Selinexor and Venetoclax Combination in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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Introduction

- Our preclinical studies showed synergistic antileukemia activity of selinexor (**SEL**), a XPO1-inhibitor and venetoclax (**VEN**) in combination (**SEL-VEN**), with potential to overcome VEN resistance by reducing MCL1.
- Here we report data from patients with relapsed or refractory (**r/r**) acute myeloid leukemia (**AML**) treated with **SEL-VEN** in a phase Ib study for high-risk hematologic malignancies (NCT03955783).

Aim

- To assess the safety and preliminary efficacy of SEL-VEN in patients with r/r AML

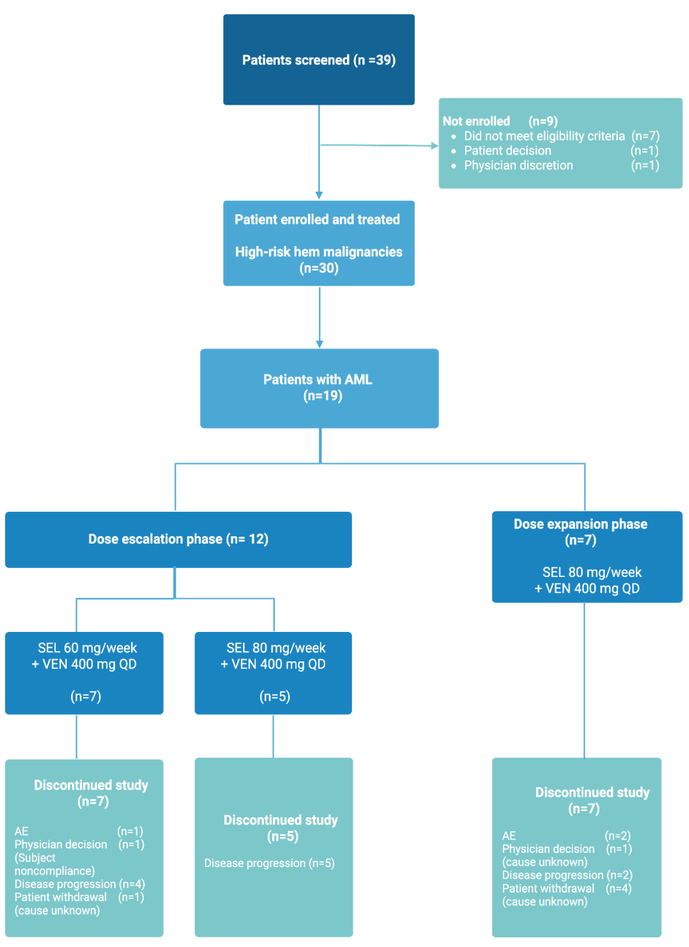
Objectives

- Primary objectives:
  - Dose escalation phase: To assess **safety** and determine **RP2D** for SEL-VEN
  - Dose expansion phase: To assess overall response rate (**ORR**)
- Secondary objectives: Event free survival (**EFS**), overall survival (**OS**), and biomarkers (baseline molecular assessment and ex-vivo sensitivity results) for response

Methods

- Investigator-initiated, multicenter, **phase Ib** study
- Adults with r/r AML, adequate organ function and performance status were eligible
- After dose escalation, **SEL 80 mg po weekly** plus VEN (po daily continuous) was deemed RP2D
- ORR: complete remission (CR)+ CR with incomplete count recovery (CRi)+ CR with partial hematologic recovery (CRh)+ partial remission (PR)+ morphologic leukemia free state (MLFS)
- A predictive analytic (PA) to assess SEL-VEN sensitivity

