DANA-FARBER Boston Children's

CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL

Phase I Trial of the Selective Inhibitor of Nuclear Export, SELINEXOR, in Relapsed Childhood Leukemia

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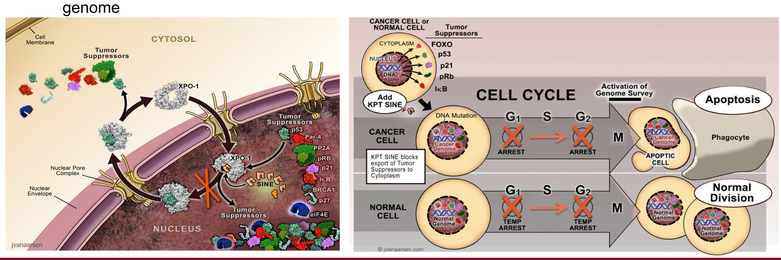
Background

Treatment of relapsed childhood leukemia remains a significant clinical challenge

Exportin: Novel Target in Relapsed Leukemia

- XPO1 (exportin) is the most well characterized nuclear export protein and mediates export of tumor suppressor proteins and many growth regulatory proteins
- XPO1 has become a compelling target in numerous malignancies
  - Inhibition prevents export of tumor suppressor proteins (TSPs)
  - Accumulation of TSPs in the nucleus reinitiates/amplifies their apoptotic function in cancer cells with damaged DNA
  - Normal cells resume normal activity after transient XPO1 inhibition because they have an intact genome



Objectives

Primary Objectives

- To evaluate the safety and tolerability of selinexor and to determine the Maximum Tolerated Dose (MTD) in patients with relapsed and/or refractory acute leukemia.

Secondary Objectives

- To determine the pharmacokinetic (PK) parameters of selinexor in children and young adults.
- To explore the anti-leukemic activity of selinexor in patients with relapsed and/or refractory acute leukemia.

Methods

Study design:

- Multi-institutional Phase 1 trial of selinexor administered twice weekly to determine the MTD or recommended phase 2 dose using a 3+3 dose escalation design.
- Supportive care: *Mandatory*: Tumor lysis syndrome prevention; antibacterial and PJP prophylaxis; antiemetic. *Strongly encouraged*: Antifungal prophylaxis (azoles prohibited) and appetite stimulant

Major Eligibility Criteria:

- Age 18 months to ≤ 21 years (must be able to swallow tablets)
- Relapsed/refractory acute leukemia: ALL (precursor/mature), AML, Mixed phenotype acute leukemia, BC-CML
- ≥ 5% blasts by morphology or flow cytometry
- CNS 1 and CNS 2 allowed (no isolated extramedullary)
- Prior bone marrow transplant is allowed (> 100 days out, no active graft vs. host disease; weaning or stable doses of steroids/calcineurin inhibitors allowed)

Dose Limiting Toxicity (DLT) Definition:

- *Non-Hematologic DLT:* Any Grade 5 event; Any Grade ≥3 non-hematologic attributable to selinexor with the specific exclusions: (nausea and vomiting, diarrhea, Grade 3 anorexia, Grade 3 weight loss, ALT/AST and/or direct bilirubin elevations that resolve to Grade ≤ 2 within ≤ 7 days, electrolyte abnormalities correctable with supportive therapy, infection, fever, tumor lysis syndrome, other metabolic or laboratory abnormalities that resolves to Grade ≤ 2 within ≤ 7 days of holding the next scheduled dose.)
- *Hematologic DLT:* Delayed count recovery

Pharmacokinetic Analysis:

- Samples for PK analysis were obtained during Cycle 1 at 0.5, 1, 2, 4, 8, 24 and 48 hours after Dose 1A administration.
- Serum concentrations of selinexor were determined by LC-MS/MS.
- PK parameters were determined using standard noncompartmental analysis using an R NonCompart package.

