AML 484

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First Results of a Phase II Study (STIMULUS-AML1) Investigating Sabatolimab + Azacitidine + Venetoclax in Patients With Newly Diagnosed Acute Myeloid Leukemia

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CONCLUSIONS

- Overall safety and tolerability of sabatolimab + AZA + VEN were comparable at two dose levels (400 and 800 mg) of sabatolimab
- Only one DLT (Troponin T elevation suggesting asymptomatic myocarditis) was observed
- No dose reduction of sabatolimab was observed
- Safety and tolerability were overall comparable to the known and previously reported safety profile of VEN + AZA doublet therapy
- Sabatolimab + AZA + VEN demonstrated preliminary clinical responses in patients with ND-AML
- These findings supported initiation of the expansion cohort of STIMULUS-AML1 at a sabatolimab 800 mg dose. Accrual in expansion cohort is ongoing

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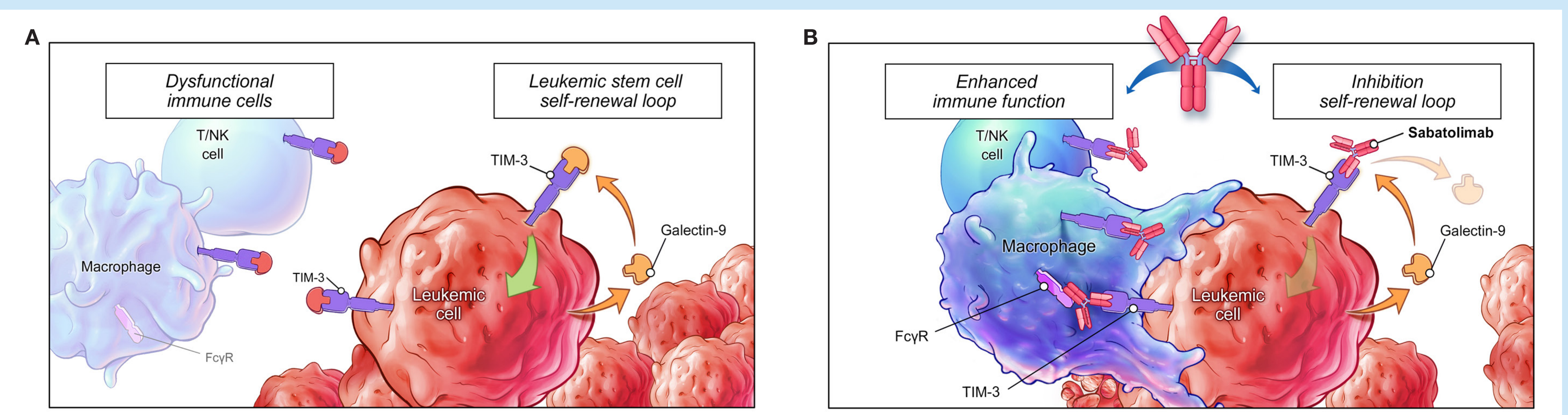
INTRODUCTION

- Treatment options for patients with newly diagnosed (ND) acute myeloid leukemia (AML) who cannot tolerate standard therapy are limited[1]
- The BCL-2 inhibitor venetoclax (VEN) in combination with the hypomethylating agent (HMA), azacitidine (AZA), has improved outcomes for patients with ND-AML who are unfit for intensive chemotherapy (IC); however, responses are often transient[2]
- TIM-3 is an immuno-myeloid regulator as it is expressed on both immune cells and leukemic stem cells in myeloid malignancies. It represents a novel target in myeloid malignancies (AML and myelodysplastic syndromes [MDS] in particular) (**Figure 1A**)[3-8]
- Sabatolimab, a novel immunotherapy targeting TIM-3, is the first compound with immuno-myeloid activity. It therefore has a potential dual mechanism to combat AML and MDS by (**Figure 1B**)[3,9-10]
  - Reactivating the immune system, boosting its ability to eliminate leukemic stem cells and blasts
  - Directly targeting TIM-3+ leukemic stem cell self-renewal and suppressing growth of cancer cells
- In a Phase Ib trial, sabatolimab + HMA showed encouraging and durable response rates in patients with higher-risk MDS and AML[3,10]
  - ND-AML, overall response rate (ORR): 42.5%; median duration of response (DOR): 12.6 months (95% CI, 5.2-18.0)
  - Very-high/high-risk MDS: ORR, 56.9%; median DOR, 17.1 months (95% CI, 6.7-not estimable [NE])
- Treatment with sabatolimab + VEN + AZA may induce different pathways of cancer cell elimination
- This poster presents preliminary findings from the completed dose-escalation part (Study Part I) of STIMULUS-AML1 (NCT04150029), a Phase II, single-arm study of sabatolimab + AZA + VEN in adult patients with AML

