Phase I Study of Selinexor, a Selective Inhibitor of Nuclear Export, in Combination with Fludarabine and Cytarabine in Children with Relapsed or Refractory Leukemia

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Background

Patients with primary refractory or first relapse of acute myeloid leukemia (AML) have complete response (CR) rates of 50-65% and overall survival of 30-40%. Specifically, CR rates for this group of patients was 59% using fludarabine and cytarabine and 48% using clofarabine and cytarabine. Outcomes are worse for patients with early relapse and are dismal for patients with second relapse. Novel and broadly active therapies are urgently needed for patients with relapsed or refractory AML.

Exportin 1 (XPO1), also called chromosome region maintenance 1 (CRM1), is the primary nuclear exporter of key tumor suppressor and regulatory proteins, including p53, p21, p27, NPM1, eIF4e and I-kB. Expression of *XPO1* is upregulated in many malignancies, including AML, leading to cytoplasmic mislocalization and functional inactivation of tumor suppressor and growth regulatory proteins. Inhibition of XPO1 can therefore potentially restore the normal tumor suppressor pathways that lead to apoptosis of neoplastic cells. Small molecule selective inhibitors of nuclear export (SINE) compounds inhibit XPO1 by covalent binding, thus blocking XPO1-mediated efflux of proteins. Preclinical studies demonstrate that selinexor (KPT-330), an orally bioavailable SINE compound, is active against a variety of AML cell lines and primary AML samples. In addition, it is active in AML xenograft models and appears to target leukemia-initiating cells while sparing normal hematopoiesis.

Objectives

- Determine a tolerable combination of selinexor, fludarabine, and cytarabine in patients with relapsed or refractory hematologic malignancies including AML, acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS)

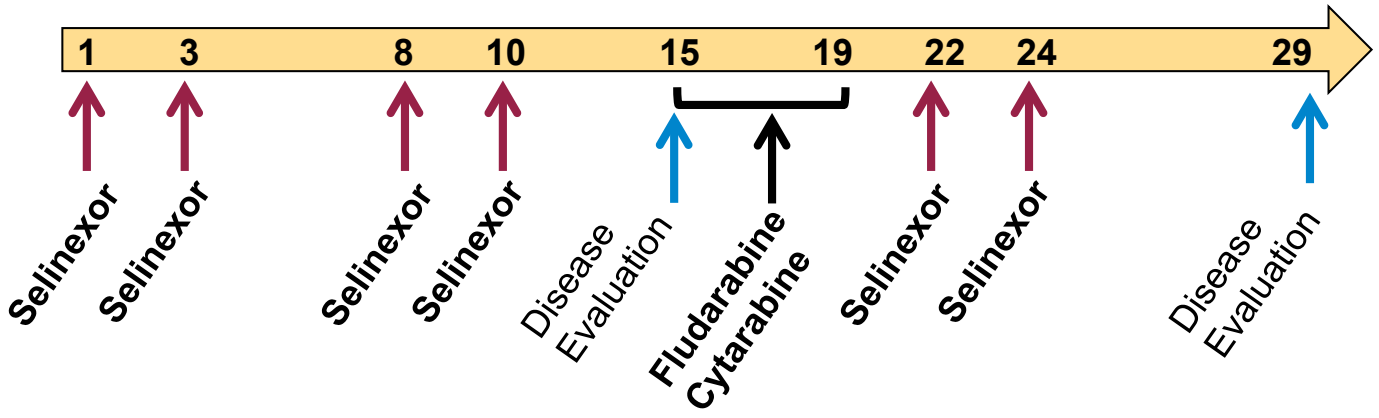
- Characterize the pharmacokinetics and pharmacodynamics of selinexor, when administered in tablet form, after the first dose and at steady-state, as well as in combination with fludarabine and cytarabine

- Estimate the overall response rate of selinexor given with fludarabine and cytarabine in patients with relapsed or refractory hematologic malignancies

Patients and Methods

Eighteen children and adolescents with relapsed AML (n=11), refractory AML (n=4), relapsed mixed phenotype leukemia (MPAL, n=2), or relapsed early T-precursor (ETP) ALL (n=1) have been enrolled on the study to date. Eight patients had previously received only chemotherapy, whereas 10 had undergone at least one prior stem cell transplant. Selinexor was given orally on days 1, 3, 8, 10, 22, and 24 and escalated according to a rolling-6 design. Fludarabine (30 mg/m^2) and cytarabine (2 g/m^2) were administered on days 15-19. Samples for PK analysis were collected on days 1 and 22. PD samples were collected on day 1. Bone marrow evaluation was performed on day 15, end of course 1, and repeated as necessary in cases of hypocellular marrows.

