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Lemzoparlimab, a Novel Anti-CD47 Monoclonal Antibody, in Combination with Azacitidine (AZA) in Patients with Newly Diagnosed Higher Risk Myelodysplastic Syndrome (HR-MDS): Initial Clinical Results

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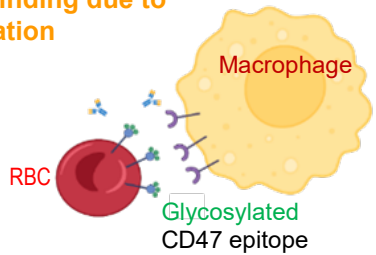
DECLARATION OF INTERESTS

I have nothing to declare.

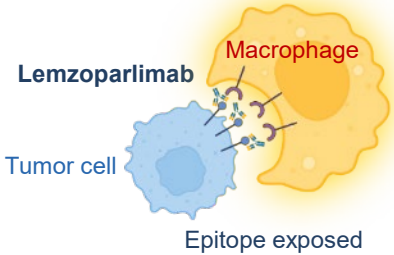
Introduction

Lemzoparlimab is a novel CD47 antibody with RBC-sparing properties

Minimal RBC binding due to CD47 glycosylation



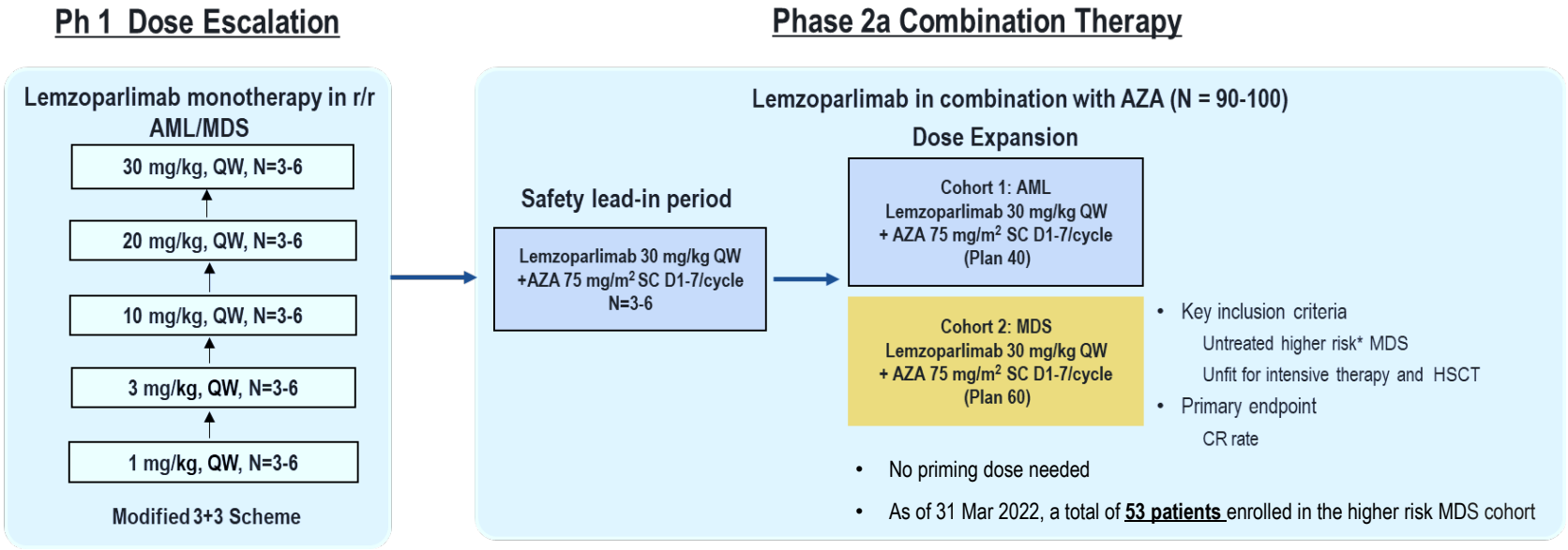
Strong tumor phagocytosis



- Blockade of CD47 and SIRPα interaction interrupts the cancer "do not eat me" signal to promote phagocytosis and is a promising investigational treatment approach[1-3]
- Lemzoparlimab is a differentiated CD47 antibody targeting a distinct CD47 epitope preferential to tumor cells due to differential CD47 glycosylation on red blood cells (RBCs)[4]
- Previous clinical reports suggest that lemzoparlimab does not induce significant anemia and does not require priming dose sequences[5-6]
- Preclinical data showed that lemzoparlimab-induced phagocytosis of leukemia cells is further enhanced in combination with azacitidine, a common treatment for patients with MDS and AML