METHODS

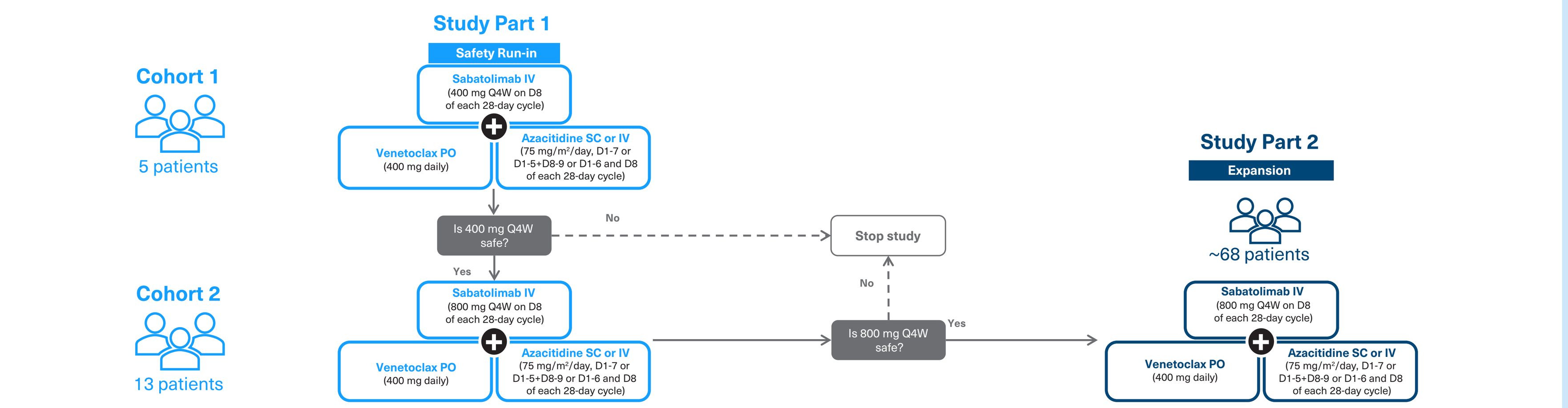
- Study Part I was a dose-escalation (safety run-in). Patients received either 400 mg (Cohort 1) or 800 mg (Cohort 2) sabatolimab every 4 weeks (Q4W) plus 400 mg VEN once a day every day, plus 75 mg/m^2 AZA on Days (D)1-7, or D1-5+D8-9, or D1-6+D8 of each 28-day cycle (**Figure 2**)[11]
- The 800 mg Q4W dose of sabatolimab was deemed safe, and the trial progressed to the expansion part where patients are receiving 800 mg sabatolimab IV Q4W on D8 plus 400 mg VEN once a day every day, plus 75 mg/m^2 AZA on D1-7, or D1-5+D8-9, or D1-6+D8 of each 28-day cycle (**Figure 2**)[11]
- This presentation reports findings from the completed dose escalation (Study Part I)
- Main eligibility criteria for STIMULUS-AML1:
  - Adult patients with ND AML (based on WHO 2016 classification[12]) not suited for intensive chemotherapy with no planned HSCT at the time of screening/enrollment
  - Patients with Eastern Cooperative Oncology Group (ECOG) performance score 0 to 3
  - Patients with previous treatment with checkpoint inhibitors, VEN, HMAs, or TIM-3–directed therapy were not eligible
  - Patients with previous treatment for AML, MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera, except with hydroxyurea, growth factors, and ruxolitinib, were not eligible
- The primary objectives were to determine the incidence of dose-limiting toxicities between Cycle 1 Day 8 and end of Cycle 2 (patients treated during the safety run-in only) and to assess the complete remission (CR) rate (patients treated during safety run-in Cohort 2 and expansion)[10]
  - The secondary objectives were to test efficacy, safety/tolerability, immunogenicity, and pharmacokinetics (PK)
  - Safety parameters included incidence and severity of adverse events (AEs) and serious AEs (SAEs), changes in laboratory values and vital signs, and incidence of notable electrocardiogram abnormalities

