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MINNEAPOLIS

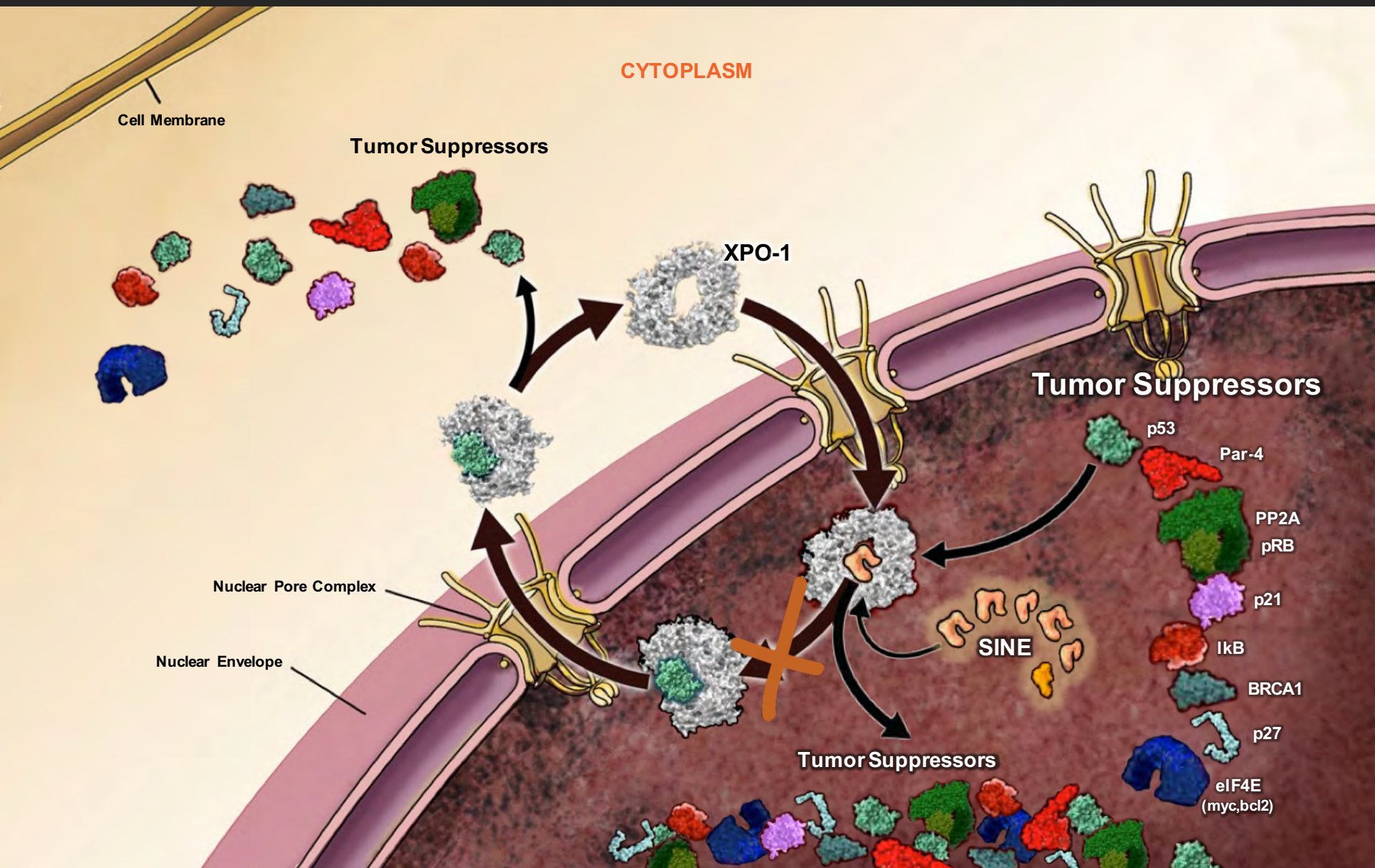
## **PHASE I STUDY OF SELINEXOR, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT, IN COMBINATION WITH FLUDARABINE AND CYTARABINE IN CHILDREN WITH RELAPSED OR REFRACTORY LEUKEMIA**