1. Willingham SB, et al. *Proc. Natl. Acad. Sci.* 2012;109(17): 6662-6667
2. Liu J, et al. *Plos One*. 2015;10(9): e0137345
3. Sikic BI, et al. *J Clin Oncol*. 2019; 37:946-953
4. Meng Z, et al. *Blood*. 2019; 134 (Supplement_1): 4063.
5. Qi J, et al. *Blood*. 2020; 136 (Supplement 1):30-31
6. Berlin J, et al. Journal for ImmunoTherapy of Cancer 2020;8:doi: 10.1136

Study design



AML: acute myeloid leukemia; MDS: Myelodysplastic syndrome;
r/r: relapsed/refractory; QW: once a week; AZA: azacitidine; CR: complete remission; HSCT: hematopoietic stem cell transplantation

*intermediate- and high-risk by IPSS-R

Baseline characteristics

- Median age was 65 years
- 70% had ECOG PS 1
- 79.2% had a high/very high IPSS-R score
- 87% had excess blasts
- 54.7% were transfusion dependent
- 13.2% had a *TP53* mutation

	Lemzoparlimab + AZA (N=53)		Lemzoparlimab + AZA (N=53)
Age, years, median (range)	65 (40,80)	**Baseline Hematology, median (range)**	
Gender, n (%)		Absolute neutrophil count (10^9/L)	1.1 (0, 16)
Male	39 (73.6%)	Platelets (10^9/L)	43 (8, 629)
Female	14 (26.4%)	White blood cells (10^9/L)	2.8 (1, 24)
ECOG Performance Status, n (%)		Hemoglobin (g/L)	71 (46, 124)
0	11 (20.8%)	**Transfusion dependent, n (%)**	29 (54.7%)
1	37(69.8%)	**Mutations, n(%)**	
2	5(9.4%)	*RUNX1*	18 (34.0%)
Risk category by IPSS-R , n (%)		*BCOR*	16 (30.2%)
Intermediate	11 (20.8%)	*U2AF1*	11 (20.8%)
High	21 (39.6%)	*ASXL1*	8 (15.1%)
Very High	21 (39.6%)	*TET2*	8 (15.1%)
WHO MDS classification, n (%)		*TP53*	7 (13.2%)
MDS-MLD	4 (7.5%)	*SF3B1*	5 (9.4%)
MDS-EB-1	21 (39.6%)	*IDH1/2*	5 (9.4%)
MDS-EB-2	25 (47.2%)	*SRSF2*	4 (7.5%)
MDS-U	1 (1.9%)	*FLT3*	1 (1.9%)
Unclassifiable/unknown/missing	2 (3.8%)	*NPM1*	1 (1.9%)

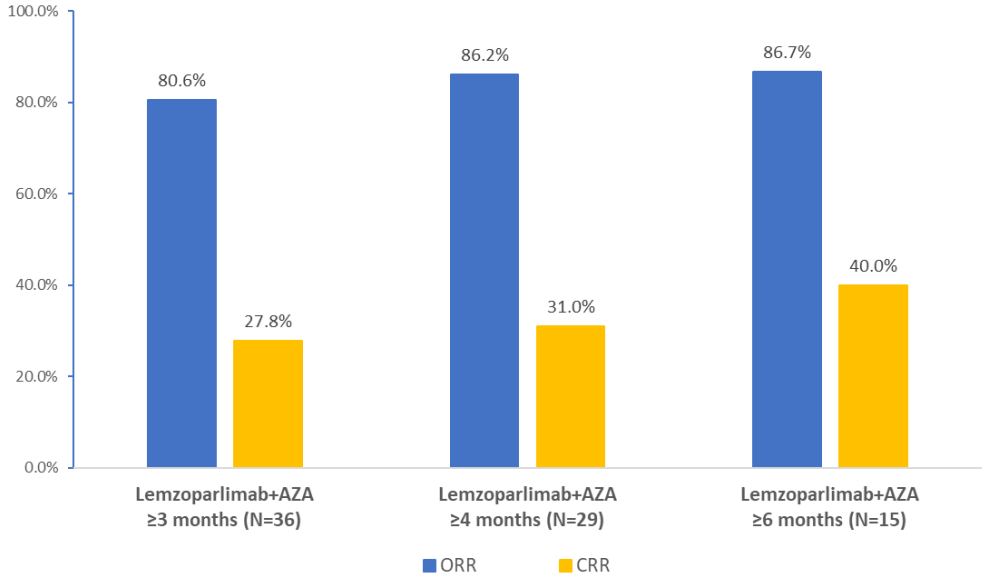
Data cutoff: date: March 31st, 2022

Lemzoparlimab combined with AZA showed promising response in higher-risk MDS patients