Figure 1. Patient Enrollment and Disposition



Results

Table 1. Baseline Characteristics of Study Population

Age (years), median (range)		67.2 (21.1, 83.8)
Sex, no (%)	Male	10 (53%)
	Female	9 (47%)
Race, no (%)	White	18 (95%)
	Black	1 (5%)
Ethnicity, no (%)	Non-Hispanic	19 (100%)
ECOG-PS, no (%)	0	5 (26%)
	1	14 (74%)
Prior lines of therapy, no (%)*	1	2 (15%)
	2	3 (23%)
	≥ 3	8 (62%)
Prior VEN exposure, no (%)		8 (42%)
Prior Allo-HSCT, no (%)		8 (42%)
Cytogenetic risk category (ELN 2022), no (%)*	Favorable	1 (6%)
	Intermediate	11 (61%)
	Adverse	6 (33%)
Baseline mutations, no (%)*	*NPM1*	3 (23%)
	IDH2	3 (23%)
	U2AF1	3 (23%)
	DNMT3A	2 (15%)
	NRAS	2 (15%)
	TP53	2 (15%)
	ASXL1	1 (8%)
	BCOR	1 (8%)
	SRSF2	1 (8%)
	RAD21	1 (8%)
	FLT3-ITD	1 (8%)
	WT1	1 (8%)

Results

Table 2. Common Treatment Emergent Adverse Events (AE)

Adverse Events	Dose Escalation (n=12)				Dose Expansion (n=6)* SEL 80 mg/wk		All Patients (n=18)*	
	SEL 60 mg/wk (n=7)		SEL 80 mg/wk (n=5)					
	All	Grade 3-5	All	Grade 3-5	All	Grade 3-5	All	Grade 3-5
Any AEs	7 (100%)	7 (100%)	5 (100%)	4 (80%)	6 (100%)	6 (100%)	18 (100%)	17 (94%)
Hematologic AEs								
Platelet count decreased	2 (29%)	2 (29%)	2 (40%)	2 (40%)	1 (17%)	1 (17%)	5 (28%)	5 (28%)
Anemia	3 (43%)	3 (43%)	2 (40%)	1 (20%)	3 (50%)	3 (50%)	8 (44%)	7 (39%)
Neutrophil count decreased	2 (29%)	2 (29%)	2 (40%)	2 (40%)	2 (33%)	2 (3%)	6 (33%)	6 (33%)
White blood cell decreased	1 (14%)	0	1 (20%)	21 (20%)	2 (33%)	2 (33%)	3 (17%)	1 (6%)
Febrile neutropenia	3 (43%)	3 (43%)	0	0	1 (17%)	1 (17%)	5 (28%)	5 (28%)
Non-Hematologic AEs								
Vomiting	4 (57%)	0	3 (60%)	1 (20%)	2 (33%)	0	9 (50%)	1 (6%)
Nausea	3 (43%)	0	4 (80%)	1 (20%)	1 (17%)	0	8 (44%)	1 (6%)
Anorexia	4 (57%)	1 (14%)	2 (40%)	0	2 (33%)	0	8 (44%)	1 (6%)
Diarrhea	4 (57%)	0	1 (20%)	0	2 (33%)	0	7 (39%)	0
Fatigue	0	0	2 (40%)	1 (20%)	4 (67%)	0	6 (33%)	1 (6%)
Dyspnea	2 (29%)	1 (14%)	2 (40%)	1 (20%)	2 (33%)	0	6 (33%)	2 (11%)
Weight loss	1 (14%)	0	1 (20%)	0	2 (33%)	0	4 (22%)	0
Limb edema	3 (43%)	0	2 (40%)	0	0	0	5 (28%)	0
Dizziness	2 (29%)	0	2 (40%)	0	1 (17%)	0	5 (28%)	0
Cough	1 (14%)	0	3 (60%)	0	0	0	4 (22%)	0
Epistaxis	2 (29%)	1 (14%)	0	0	2 (33%)	1 (17%)	4 (22%)	2 (11%)
Generalized muscle weakness	1 (14%)	0	1 (20%)	1 (20%)	2 (33%)	0	4 (22%)	1 (6%)
Hyponatremia	0	0	1 (20%)	0	3 (50%)	1 (17%)	4 (22%)	1 (6%)
Dysgeusia	1 (14%)	0	2 (40%)	0	1 (17%)	0	4 (22%)	0
Sepsis	0	0	1 (20%)	1 (20%)	1 (17%)	1 (17%)	2 (11%)	2 (11%)
Rash	1 (14%)	1 (14%)	1 (20%)	1 (20%)	0	0	2 (11%)	2 (11%)
Disease progression	1 (14%)	1 (14%)	1 (20%)	1 (20%)	0	0	2 (11%)	2 (11%)