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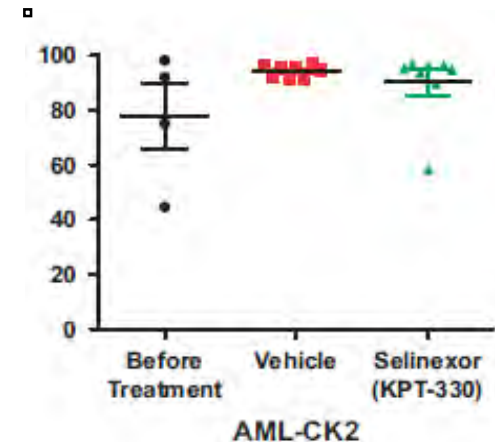
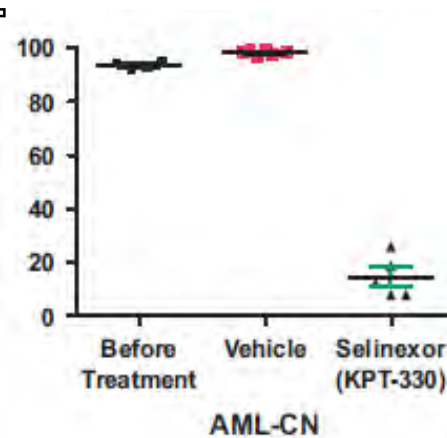
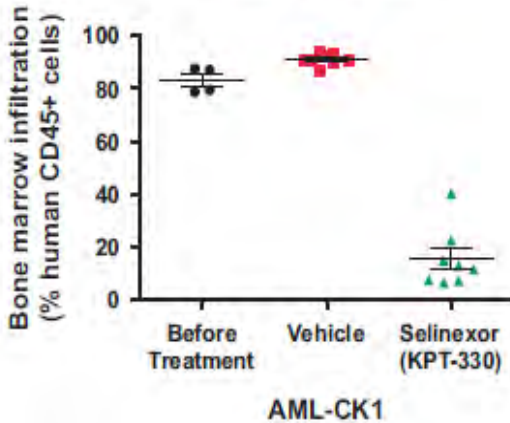
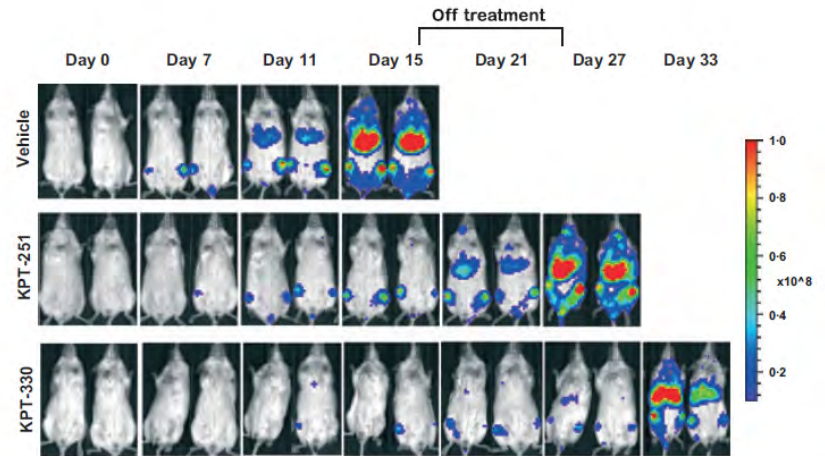
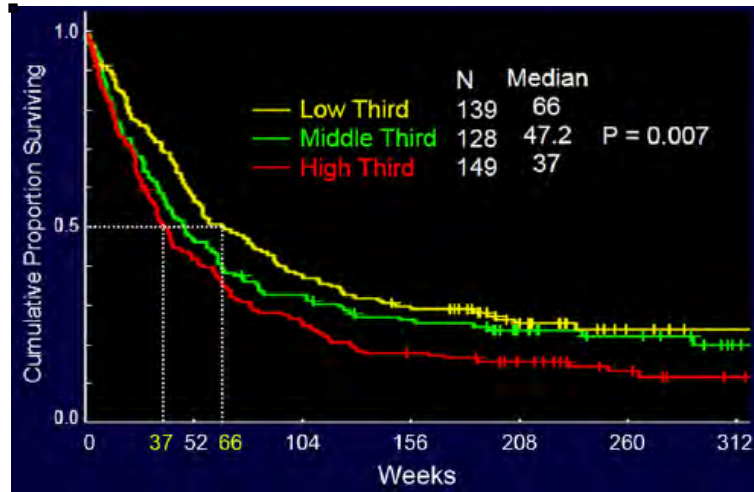