BOR (%)	Time Since First Dose (ES N=47)		
	≥ 3m (N=36)	≥ 4m (N=29)	≥ 6m (N=15)
ORR	80.6	86.2	86.7
CR (95% CI)	27.8 (14.2, 45.2)	31.0 (15.3, 50.8)	40.0 (16.3, 67.7)
mCR with HI	13.9	17.2	13.3
mCR	30.6	27.6	20.0
HI	8.3	10.3	13.3
SD	16.7	10.3	13.3
PD	2.8	3.4	0

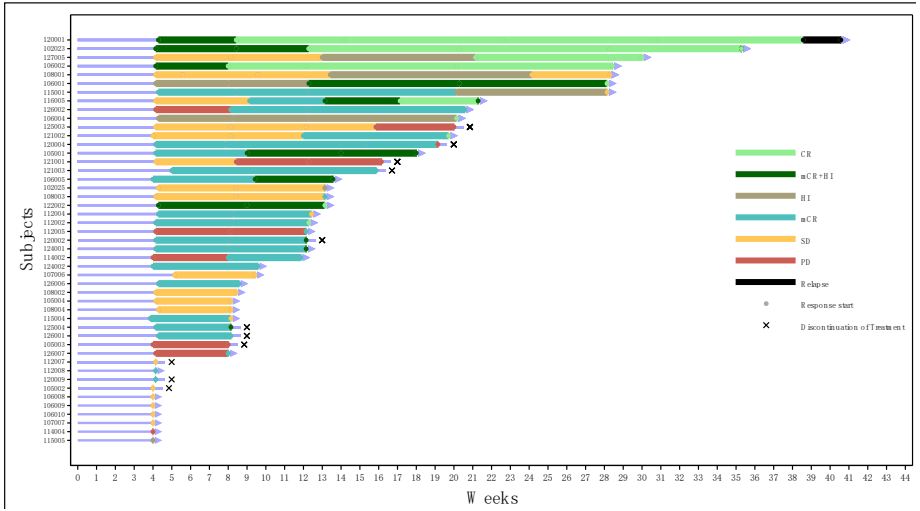
BOR: Best of response; ORR: overall response rate; mCR: marrow complete remission; HI: hematologic improvement; SD: stable disease; PD: disease progression
ES (Evaluable analysis set): Defined as subjects with at least one post-baseline tumor assessment

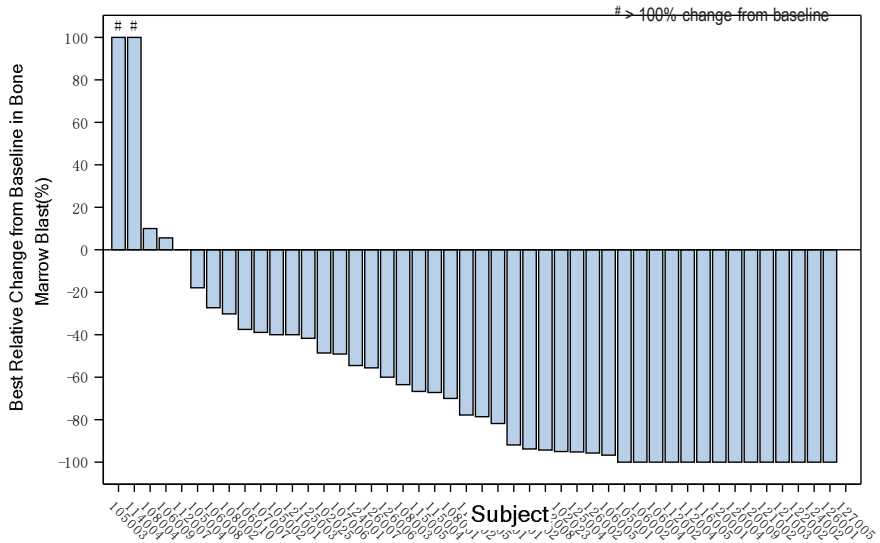
Data cutoff: date: March 31st, 2022



- CRR increased over time on therapy
- 31% and 40% CR rates achieved in subjects with time since first dose ≥ 4 months and ≥ 6 months, respectively