DOSING SCHEME



Patient Demographics and Clinical Characteristics

Patient number	Selinexor dose level	Age (years)	Gender	Disease Type	Disease status	Prior HSCT	No. of doses received	Pre-Study MRD (%)	Day 15 MRD (%)	Day 29-35 MRD (%)	Final MRD (%)	Response	Subsequent Transplant
1	30 mg/m^2	6	Male	AML	1st Relapse	Yes	6	40	51	25	31	NR	No
2	30 mg/m^2	18	Female	AML t(6;12)	Refractory	No	2	53	NE	NE	NE	NE	Yes
3	30 mg/m^2	19	Male	Secondary AML -7	1st Relapse	Yes	6	5	57	13	ND	NR	Yes
4	30 mg/m^2	6	Male	MPAL	2nd Relapse	Yes	6	59	12	0.5	0.35	CRi	Yes
5	40 mg/m^2	15	Female	AML t(6;9)	2nd Relapse	Yes	6	43	<0.1	<0.1	<0.1	CRi	Yes
6	40 mg/m^2	11	Male	AML	2nd Relapse	Yes	12	23^{ł}	39	<0.1	<0.1	CR	Yes
7	40 mg/m^2	17	Male	AML -7	1st Relapse	Yes	6	16	15	<0.1	<0.1	CR	Yes
8	55 mg/m^2	2	Female	AMKL	2nd Relapse	Yes	6	5	19	26	ND	NR	No
9	55 mg/m^2	4	Female	ALL -> MPAL t(4;11)	2nd Relapse	Yes	6	72	60	<0.1	4.6	PR	No
10	55 mg/m^2	16	Male	AML	1st Relapse	No	6	75	39	3.4	16	PR	Yes
11	55 mg/m^2	5	Female	AML t(3;5)	1st Relapse	No	6	28	9.5	<0.1	21	NR	No
17	55 mg/m^2	16	Female	AML	Refractory	No	6	45	65	0.8	pending	pending	pending
18	55 mg/m^2	6	Male	AML	1st Relapse	No	6	22	24	pending	pending	pending	pending
12	70 mg/m^2	13	Female	AML t(8;21)	1st Relapse	No	11	30	28	<0.1	<0.1	CR	Yes
13	70 mg/m^2	4	Female	AML	Refractory	No	9	16	<0.1	<0.1	<0.1	CR	Yes
14	70 mg/m^2*	5	Male	AML	Refractory	No	4	86‡	NR	13	50	NE	pending
15	70 mg/m2	13	Male	AML -> ETP-ALL	2nd Relapse	Yes	6	90	82	<0.1	ND	NE	No
16	70 mg/m^2*	1	Male	AML	1st Relapse	Yes	4	83	77	NE	NE	NE	pending

Abbreviations: MRD, minimal residual disease; HSCT hematopoietic stem cell transplant; NR, No response; PR, partial response; CRi, complete response with incomplete count recovery; CR, complete response; NE, not evaluable; ND, not done