Subjects

Subject Characteristics	N(%)
Gender	
Female	8 (50)
Leukemia Type	
AML	12 (75)
ALL	4 (25)
Disease status	
First Relapse	4(25)
Primary Refractory	5(31)
Second Relapse	4(25)
Other Relapse	3(19)
Prior HSCT	6(38)

Treatment Regimen

Week	1		2		3		4		
Day	1	3	1	3	1	3	1	3	7
Selinexor Dose (twice weekly)	1A	1B	2A	2B	3A	3B	4A	4B	**Disease Evaluation**
IT Triples	X				X*				

*Patients with CNS leukemia only

Initial Schema	
Dose Level	Dose
-1	20 mg/m^2
1	**30 mg/m^2**
2	40 mg/m^2
3	54 mg/m^2

Amendment 4 (Adult MTD identified)	
Dose Level	Dose
-1	20 mg/m^2
1	30 mg/m^2
2	**56 mg/m^2**
3	70 mg/m^2

Amendment 10 (DLT at 56 mg/m^2)	
Dose Level	Dose
-1	20 mg/m^2
1	**30 mg/m^2**
2	**40 mg/m^2**
3	50 mg/m^2

Amendment 24 (cap at 40 mg/m^2)	
Dose Level	Dose
-1	20 mg/m^2
1	30 mg/m^2
2	**40 mg/m^2**

Toxicity Results

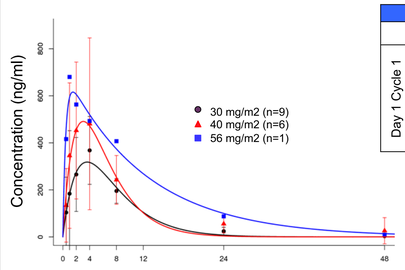
The common Grade ≥ 2 selinexor treatment-related AEs experienced throughout treatment were hyponatremia (31%), elevated alanine aminotransferase (25%), nausea (25%), hyperkalemia (25%), elevated aspartate aminotransferase (19%) and diarrhea (19%).

Cycle 1 worst grade toxicity (≥ Grade 3) possibly, probably, or definitely attributable to Selinexor

	30 mg/m^2 (n=9)			40 mg/m^2 (n=6)		56 mg/m^2 (n=1)
Toxicity Description	**Gr 3**	**Gr 4**	**Gr 5**	**Gr 3**	**Gr 4**	**Gr 3**
Alanine aminotransferase increased	1	1		1		
Anorexia				1		
Aspartate aminotransferase increased		1		1		
Cognitive disturbance						**1 (DLT)**
Dehydration						1
Hyperglycemia	1			1		
Hyperkalemia	1					
Hypoalbuminemia	1					
Hypocalcemia	1					
Hypokalemia		1				
Hypomagnesemia	1					
Hyponatremia	3			1		1
Pancreatitis			**1(DLT)#**			
Tumor lysis syndrome		1			1	

After 6 doses of selinexor, subject developed sudden onset of hemorrhagic pancreatitis associated with abdominal pain, anemia, hyperglycemia, elevated lipase and persistent hypotension despite maximum medical support. Subject had prior history of typhlitis and abdominal surgery 4 months prior to study entry. This AE was determined to be possibly attributable to selinexor and therefore met DLT criteria.

Pharmacokinetic Analysis Results



		30 mg/m^2			40 mg/m^2			56 mg/m^2
	hr	n	Conc (ng/mL) Mean	SD	n	Conc (ng/mL) Mean	SD	Conc (ng/mL) (n=1)
Day 1 Cycle 1	0.5	9	103.80	150.24	6	134.38	156.43	416
	1	9	183.83	267.84	6	345.68	309.13	680
	2	8	265.50	157.40	6	452.47	290.94	563
	4	9	367.89	144.28	6	480.80	365.20	493
	8	7	195.29	52.33	6	242.40	103.62	407
	24	9	24.28	16.46	6	55.52	38.80	87.5
	48	9	3.01	2.15	6	26.30	55.75	9.18