Durable response and change of bone marrow blasts

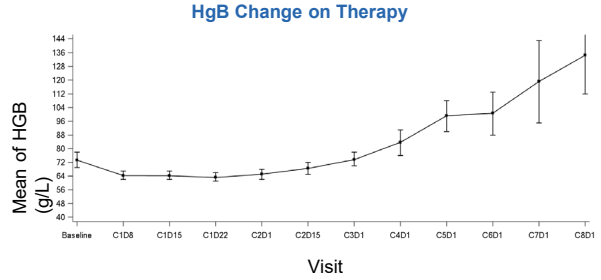


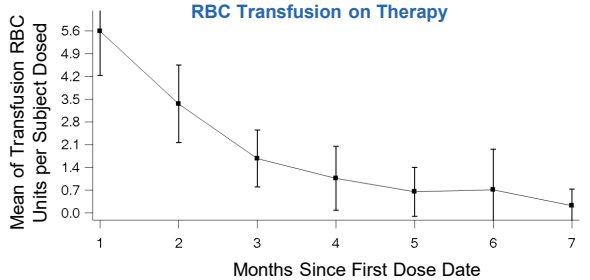


- Medium follow-up time is 3.7 months
- Medium time to response (TTR) is 1.0 month
- Medium time to CR (TTCR) is 2.7 months, though CR rate continues to improve even to 5-6 months
- As of the cutoff date Mar. 31st 2022, 27/33 responders are on treatment; the longest duration of response (DOR) is up to ~10 months
- Only 4/47 patients had blast count worsening as their best response

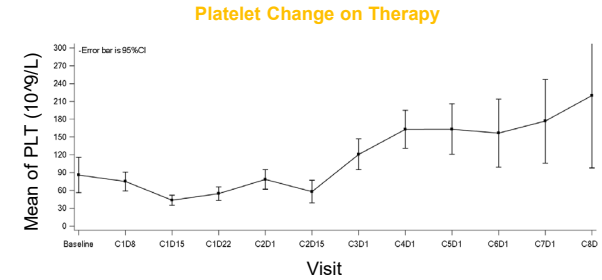
Improvement on HgB/PLT levels and transfusion

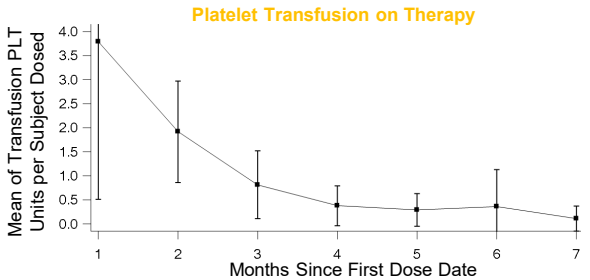
HgB





PLT

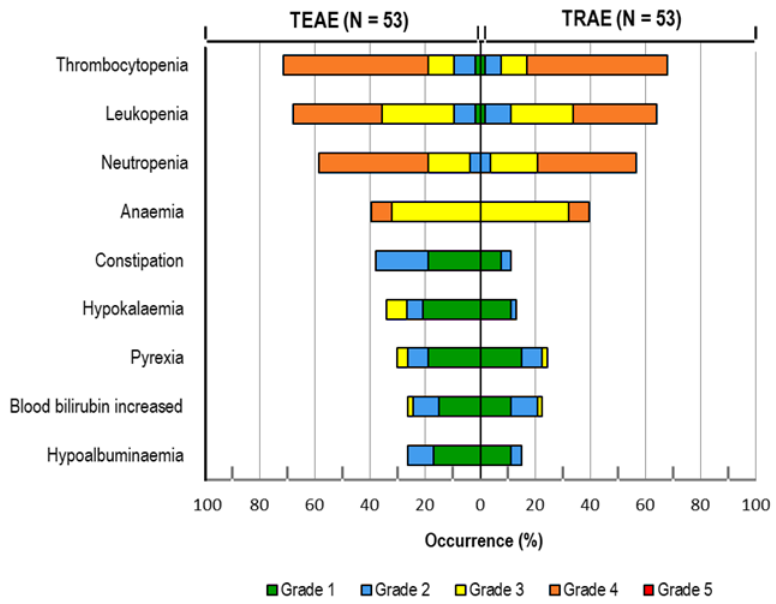




- A transient and mild decrease of hemoglobin (HgB) within 10~15% was observed in the first cycle with combination treatment and then recovered to baseline after cycle 2
- The majority of patients showed significant improvement in HgB and platelet (PLT) levels associated with a decrease in transfusion frequency and amount over time
- 9 out of 29 patients (31.0%) with transfusion dependence at baseline became transfusion independent. Among them, 8 out of 24 patients (33.3%) with RBC transfusion dependence at baseline became RBC transfusion independent