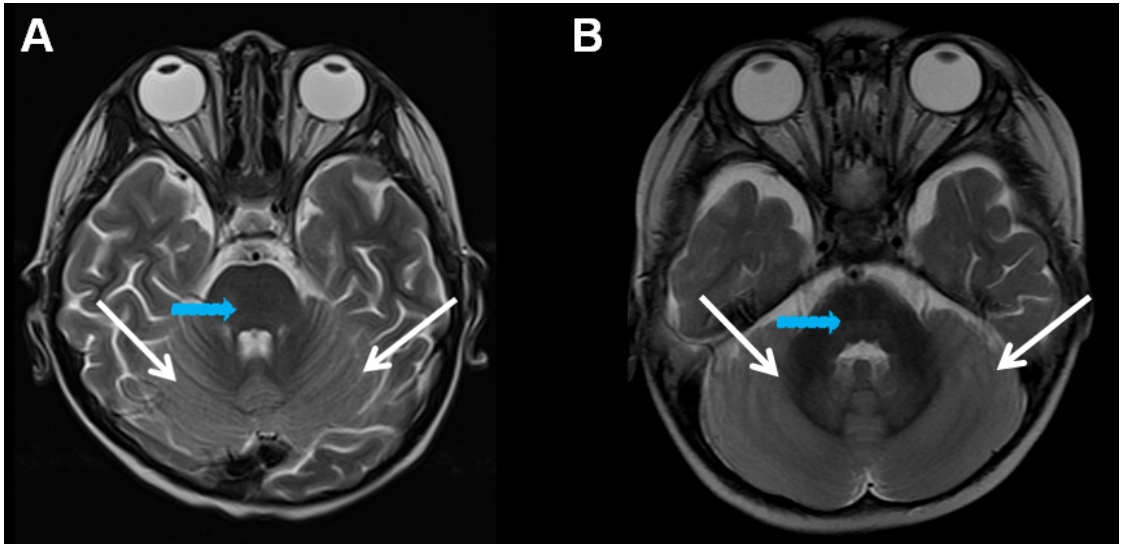
All 1st relapse patient had early relapse *Dose-limiting toxicity łEstimated by morphology ‡Peripheral blood MRD

Safety Profile

Number of patients with grade 3 or 4 adverse events				
Toxicity	30 mg/m^2 4 patients	40 mg/m^2 3 patients	55 mg/m^2 6 patients*	70 mg/m^2 5 patients
Gastrointestinal disorders				
Nausea / Vomiting		1		
Infections and infestations				
Febrile neutropenia	2	1	3	3
Anorectal infection	1			1
Encephalitis infection	1			
Infections, other	1	1	1	4
Lung infection	1		1	2
Meningitis	1			
Metabolism / nutrition disorders				
ALT or AST increased	1	3	1	2
Bilirubin increased	1			
Lipase increased				
Weight loss / anorexia			1	1
Hyperglycemia	1		2	2
Hyperkalemia	2			
Hypocalcemia	1		1	
Hypokalemia	4	1	1	3
Hypomagnesemia	1			
Hyponatremia	4	2	3	4
Hypophosphatemia	2	1	2	3
Nervous system disorders				
Ataxia				1
Cognitive disturbance				1
Leukoencephalopathy				1
Syncope		1		
*Data collection is ongoing for two patients				

The most common Grade 3 non-hematologic toxicity related to selinexor was hyponatremia, which was easily corrected in all cases. Two cases of cerebellar toxicity were observed at dose level 4, thus defining the dose-limiting toxicity (DLT) and establishing 55 mg/m^2 as the maximum tolerated dose (MTD). No CNS related toxicity was observed in this trial at doses ≤ 55 mg/m^2. Among 1300 adults dosed with selinexor only, one additional case of cerebellar toxicity occurred in a patient with pancreatic cancer treated with 85 mg/m^2 (125 mg flat dose).