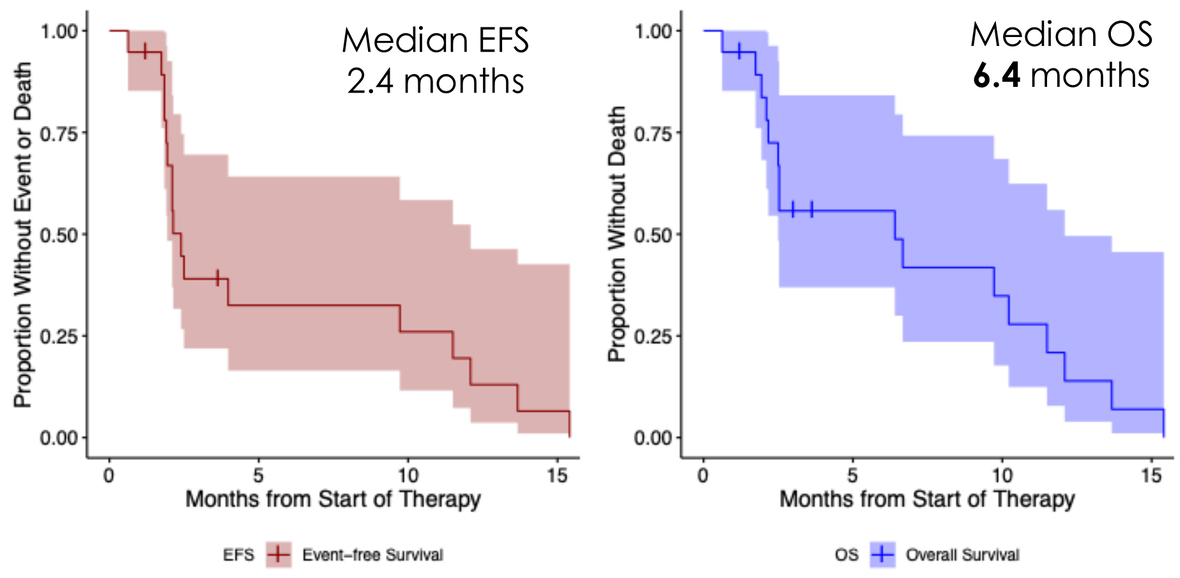
* One patient did not have adverse event information

G5 TEAEs in 3 patients (fever, respiratory failure, and intracranial hemorrhage), all 3 instances deemed related to AML

Table 3. Treatment Response with SEL-VEN

		SEL Dose Cohorts		Overall (n=19)
		60 mg/wk (n=7)	80 mg/wk (n=12)	
Number of treatment cycles, median (range)		2 (1-3)	3 (2-8)	3 (1-8)
Duration of treatment (months), median (range)		1.6 (0.3- 2.5)	2.3 (1.2-8.1)	1.9 (0.3-8.1)
Best Response (IWG 2003)	ORR	1 (14%)	3 (25%)	**4 (21%)**
	Cytogenetic CR	0	2 (17%)	2 (11%)
	PR	1 (14%)	0	1 (5%)
	MLFS	0	1 (8%)	1 (5%)
	Not evaluable	3 (43%)	3 (25%)	6 (32%)
Best Response (ELN 2022)	ORR	1 (14%)	3 (25%)	**4 (21%)**
	CR	0	2 (17%)	2 (11%)
	PR	1 (14%)	0	1(5%)
	MLFS	0	1 (8%)	1 (5%)
	Not evaluable	3 (43%)	3 (25%)	6 (32%)

Figure 2. EFS and OS of Study Population



Summary

- SEL-VEN was **feasible** in a heavily pretreated AML cohort, **with no new toxicity signal**
- ORR was 21%, and 2 patients experienced **durable CR**, confirming SEL-VEN activity
- Analysis is underway to assess utility of PA to predict SEL-VEN response
- Second-generation XPO1 inhibitor eltanexor with VEN (**NCT06399640- ongoing**) could provide a more tolerable XPO1 inhibitor-based regimen to overcome VEN-resistant AML

References

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