Lemzoparlimab combined with AZA is well tolerated

TEAEs in > 25% patients



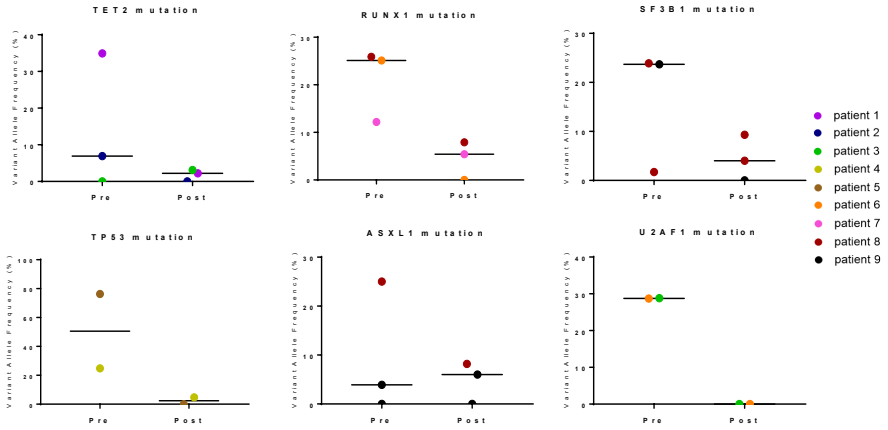
Hematologic conditions at baseline

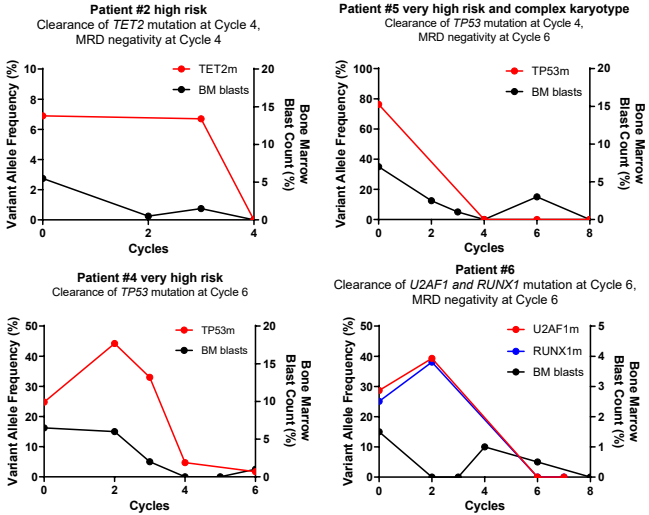
- 74% of patients had grade ≥3 anemia, 51% of patients had grade ≥3 thrombocytopenia, and 45% of patients had grade ≥3 neutropenia

Treatment-emergent adverse events

- Most commonly reported treatment-emergent adverse events (TEAEs) within all grades and in grade ≥3 were hematological events
- Grade 3/4 anemia was 39.6%
- Infusion-related reactions were reported in 5 patients (9.4%); all were grade 1/2
- TEAEs leading to treatment discontinuation occurred in 6 patients (11.3%)
- Grade 5 TEAEs occurred in 3 patients (5.7%), including pneumonia, acute coronary syndrome, and metabolic acidosis in one patient each. One event of pneumonia was reported as related to study drugs

Reduction of gene mutation burden and MRD





Representative patients with reduction of gene mutation burden and MRD

- Paired pre- and post-treatment bone marrow samples were collected for next-generation sequencing from CR patients with ≥ 3 cycles of treatment
- Mutation burdens of a panel of genes dramatically reduced, including *TP53*, *TET2*, *RUNX1*, *ASXL1*, *U2AF1,* and *SF3B1,* which were associated with poor prognosis in MDS
- 56% of CR patients achieved minimal residual disease (MRD) negativity

Conclusion

- Lemzoparlimab is a differentiated CD47 antibody binding to the distinct epitope with RBCs sparing property.
- For patients enrolled 3 months or longer before analysis, the ORR is 80.6% and for patients enrolled 6 months or earlier the ORR is 86.7%, CR rate 40%, and follow up for all patients remains ongoing.
- Lemzoparlimab does not require priming dosing and no new safety signals are observed in combination with azacitidine.
- For the subjects achieving CR after treatment, frequency of gene mutations such as *TP53*, *TET2* and *RUNX1* significantly decreased.
- A randomized phase 3 trial in higher-risk MDS is planned.

Acknowledgements

The support and time of participating patients and their families is gratefully acknowledged.