PK Parameter	30 mg/m^2	40 mg/m^2
$AUC_{0\text{-}48h}$ (h*ng/mL)	4093 ± 1235	6297 ± 1342
C_{max} (ng/mL)	436 ± 195	644 ± 361
T_{max} (hours)	3.2 ± 1.2	2.0 ± 1.2
$t_{1/2}$ (hours)	6.7 ± 1.6	6.2 ± 1.4

AUC=area under the curve; C_{max}=maximum serum concentration; $t_{1/2}$=half-life; T_{max} = time to maximum

DLT and Response Results

Case	Cohort	Disease	Gender	Age (yrs)	# Doses (Cycle 1)	Evaluable for DLT?	DLT?	Best Response
1	30 mg/m^2	AML	F	12.1	8	Yes	No	RD w/CB (2 cycles)
2	56 mg/m^2	AML	F	18.3	6	Yes	Yes (Gr. 3 cognitive impairment)	RD w/CB
3	30 mg/m^2	AML	M	9	5	No	NE	PD w/o CB
4	30 mg/m^2	AML	M	2.3	6	No	NE	PD w/o CB
5	30 mg/m^2	ALL	M	6.1	8	Yes	No	RD w/CB
6	30 mg/m^2	AML	M	13.3	6	Yes	Yes (Gr. 5 pancreatitis)	RD w/CB
7	30 mg/m^2	ETP-ALL	M	8.5	2	No	NE (Grade 4 TLS)	NE
8	30 mg/m^2	T-ALL→AML	F	17.4	7	Yes	No	RD w/o CB
9	30 mg/m^2	AML	M	9.7	8	Yes	No	RD w/CB (3 cycles)
10	30 mg/m^2	ETP-ALL	M	9	7	Yes	No	PD w/CB
11	40 mg/m^2	ALL	M	11	8	Yes	No (Grade 4 TLS)	PR (M2 marrow)
12	40 mg/m^2	AML	F	3	8	Yes	No	RD w/CB
13	40 mg/m^2	AML	F	4.2	8	Yes	No	RD w/CB
14	40 mg/m^2	ALL	F	9.2	8	Yes	No	RD w/CB
15	40 mg/m^2	AML	F	21.7	8	Yes	No	CRp
16	40 mg/m^2	AML	F	2.3	8	Yes	No	RD w/o CB

CRp – Complete remission with incomplete platelet recovery; DLT – Dose limiting toxicity; NE – not evaluable, PD – Progressive disease; PR – Partial remission; RD w/CB – resistant disease with clinical benefit; WC – withdrew consent

Clinical benefit experienced by 11 of 16 patients (69%)	
Decreased red cell transfusion	43.8%
Decreased platelet transfusion	37.5%
Clearance of peripheral blasts	31.3%
Decreased Pain	31.3%
Decreased fatigue	25%
Improved neutrophil count	18.8%
Disease stabilization	12.5%
Other Clinical Benefit	12.5%

Best Response Summary	
Response	N (%)
CRp	1 (6.3)
PR	1 (6.3)
Overall Response Rate	2 (12.5)
Resistant Disease with Clinical Benefit	8 (50)
Resistant Disease *without* Clinical Benefit	2 (12.5)
Progressive Disease with Clinical Benefit	1 (6.3)
Progressive Disease *without* Clinical Benefit	2 (12.5)
Not evaluable	1 (6.3)

Conclusions

- Selinexor administered twice weekly as a single agent was well tolerated in children with relapsed/refractory acute leukemia.
- Two DLT's were encountered; pancreatitis and cognitive disturbance.
  - Both are unusual events that have not been encountered in any other trial (adult or pediatric)
- The recommended phase 2 dose in this population is 40 mg/m^2 twice weekly for 28 days.
- PK analysis was similar to that previously described. (Alexander *et al*, JCO 34:4094-4101, 2016; Abdul *Razak et al* JCO 34:4142-4150, 2016)
- Single agent activity has been identified.
  - ORR is 12.5% [1 CRp (AML), 1 PR (ALL)]
  - 11 of 16 patients derived a clinical benefit
  - 2 of 4 patients with ALL experienced Grade 4 TLS.

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