Figure 1. Sabatolimab Targets TIM-3 Expressed on Immune and Leukemic Cells



FcγR, Fc gamma receptor; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

Figure 2. Study Design



RESULTS

Patient Disposition and Characteristics

- As of the Sep 6, 2021, data cutoff, 18 patients have been treated in part 1 of the study with sabatolimab + AZA + VEN (Cohort 1, n=5; Cohort 2, n=13)
- Demographics and baseline characteristics were generally well balanced between the 2 dose levels (**Table 1**)
  - The median age was 77.0 years (range, 70-88 years)
  - Most patients had an ECOG PS of 0-2 (n=17, 94.4%; **Table 1**)
- Treatment was ongoing for 9 (50%) patients (Cohort 1, n=1; Cohort 2, n=8; **Table 2**)
  - Reasons for study treatment discontinuation included AEs (n=3), progressive disease (n=3), planned stem cell transplant (n=2), and physician decision (n=1; **Table 2**)

Table 1. Baseline Patient and Disease Characteristics

Characteristic	Cohort 1 400 mg sabatolimab + AZA + VEN (n=5)	Cohort 2 800 mg sabatolimab + AZA + VEN (n=13)	All Patients (N=18)
Median age, years (range)	74.0 (73-85)	78.0 (70-88)	77.0 (70-88)
Sex (male), n (%)	4 (80.0)	9 (69.2)	13 (72.2)
Race, n (%)			
Caucasian	5 (100.0)	12 (92.3)	17 (94.4)
Unknown	0	1 (7.7)	1 (5.6)
Ethnicity, n (%)			
Non-Hispanic or Latino	5 (100)	13 (100.0)	18 (100.0)
Median Weight, kg (range)	71.1 (66-83)	75.0 (55-101)	73.1 (55-101)
ECOG PS, n (%)			
0	1 (20.0)	4 (30.8)	5 (27.8)
1	2 (40.0)	5 (38.5)	7 (38.9)
2	2 (40.0)	3 (23.1)	5 (27.8)
3	0	1 (7.7)	1 (5.6)

AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; kg, kilograms; VEN, venetoclax.

Table 2. Patient Disposition

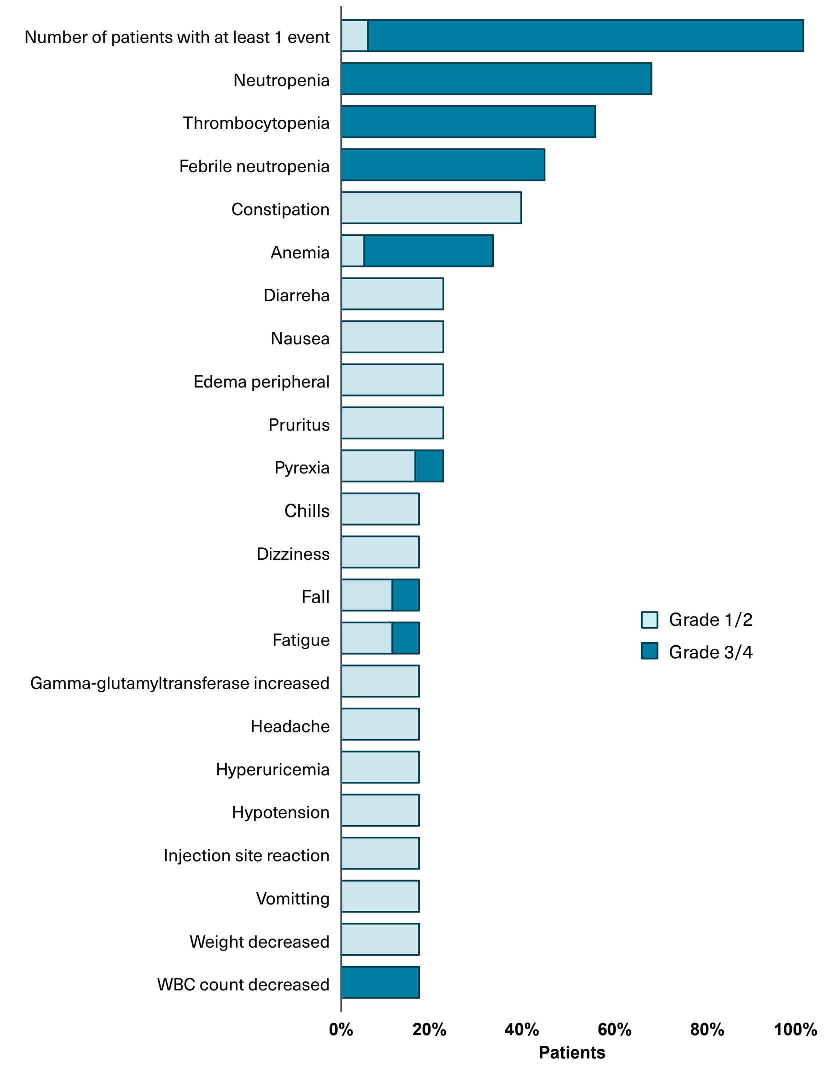
Characteristic	Cohort 1 400 mg sabatolimab + AZA + VEN (n=5)	Cohort 2 800 mg sabatolimab + AZA + VEN (n=13)	All Patients (N=18)
Treatment ongoing,[a] n (%)	1 (20.0)	8 (61.6)	9 (50.0)
Discontinued from treatment, n (%)	4 (80.0)	5 (38.5)	9 (50.0)
Reason for discontinuation, n (%)			
Adverse event	1 (20.0)	2 (15.4)	3 (16.7)
HSCT Planned	1 (20.0)	1 (7.7)	2 (11.1)
Physician decision	0	1 (7.7)	1 (5.6)
Progressive disease	2 (40.0)	1 (7.7)	3 (16.7)