# Selinexor: Novel Anti-Cancer Agent: Restores Tumor Suppressors & Reduces Oncoproteins





# XPO1 expression is prognostic and selinexor is active in leukemia models



# Objectives

## Primary:

- Determine the safety profile and maximal tolerated dose of selinexor when given in combination with fludarabine and cytarabine

## Secondary:

- Characterize the pharmacokinetics of oral selinexor 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

# Trial design

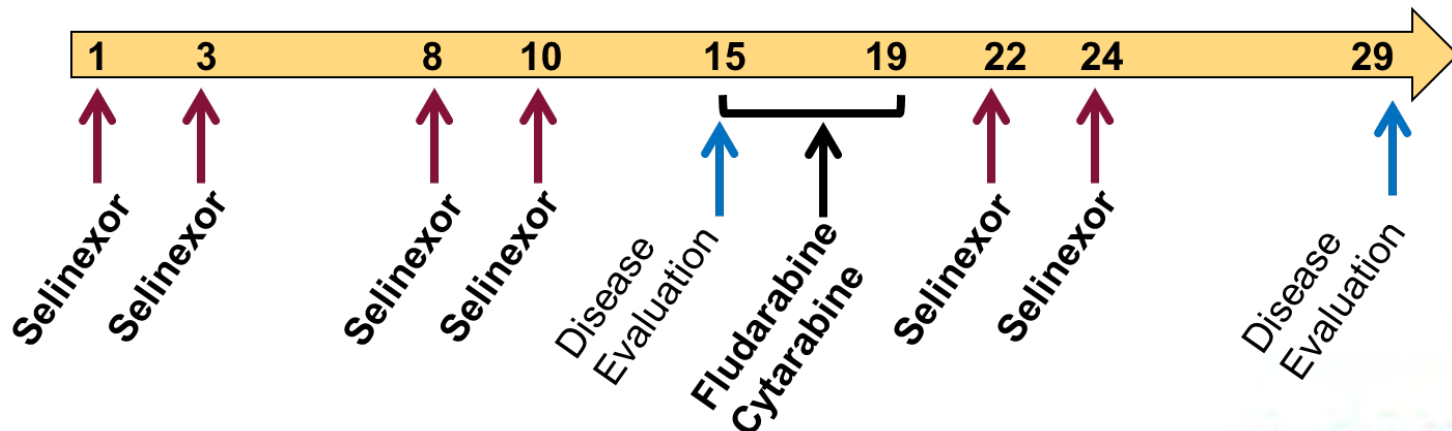
## Inclusion Criteria

- Any relapse of AML, MPAL
- 2<sup>nd</sup> or greater relapse ALL

St. Jude Children's Research Hospital  
Stanford Children's Health  
Children's Hospital of Michigan  
Cook Children's Medical Center  
Duke University Medical Center  
Phoenix Children's Hospital  
University of Chicago

## Phase 1 with expansion planned at MTD

- Combination therapy
- Rolling 6 design
- Four dose levels of selinexor (30mg/m<sup>2</sup>, 40mg/m<sup>2</sup>, 55mg/m<sup>2</sup>, 70mg/m<sup>2</sup>)