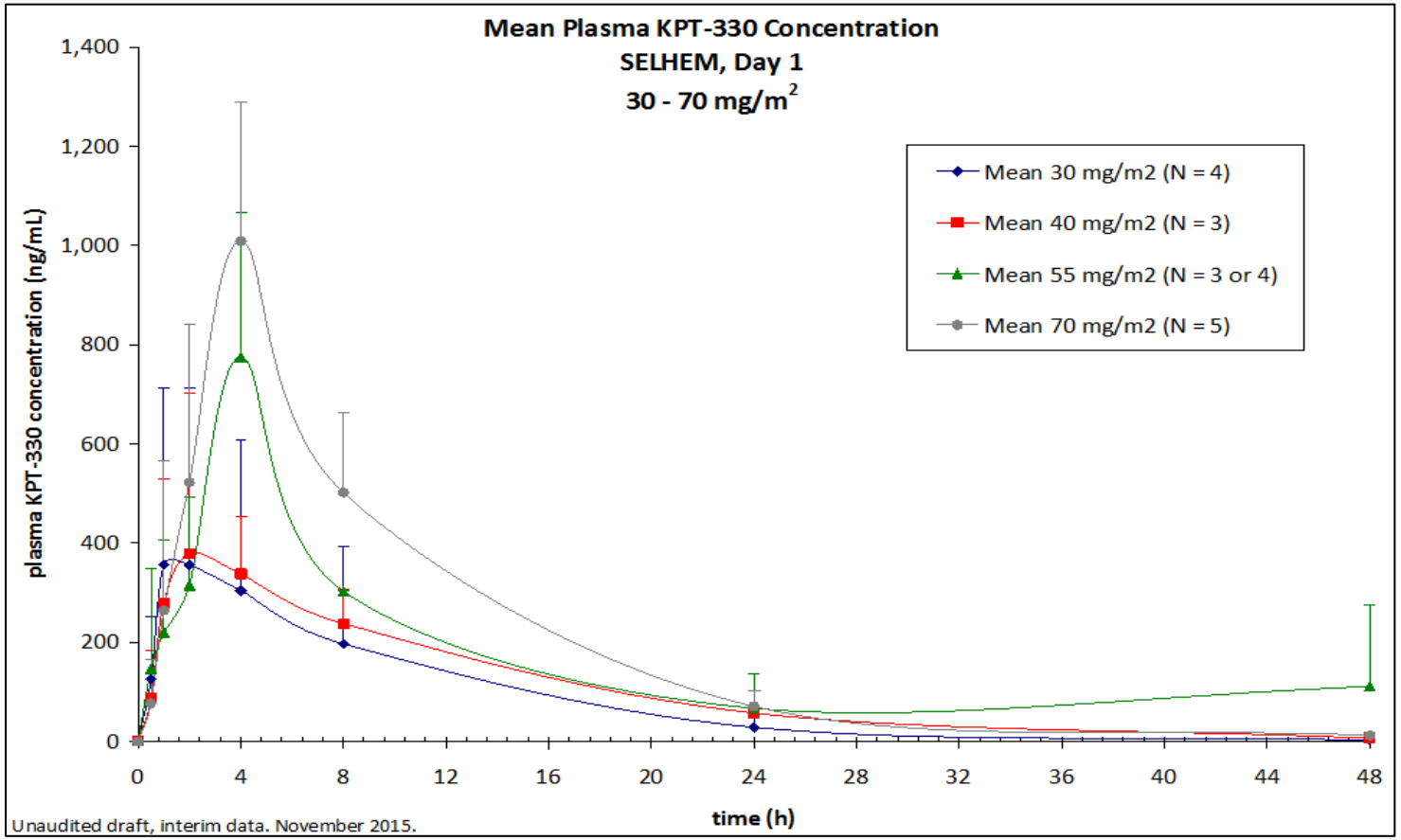
Dose Limiting Toxicity



Axial T2W MRI of the two patients with dose limiting toxicity at 70 mg/m^2. Both cases show diffuse cerebellar edema and hyperintensity (white arrows), sparing the brainstem (blue arrows), deep cerebellar nuclei, and cerebrum.

