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Primary results STIMULUS-AML1: a Phase II trial of sabatolimab combined with AZA and VEN as frontline therapy for unfit AML patients

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INTRODUCTION

- Outcomes of newly diagnosed patients with acute myeloid leukemia (AML) unfit for intensive chemotherapy have improved with the use of azacitidine and venetoclax (AZA+VEN).
- However, response and survival remain poor, especially in patients with TP53 mutation.
- Sabatolimab (MGB453) is a monoclonal antibody targeting TIM-3.
- TIM-3 is an immune checkpoint expressed on normal immune and on leukemic blasts, which inhibition can result in immunoregulatory as well as antileukemic effects.
- Sabatolimab is safe, being extensively studied in higher risk myelodysplastic syndromes (MDS).

METHODS

Aim: STIMULUS-AML1 (NCT04150029) is an international, multi-center, single arm phase II trial, that evaluated the safety and efficacy of MGB453 in combination with AZA+VEN as first line treatment for unfit AML patients.

Patient population: patients ≥18 years-old with newly diagnosed AML not suitable for intensive chemotherapy.

Study design: after dose escalation, testing MGB453 400mg and 800mg, dose expansion cohort received MGB453 800mg intravenously (IV) on Day (D) 8 of every cycle. All patients received AZA 75mg/m^2/day (IV or subcutaneous) on D1–7 (or D1–5,8,9), and VEN 400mg orally daily (D1-D28). Cycle duration was 28 days, and the study treatment was given until the participant experienced disease progression or unacceptable toxicity.

Study initiation date: 17-Sep-2020 (first patient first visit (FPFV))

Early termination date: 25-Oct-2024 (last patient last visit (LPLV))

Primary endpoint:

- Complete remission (CR) rate as per investigator assessment (ELN 2017), when all patients completed at least 12 cycles of treatment or discontinued earlier.

Secondary endpoints:

- Duration of CR,
- CR/CR with incomplete hematologic recovery (CRi) rate and duration (ELN 2017),
- CR/CR with partial hematologic recovery (CRh) rate and duration (derived as per ELN 2022),
- Overall survival (OS),
- MRD negativity rate (LAIP < 0.1% by MFC-MRD assessed centrally),
- Safety (CTCAEv5.0).

RESULTS

Five patients were initially enrolled in MGB453 400mg+AZA+VEN cohort (no dose limiting toxicity observed), before a total of 85 patients received MGB453 800mg+AZA+VEN (as part of dose escalation and dose expansion cohorts). The study was conducted in 10 countries, 28 sites.

The demographics and disease history of subjects enrolled in this study were similar with other reported AML studies (Table 1).

In MGB453 800mg+AZA+VEN cohort, median follow up from enrollment to data cut-off (LPLV) was 31 months (28 - 43 months). Median duration of study treatment was 5.9 months (0.3 - 37.6 months), and 25.9% of patients received treatment for 12 months or more. Disease relapse (21.2%), progression (18.8%), and adverse events (AEs) (12.9%) were main reasons for treatment discontinuation.

Table 1. Demographics and disease history

	MGB453 800mg+AZA+VEN (N=85)	
Age (years) Median	77.0	
Male sex -n (%)	47 (55.3)	
De novo disease status -n (%)	75 (88.2)	
Cytogenetic abnormality -n (%)	53 (62.4)	
Risk classification -n (%)	ELN 2017[1]	ELN 2022[2]
Favorable	14 (16.5)	12 (14.1)
Intermediate	19 (22.4)	18 (21.2)
Adverse	51 (60.0)	54 (63.5)
Missing	1 (1.2)	1 (1.2)

Primary and Secondary Endpoints

The CR rate observed in MGB453 800mg+AZA+VEN cohort was 47.1% (Table 2). The study did not meet the primary objective, defined as observed CR rate >61% and lower bound of 95% CI >50%.

Table 2. Best Overall Response (N=85)

	ELN 2017 Inv. assessment n (%) (95% CI)	ELN 2022 Derivation n (%) (95% CI)
CR	40 (47.1) (36.1,58.2)	34 (40.0) (29.5,51.2)
CRi	19 (22.4)	9 (10.6)
CRh	-	9 (10.6)
MLFS	0	4 (4.7)
PR	5 (5.9)	7 (8.2)
SD/No Response/PD/Unk	21 (24.7)	22 (25.9)
CR+CRi	59 (69.4) (58.5, 79.0)	-
CR+CRh	-	43(50.6) (39.5, 61.6)

Inv: investigator; CR: Complete Remission; CRi: CR with Incomplete Hematologic Recovery; CRh: CR with Partial Hematologic Recovery; MLFS: Morphologic Leukemia Free State; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease; Unk: unknown

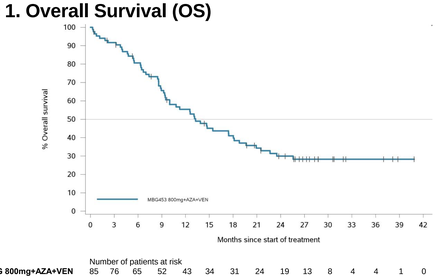
Duration of response

The median duration of CR for 40 patients with CR was 10.3 months (95% CI: 6.3, NE). The median duration of CR/CRi for 59 patients with CR/CRi was 8.5 months (95% CI: 6.0, 13.7). The median duration of CR/CRh for 43 patients with CR/CRh was 12.5 months (95% CI: 6.8, 14.8).