# Patient characteristics

18 patients enrolled

Disease	Number of patients
AML	15
MPAL	2
ETP-ALL	1

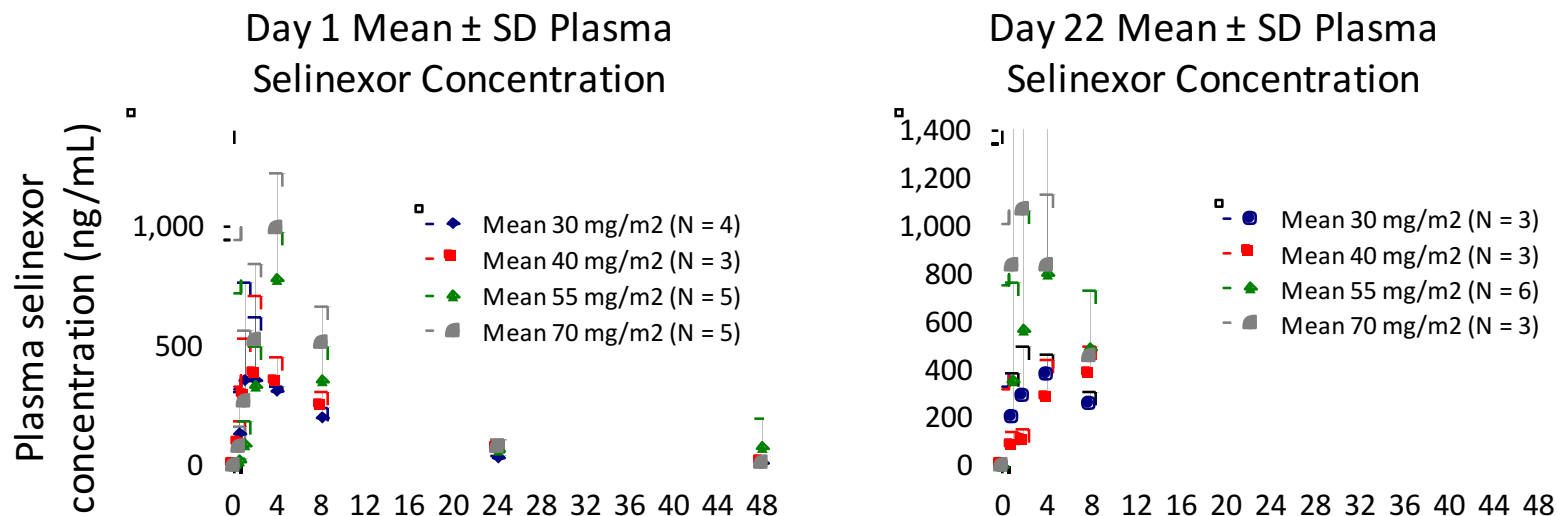
	Number of patients
Refractory	4
1st Relapse (all early)	7
2nd Relapse	7
Previous Transplant	10

17 eligible for toxicity evaluation

15 eligible for response evaluation

Selinexor dose	Disease type
30 mg/m <sup>2</sup>	AML
30 mg/m <sup>2</sup>	AML t(6;12)
30 mg/m <sup>2</sup>	Secondary AML -7
30 mg/m <sup>2</sup>	MPAL
40 mg/m <sup>2</sup>	AML t(6;9)
40 mg/m <sup>2</sup>	AML
40 mg/m <sup>2</sup>	AML -7
55 mg/m <sup>2</sup>	AML, M7
55 mg/m <sup>2</sup>	ALL -> MPAL t(4;11)
55 mg/m <sup>2</sup>	AML, M0
55 mg/m <sup>2</sup>	AML, t(3;5)
55 mg/m <sup>2</sup>	AML
55 mg/m <sup>2</sup>	AML, t(9;11)
70 mg/m <sup>2</sup>	AML, t(8;21)
70 mg/m <sup>2</sup>	AML
70 mg/m <sup>2</sup> *	AML
70 mg/m <sup>2</sup> *	AML -> ETP-ALL
70 mg/m <sup>2</sup> *	AML