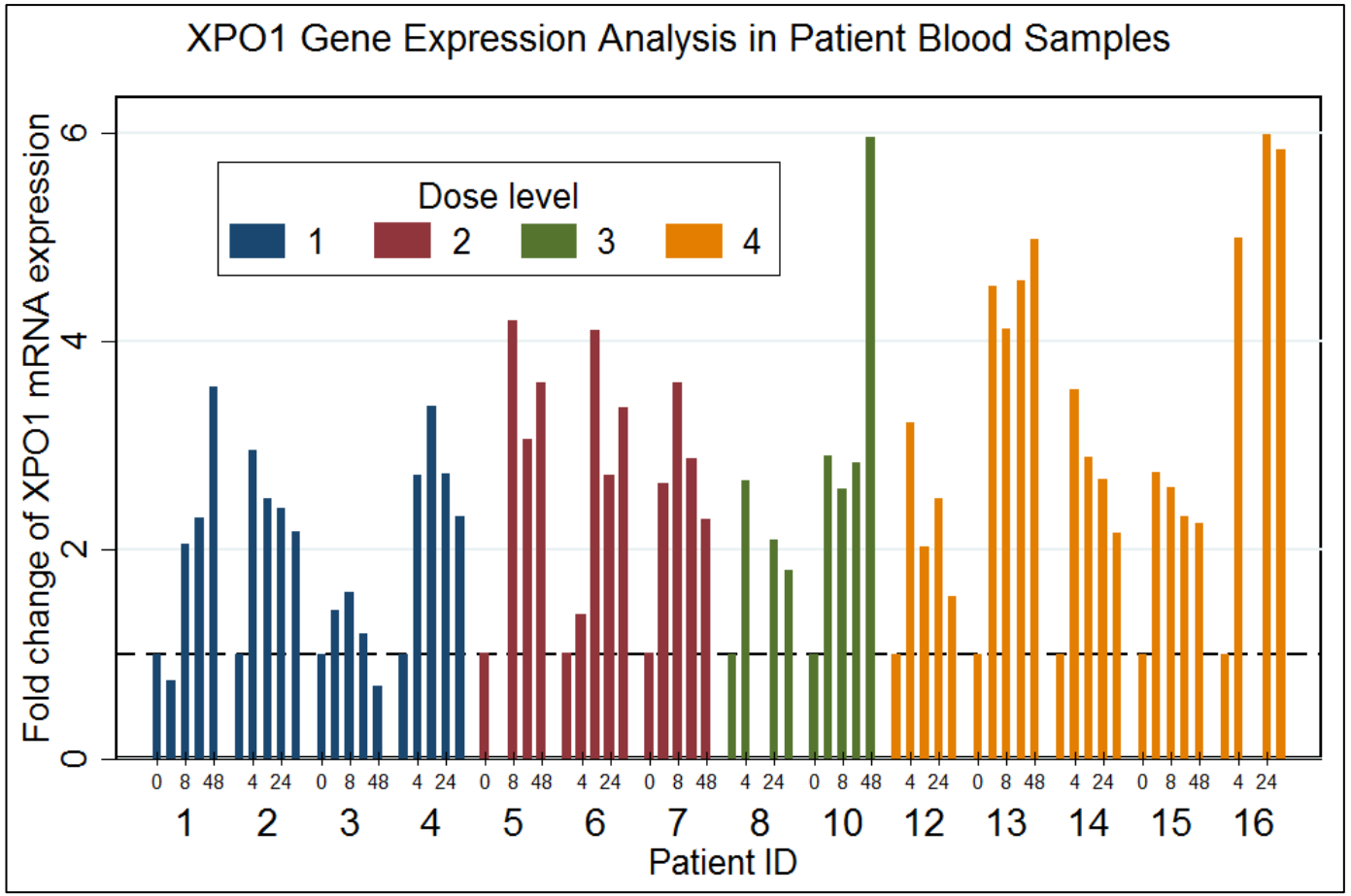
At a selinexor dose of 70 mg/m^2, two patients experienced grade III CNS toxicity. Patient 14 had pain, weakness and aphasia after receiving selinexor as well as fludarabine and cytarabine. Patient 16, after receiving selinexor monotherapy, had significant truncal ataxia. Both patients had imaging changes consistent with cerebellar toxicity. The patients were taken off protocol therapy and improved over the course of weeks.

Pharmacokinetics / Pharmacodynamics



Mean plasma selinexor concentration in pediatric patients showed little separation between the 30 and 40 mg/m^2 dose levels, with an increase in exposure evident at the 55 and 70 mg/m^2 dose levels. Plasma concentration levels in pediatric patients are similar to unpublished results in adult patients.

Pharmacokinetics / Pharmacodynamics



Inhibition of XPO1 was assessed by qRT-PCR of *XPO1*, which is upregulated at the RNA level in response to XPO1 protein inactivation. Thirteen of fourteen patients assessed demonstrated at least 2-fold induction of *XPO1*. Increased expression persisted for at least 48 hours, indicating prolonged inhibition by selinexor. Further testing of patients from dose level 3 is ongoing.

Disease Response

- At the time of this report, 12 patients were evaluable for response to therapy. Response was assessed by flow cytometric examination of the bone marrow between days 29 and 36, and repeated if necessary.

- Four patients had no response (NR), 2 had partial responses (PR), 2 had complete responses with incomplete count recovery (CRi), and 4 had CR, resulting in an overall (PR + CRi + CR) response rate of 67% (95% confidence interval 35-90%).

Conclusions

- Selinexor in combination with fludarabine and cytarabine is tolerable at doses up to 55 mg/m^2 in pediatric patients with relapsed or refractory leukemia
- Two DLTs of severe reversible cerebellar toxicity occurred at a dose of 70 mg/m^2
- Selinexor pharmacokinetic parameters are generally dose proportional
- All patients who received selinexor at 40 mg/m^2 or higher showed evidence of XPO1 target inhibition
- The response rate was 67% in this small group of heavily pretreated patients with high-risk features
- Based on the overall response we observed thus far, an expansion cohort will be open to enrollment