A Phase 1 Clinical Trial of Selinexor in Combination with Decitabine in Patients with Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

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Introduction

- Long-term survival for patients with acute myeloid leukemia (AML) remains poor and novel therapies that are both effective and well tolerated are urgently needed.
- Exportin-1 (XPO1), a nuclear transport protein critical for the export of tumor suppressor proteins (TSPs) and select mRNAs to the cytoplasm, is highly expressed in AML and correlates with poor survival.
- Selinexor, an oral, first-in-class, selective inhibitor of nuclear export, blocks XPO1 function.
- We previously reported that sequential treatment of AML blasts using the hypomethylating agent decitabine followed by selinexor exhibited strong anti-leukemic effects *in vivo* by sequestering TSPs in the nucleus (Ranganathan, Blood 2015).
- Based on these findings, a phase I dose-escalation study was initiated to evaluate the safety, feasibility, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and preliminary clinical activity of selinexor in combination with decitabine in poor-risk AML patients (NCT02093403).

Methods

- Adults with relapsed or refractory AML and older (age ≥60) unfit patients with untreated AML were eligible.
- Patients received 10-day decitabine induction(s) at 20 mg/m^2 on days 1-10 for up to four 28-day cycles in combination with selinexor, initially, at a dosing schedule of once daily twice a week on days 11, 13, 18, 20, 25 and 27. The dosing schedule was changed to days 11, 13, 18 and 20 after the first three patients on dose level 1 were treated.
- Bone marrow assessments were done for all patients after cycle 1 and following completion of subsequent cycles only if there were no circulating peripheral blood blasts. Patients with <5% marrow blasts after any cycle received 5-day decitabine maintenance with selinexor as described.
- Selinexor dose escalation followed a 3+3 study design, with selinexor doses ranging from 23 mg/m^2 to 55 mg/m^2 (see below).
- Primary objectives were safety, tolerability, delineation of toxicities and identification of the maximum tolerated dose (MTD).

Dose Level	Selinexor Dose (mg/m^2)
-1	17
1	23
2	30
3	40
4	55

Results

Patients

- 24 patients with AML were enrolled (see Table 1 for baseline characteristics)
- 19 had relapsed or refractory disease (median of 3 prior lines of treatment, range, 1-4).

Table 1. Baseline Patient Characteristics (n=24)

Characteristics		n (%)
Age		
	Median (Range)	60 (23-83)
Gender		
	Female	13 (54.2)
	Male	11 (45.8)
Race		
	Black	4 (16.7)
	White	20 (83.3)
Type		
	Refractory	8 (33.3)
	Relapsed	11 (45.8)
	Untreated	5 (20.8)
ELN genetic group		
	Adverse	7 (30.4)
	Favorable	3 (13.0)
	Intermediate I	10 (43.5)
	Intermediate II	3 (13.0)
	Unknown	1
FLT3-ITD mutation		
	Yes	5 (21.7)
	No	18 (78.3)
	Unknown	1
CEBPA mutation		
	Yes	1 (4.8)
	No	20 (95.2)
	Unknown	3
NPM1 mutation		
	Yes	7 (31.8)
	No	15 (68.2)
	Unknown	2
Prior MDS/MPN		
	Yes	1 (4.2)
	No	23 (95.8)
Bone Marrow Blast %		
	Median (Range)	50 (2-92)
WBC (K/μL)		
	Median (Range)	2.7 (0.5-61.9)
ANC (K/μL)		
	Median (Range)	0.5 (0-80)
HGB (g/dL)		
	Median (Range)	8.4 (6.1-13.6)
Platelet (K/μL)		
	Median (Range)	42.5 (7.3-196)

Abbreviations: ANC, absolute neutrophil count; ELN, European LeukemiaNet; HGB, hemoglobin; MDS/MPN, myelodysplastic syndrome/ myeloproliferative neoplasm; WBC, white blood cell.