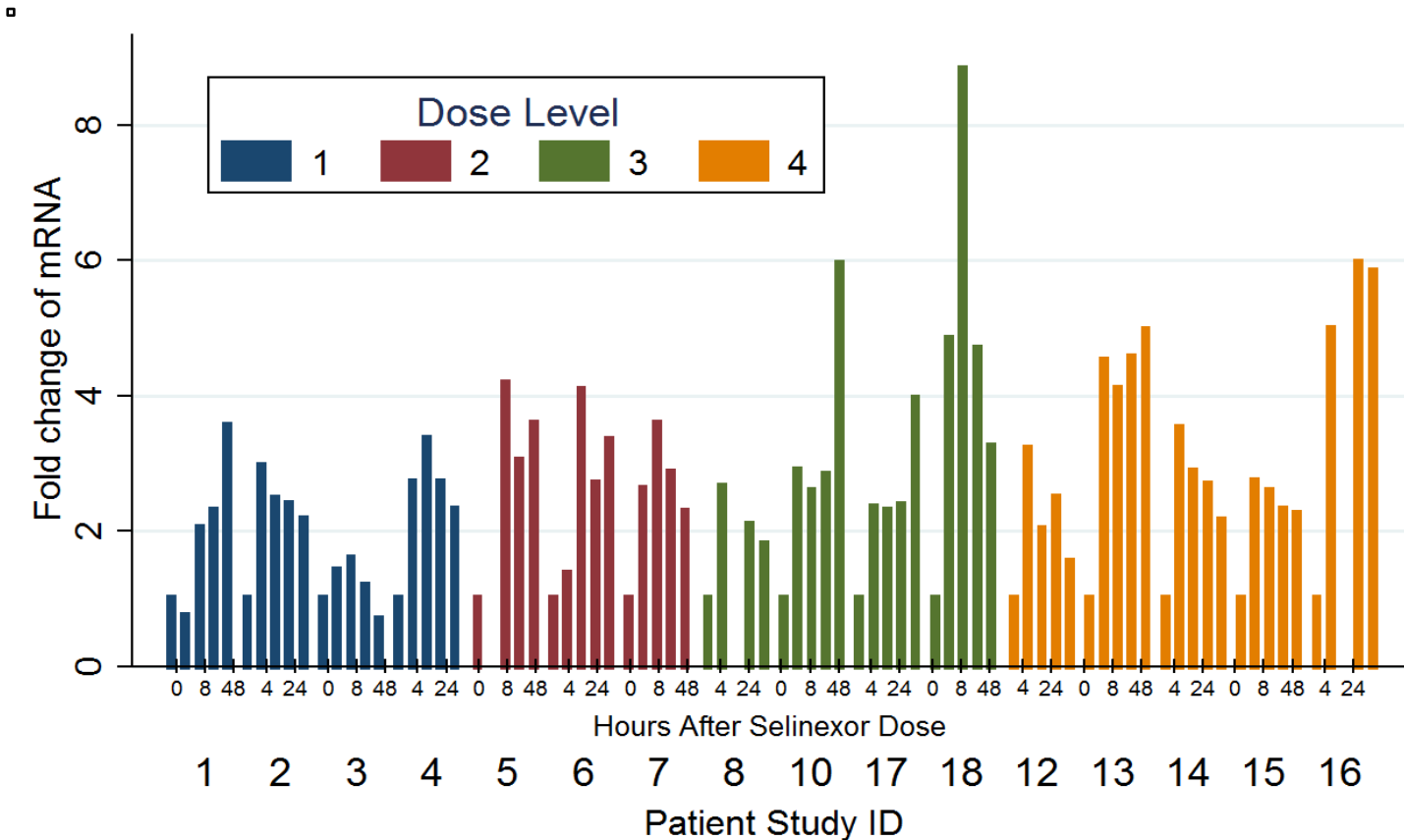
# PK testing shows dose proportional levels