[a]Ongoing at time of data cutoff on September 6, 2021.
HSCT, hematopoietic stem cell transplant.

Safety

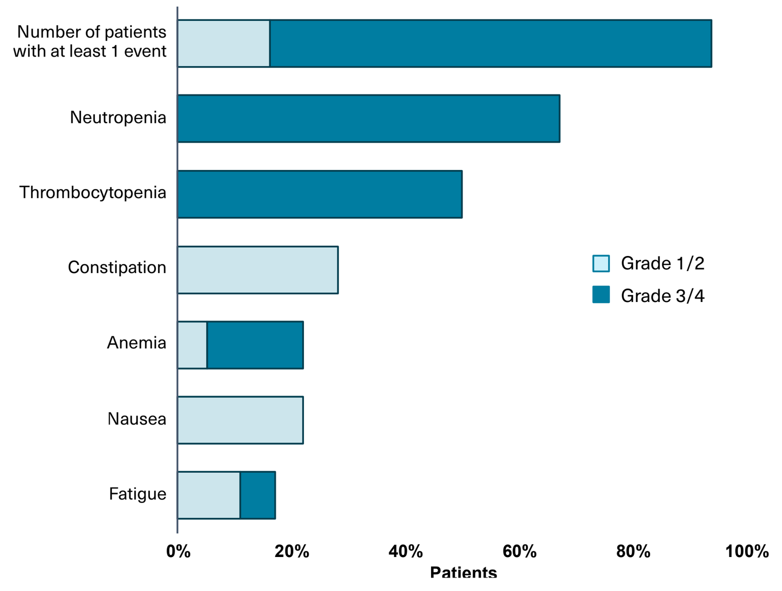
- Consistent with AEs often observed during AZA + VEN therapy[2]
- The 5 most common AEs regardless of relationship to study treatment were neutropenia (all grades: 67%; grade ≥3: 67%), thrombocytopenia (56%; 56%), febrile neutropenia (44%; 44%), constipation (39%; 0%), and anemia (33%; 28%; **Figure 3**)
  - The 5 most common treatment-related AEs were neutropenia (67%; 67%), thrombocytopenia (50%; 50%), constipation (28%; 0%), anemia (22%; 17%), and nausea (22%; 0%)
- Serious AEs were reported in 14 (78%) patients; the most common (reported in >1 patient) was febrile neutropenia (44%)

Figure 3. AEs regardless of study treatment in at least 15% of patients*



*AEs present in at least 10% of patients included: abdominal pain, alanine aminotransferase increased, aspartate aminotransferase increased, back pain, blood alkaline phosphatase increased, blood creatine increased, cellulitis, decreased appetite, erythema, hypokalaemia, hypomagnesemia, hyponatremia, hypoxia, injection site erythema, lymphocyte count decreased, night sweats, paraesthesia, pneumonia, rash maculo-papular, and tendon disorder.
AE, adverse event; WBC, white blood cell.

Figure 4. AEs suspected to be treatment-related in at least 15% of patients*



*AEs present in at least 10% of patients included: diarrhea, dizziness, febrile neutropenia, injection site erythema, vomiting, and white blood cell count decreased.
AE, adverse event.

