calreticulin (CALR) expression on CD33+ blasts, CD91 (receptor for CALR) on macrophages, and the percentages of immune cell infiltrates including CD8+ T cell, Treg and macrophages by flow cytometry.

Pharmacogenetics profiles

- Gene mutational status of 267 MDS driver genes were generated from baseline bone marrow samples by next generation sequencing (NGS) from 47 MDS patients with ≥ 3 cycles of treatment and VAF >2% as sensitivity.

Table 1. Among 28 efficacy evaluable patients as of March 31st, 2022. Clinical response between MDS patients with *TP53* mutation (n=4) and wild-type *TP53* (n=24).

Best overall response	All (28)	*TP53* Mutant (n=4)	*TP53* wild type (n=24)
ORR	23 (82.1%)	4 (100%)	19 (79%)
CR	10 (35.7%)	2 (50%)	8 (33.3%)
M-CR (W or W/O HI)	13 (46.4%)	2 (50%)	11 (45.8%)
SD	5 (17.9%)		5 (20.8%)

References:
1. Meng Z, et al. Blood. 2019; 134 (Supplement_1): 4063.
2. Xiao Z, et al. Proffered Paper presented at: ESMO Congress; 09-13 September 2022; Paris, France. Abstract 3823.

RESULTS

Increase of CALR expression, a pro-phagocytotic signal, in blast cells from responders after treatment

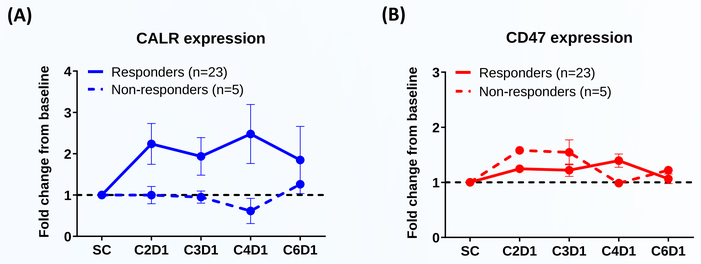

Figure 1. Changes of calreticulin and CD47 expression in blast cells after treatment in clinical responders and non-responders. (A) CALR expression increased after treatment in responders but not in non-responders. (B) CD47 expression in blasts was slightly increased after treatment while there was no difference between responders and non-responders.

Higher ratio of CD8/Treg and macrophage infiltrates in bone marrow from responders after treatment

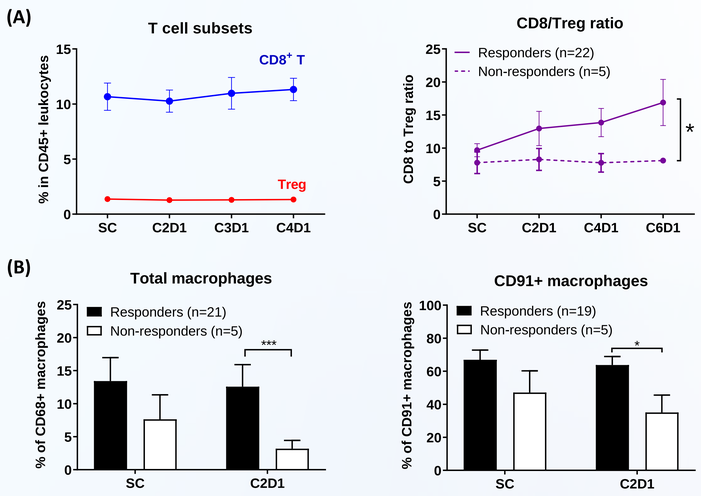

Figure 2. Higher CD8/Treg ratio and macrophage infiltrates in bone marrow was observed in responders than in non-responders after treatment. (A) The percentages of CD8+ T cells, Treg cells and its ratio in bone marrow after treatment (B) The percentages of total macrophages and CD91+ activated macrophages at baseline and cycle 2 day 1 post treatment in responders and non-responders. ***, p<0.001; *, p<0.05 by *Student's* t test.

Higher CALR increase after treatment and immune cell infiltration at baseline observed in MDS patients with *TP53* mutation

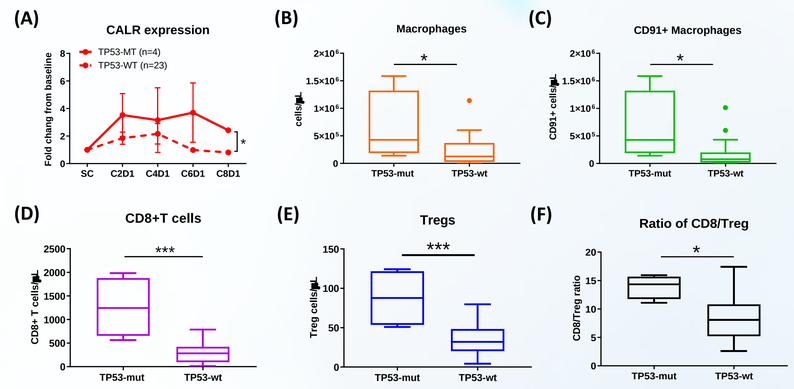

Figure 3. MDS patients with *TP53* mutations showed increase in CALR expression in blasts after treatment (A) and more immune cell infiltrates at baseline, including Mϕ, CD8+T cell, Treg and higher ratio of CD8/Treg as compared to *TP53* wild-type patients (B-D). ***, p<0.001; *, p<0.05 by *Student's* t test.

Enhanced *in vitro* phagocytosis effect of lemzoparlimab in *TP53* mutant leukemia cells harboring higher CD47 expression

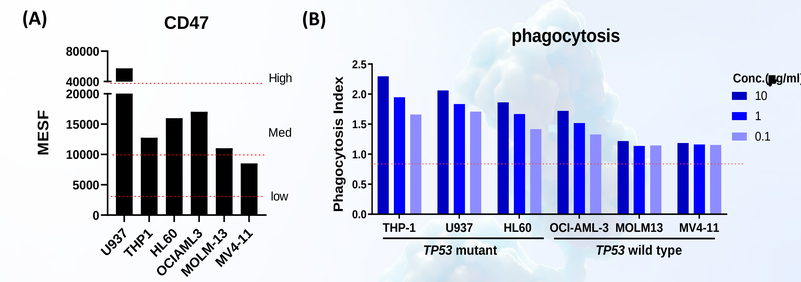

Figure 4. *In vitro* phagocytosis activity by lemzoparlimab was enhanced in *TP53* mutated cell lines which had higher CD47 expression than *TP53* wild-type cell lines.

CONCLUSION

- Increased CALR expression in blasts and higher immune infiltrates was probably associated with better clinical response to combination treatment, including patients harboring *TP53* mutations.
- Our results highlight the important role of activation of tumor derived pro-phagocytic signal and effector immune cells in clinical benefits observed with lemzoparlimab and AZA treatment in HR-MDS.