Selinexor Dose (mg/m <sup>2</sup> )	Day 1						Day 22			
	No. of patients	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hours)	AUC <sub>0-8h</sub> (ng*h/mL)	AUC <sub>0-48</sub> (ng*h/mL)	t <sub>1/2</sub> (hours)	No. of patients	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hours)	AUC <sub>0-8h</sub> (ng*h/mL)
30	4	537 $\pm$ 281	3 $\pm$ 1.5	2171 $\pm$ 618	4351 $\pm$ 513	6 $\pm$ 1	3	414 $\pm$ 124	4 $\pm$ 1	2239 $\pm$ 494
40	3	475 $\pm$ 157	2 $\pm$ 3.5	2311 $\pm$ 934	5440 $\pm$ 940	7 $\pm$ 2	3	420 $\pm$ 87	4 $\pm$ 2	1785 $\pm$ 376
55	4	776 $\pm$ 200	4 $\pm$ 0	5663 $\pm$ 3438	9838 $\pm$ 2413	8 $\pm$ 2.5	6	976 $\pm$ 665	3 $\pm$ 1	4627 $\pm$ 2484
70	5	996 $\pm$ 224	4 $\pm$ 1	4986 $\pm$ 979	10564 $\pm$ 1638	7 $\pm$ 1	3	1188 $\pm$ 474	2 $\pm$ 1	7035 $\pm$ NA



# PD testing shows on target activity



Change in levels of *XPO1* mRNA by dose and duration of selinexor exposure



# Cerebellar toxicity is a reversible dose limiting toxicity in pediatrics

Maximal Tolerated Dose is 55 mg/m<sup>2</sup>

Cerebellar Toxicity – Occurred at 70 mg/m<sup>2</sup> of selinexor

- First Case – pain, aphasia, weakness, ataxia
  - MRI – restricted diffusion in cerebellum
- Second Case – significant ataxia, truncal instability
  - MRI – restricted diffusion in cerebellum

Hyponatremia

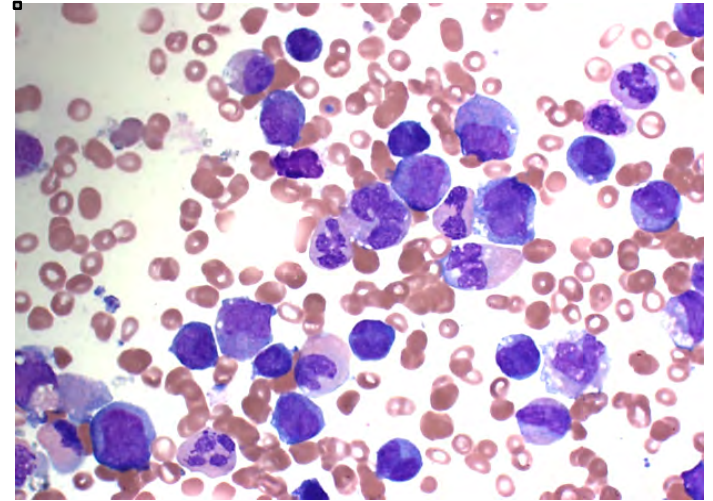
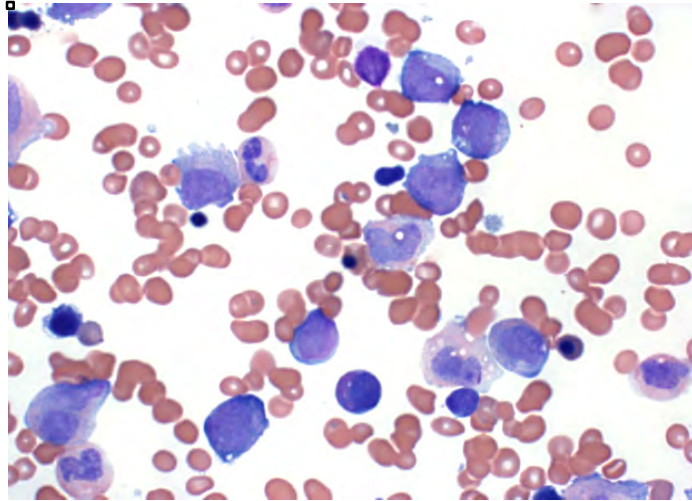
- Grade 3 hyponatremia in 12 of 17 evaluable cases
- Nadir: range 123-132 mEq/L, median 128.5 mEq/L
- Asymptomatic and easily correctable in all cases