Overall Survival (OS)

Median OS was 13.3 months (95% CI: 9.5, 18.1) in the MBG453 800mg+AZA+VEN cohort (Figure 1). An estimated 55.4% and 29.9% of patients were alive at 12 and 24 months, respectively.

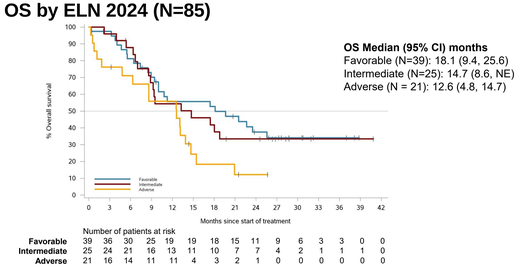
Figure 1. Overall Survival (OS)



OS ELN 2024[3]

Median OS in patients with TP53 mutations (TP53^{mut}) treated with MBG453 800mg+AZA+VEN was 12.6 months (95% CI: 4.8, 14.7) (Figure 2).

Figure 2. OS by ELN 2024 (N=85)



OS Median (95% CI) months
Favorable (N=39): 18.1 (9.4, 25.6)
Intermediate (N=25): 14.7 (8.6, NE)
Adverse (N = 21): 12.6 (4.8, 14.7)

Table 3. ELN 2024 Risk Group (N=85)

	CR N (%) (95% CI)	ORR* N (%) (95% CI)
Favorable FLT3-ITD^{neg} and NRAS^{wt} and KRAS^{wt} and TP53^{wt} (N=39)	19 (48.7%) (32.4, 65.2)	29 (74.4%) (57.9,87.0)
Intermediate FLT3-ITD^{pos} and/or NRAS^{mut} and/or KRAS^{mut} and TP53^{wt} (N=25)	10 (40.0%) (21.1, 61.3)	19 (76.0%) (54.9,90.6)
Adverse TP53^{mut} (N = 21)	11 (52.4%) (29.8, 74.3)	16 (76.2%) (52.8,91.8)

neg: negative; pos: positive; wt: wild-type; mut: mutant; ORR: CR+CRi+PR

TP53 mutation

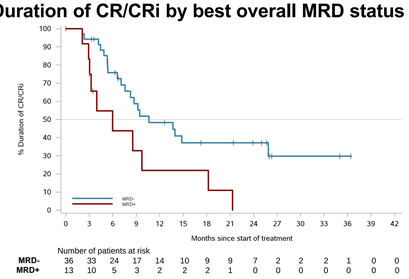
Out of 21 patients with TP53 mutant, 5 had TP53 variant allele frequency (VAF) <10%, 7 had VAF 10-50%, and 9 had VAF >50%.

Patients with VAF >=10% (N=16) had a median OS of 12.6 (4.8, 13.9) months vs <10% (N=5) 20.9 (1.1, NE) months.

MRD Negativity

Out of 59 patients with CR/CRi, 49 were evaluable for MRD, among which 36 (73.5%) achieved MRD negativity. Most patients achieved MRD negativity within 4 cycles of treatment, 32/49 (65.3%) The median duration of CR/CRi was longer (10.6months; 95% CI: 7.1, 25.9) for patients with MRD negative, than patients with MRD positive (6.0 months; 95%CI: 2.9, 18.2) (Figure 3).

Figure 3. Duration of CR/CRi by best overall MRD status

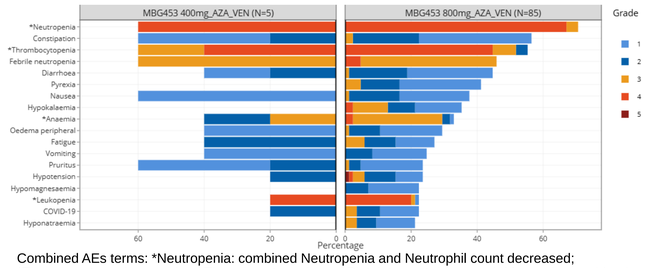


Safety

In the MGB453 800mg+AZA+VEN cohort (N=85), the most common combined AEs terms were neutropenia (70.6%), constipation (56.5%), thrombocytopenia (55.3%), and febrile neutropenia (45.9%) (Figure 4).

Out of 90 patients treated, 12 (13.3%) patients died on treatment (anytime during study treatment or within 30 days after end of treatment), mostly due to study indication (5.6%) or due to infections and infestations (3.3%).

Figure 4. Percentage of patients with AE rate >20% (MBG453 800mg)



Combined AEs terms: *Neutropenia: combined Neutropenia and Neutrophil count decreased; *Thrombocytopenia: combined Thrombocytopenia and Platelet count decreased; *Anaemia: combined Anaemia and Haemoglobin decrease; *Leukopenia: combined Leukopenia and White blood cell count decreased.

KEY FINDINGS & CONCLUSIONS

- MGB453 given in combination with AZA+VEN is safe.
- Despite not meeting the primary endpoint, the CR rate is higher than in the historical data[4].
- Patients with TP53 mutations might benefit from the addition of MGB453 to AZA+VEN, having higher CR rates and longer OS than in recently published reports[3,5]. Further investigations with increased patient numbers are needed.

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https://tinyurl.com/ZeidanPS1483

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References

1. Döhner et al , Blood, 2017 **2.** Döhner et al , Blood, 2022 **3.** Döhner et al., Blood, 2024
4. DiNardo et al., NEJM, 2021. **5.** Zeidner et al., JCO, 2025

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