Results

Safety and Tolerability

- After two patients in dose level 1 (selinexor dosing of 23mg/m^2) withdrew consent during cycle 1 due to grade 1 or 2 GI toxicities (nausea, anorexia), dosing of selinexor was limited to days 11, 13, 18, and 20 of each cycle (twice weekly for only 2 weeks instead of 3 weeks).
- MTD was not reached, and there were no DLTs in this study. At the maximum administered dose of 55 mg/m^2, three patients were treated with no grade ≥ 3 drug-related toxicities, but two patients declined continuation of study therapy after cycle 1, due to chronic low-level GI toxicities.
- Based on this and also emerging experience from a separate trial with single-agent selinexor, dosing of selinexor was changed to a flat dose of 60mg (~35 mg/m^2) given twice weekly.
- Six additional pts were enrolled at 60 mg of selinexor with improved tolerability; this is the RP2D.
- Most common grade ≥ 3 nonhematologic toxicities, regardless of attribution, were hyponatremia, febrile neutropenia, hypertension, sepsis, hyperglycemia and hyperphosphatemia and lung infection (Table 2).
- The median number of treatment cycles given was 1 (range 1-4). The median number of treatment cycles given to responders was 2 (range 1-4)
- Three responders were able to receive at least one cycle of 5-day maintenance therapy.

Table 2. Common grade ≥ 3 nonhematologic toxicities during all cycles (24 patients)

Toxicity	Number of patients with grade ≥ 3, n (%)
Hyponatremia	17 (70.8)
Febrile neutropenia	11 (45.8)
Hypertension	10 (41.7)
Sepsis	10 (41.7)
Hyperglycemia	9 (37.5)
Hypophosphatemia	8 (33.3)
Lung infection	7 (29.2)
Catheter related infection	4 (16.7)
Acute kidney injury	3 (12.5)
QT prolongation	3 (12.5)
Fatigue	3 (12.5)
Hypokalemia	3 (12.5)
Hypotension	3 (12.5)
Respiratory failure	3 (12.5)
Acidosis	2 (8.3)
Increased aPTT	2 (8.3)
Alanine aminotransferase increased	2 (8.3)
Death	2 (8.3)
Diarrhea	2 (8.3)
Ejection fraction decreased	2 (8.3)

Results

Efficacy

- Of the five previously untreated patients, two achieved complete response (CR), and 2 had CR with incomplete count recovery (CRi) (Table 3).
- Of these responders, patients presented with normal karyotype (n=2), monosomy 7 (n=1), and del(7q), +13 (n=1). The latter two patients achieved cytogenetic remission.
- Of the 19 relapsed or refractory patients, three had induction death unrelated to treatment. Of the remaining 16 patients in this group, two achieved CR, two had CRi, one had marrow CR (mCR).
- For untreated patients, the CR/CRi/mCR rate was 80% and, for relapsed and refractory patients, the CR/CRi/ mCR rate was 26.3%.
- Six of the relapsed/refractory patients subsequently underwent allogeneic stem cell transplant (four with no evidence of AML at the time of transplant).

Table 3. Patient disease responses n (%)

Best response (%)	All (n=24)	Elderly untreated (n=5)	Relapsed/ Refractory (n=19)
ORR (CR/CRi/mCR)	9 (37.5)	4 (80)	5 (26.3)
CR	4 (16.7)	2 (40)	2 (10.5)
CRi	4 (16.7)	2 (40)	2 (10.5)
mCR	1 (4.2)	0 (0)	1 (5.3)

Abbreviations: CR, complete response; CRi, complete response with incomplete count recovery; mCR, marrow CR

Conclusions

- The combination of selinexor and decitabine is an active regimen in poor-risk AML patients, with CR/CRi/mCR rate of 80% in older untreated and 26.3% in relapsed or refractory AML patients. The total CR/CRi/mCR rate was 37.5%.
- Modification of selinexor treatment (flat dose of 60 mg given twice weekly for 2 weeks after decitabine) improved tolerability of the regimen.

References

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Disclosures

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