- Three patients discontinued due to treatment-related AEs (platelet count decreased [n=2], troponin level increased/asymptomatic myocarditis [n=1]; **Table 3**)
- AEs led to AZA and VEN discontinuation in 2 patients each. All were treatment-related (**Table 3**)
- Six patients had dose interruption of sabatolimab, all due to AE, and all in Cohort 2 (**Table 4**)
- No sabatolimab dose reduction was observed
- Fourteen patients had dose interruption of VEN due to AEs (**Table 4**)
- Five patients had dose reduction of VEN (none due to AEs)

Table 3. AEs leading to treatment discontinuation

Characteristic	Cohort 1 400 mg sabatolimab + AZA + VEN (n=5)		Cohort 2 800 mg sabatolimab + AZA + VEN (n=13)		All Patients (N=18)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
AEs leading to sabatolimab discontinuation, n (%)	1 (20.0)	1 (20.0)	2 (15.4)	1 (7.7)	3 (16.7)	2 (11.1)
Treatment-related	1 (20.0)	1 (20.0)	2 (15.4)	1 (7.7)	3 (16.7)	2 (11.1)
AEs leading to AZA discontinuation, n (%)	1 (20.0)	1 (20.0)	1 (7.7)	1 (7.7)	2 (11.1)	2 (11.1)
Treatment-related	1 (20.0)	1 (20.0)	1 (7.7)	1 (7.7)	2 (11.1)	2 (11.1)
AEs related to VEN discontinuation, n (%)	1 (20.0)	1 (20.0)	1 (7.7)	1 (7.7)	2 (11.1)	2 (11.1)
Treatment-related	1 (20.0)	1 (20.0)	1 (7.7)	1 (7.7)	2 (11.1)	2 (11.1)

AE, adverse event; AZA, azacitidine; VEN, venetoclax.

Table 4. Dose adjustments

Category	Cohort 1 400 mg sabatolimab + AZA + VEN (n=5)	Cohort 2 800 mg sabatolimab + AZA + VEN (n=13)	All Patients (N=18)
Patients with at least one dose interruption of sabatolimab by reason, n (%)	0	6 (46.2)	6 (33.3)
Adverse event	0	6 (46.2)	6 (33.3)
Patients with at least one dose interruption of AZA by reason, n (%)	2 (40.0)	8 (61.5)	10 (55.6)
Adverse event	1 (20.0)	7 (53.8)	8 (44.4)
Technical problems	1 (20.0)	1 (7.7)	2 (11.1)
Patients with at least one dose interruption of VEN by reason, n (%)	4 (80.0)	10 (76.9)	14 (77.8)
Adverse event	4 (80.0)	10 (76.9)	14 (77.8)
As per protocol	0	1 (7.7)	1 (5.6)
Concomitant medication affecting drug exposure	1 (20.0)	0	1 (5.6)
Dosing error	2 (40.0)	1 (7.7)	3 (16.7)
Patients with at least one dose reduction of sabatolimab, n %)	0	0	0
Patients with at least one dose reduction of AZA by reason, n (%)	1 (20.0)	1 (7.7)	2 (11.1)
Adverse event	0	1 (7.7)	1 (5.6)
Physician decision	1 (20.0)	0	1 (5.6)
Patients with at least one dose reduction of VEN by reason, n (%)	1 (20.0)	4 (30.8)	5 (27.8)
Dosing error	0	1 (7.7)	1 (5.6)
Physician decision	1 (20.0)	3 (23.1)	4 (22.2)
Patient decision	0	1 (7.7)	1 (5.6)

AE, adverse event; AZA, azacitidine; VEN, venetoclax.

- Only 1 patient experienced DLT (elevated grade 3 troponin T diagnosed as asymptomatic myocarditis; Cohort 2). Details about this DLT are as follows:
  - The patient with this DLT was discontinued from sabatolimab at the end of Cycle 1
  - The DLT was reported 2 weeks after administration of sabatolimab. Troponin T levels continued to increase for the following 2 weeks after treatment discontinuation
  - A cardiac MRI performed on Study Day 65 showed findings consistent with healing myocarditis. According to the cardiologist, imaging findings resembled those noted following treatment with immune checkpoint inhibitors
  - Elevated troponin T levels decreased without further intervention and the patient remained totally asymptomatic

Efficacy

- The disease response assessment was determined according to ELN 2017/IWG AML 2003 criteria[13]
- In Cohort 1, 4 patients were in clinical remission including CR (n=1) or CR with incomplete hematologic recovery (CRi; n=3) and stable disease was observed in 1 patient
- In Cohort 2, among 13 patients, 9 patients were responding including CR (n=3), CRi (n=5), and morphological leukemia-free state (n=1). Stable disease was observed in 2 patients and disease progression reported in 2 patients
- The efficacy follow-up was limited for efficacy evaluation in Cohort 2, as all patients got solely one disease response assessment at the time of the data cut-off

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Disclosures

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