# Selinexor can induce differentiation

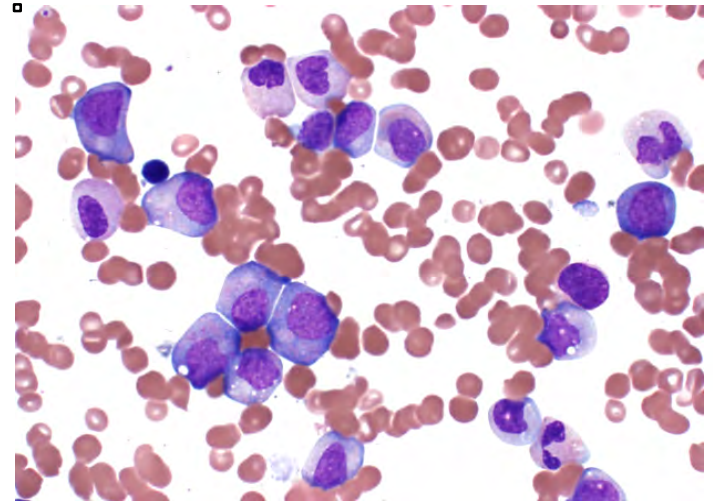
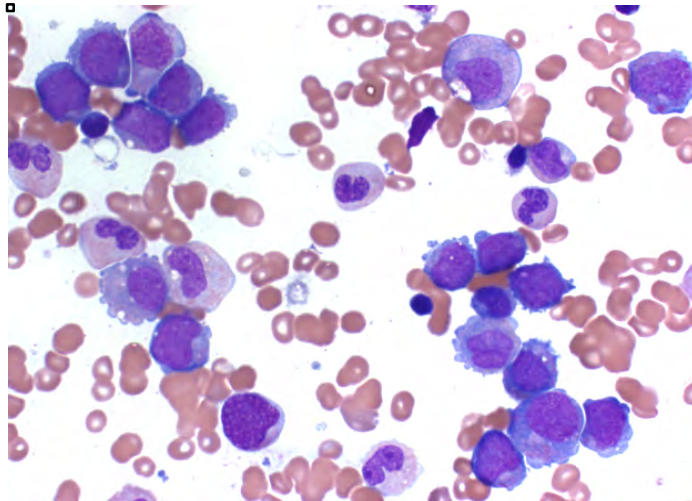
Day 0

Day 15

t(6;9)  
2nd relapse



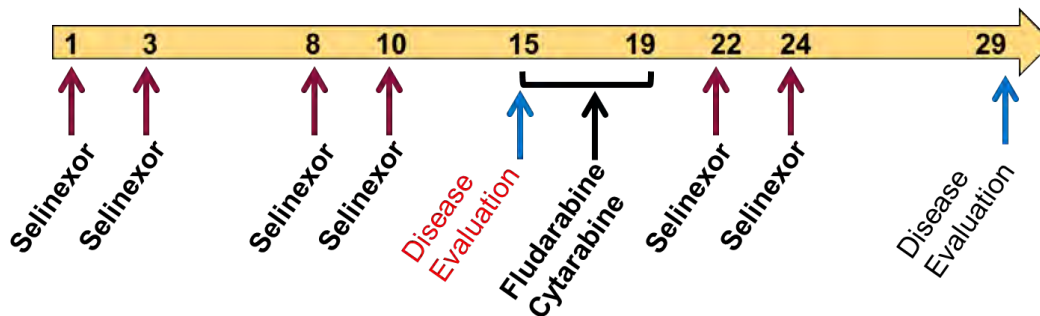
t(8;21)  
1<sup>st</sup> relapse



# MRD negative complete responses observed at day 15 and end of course 1

## Single Agent Response (Day 15)

- 2 patients with CR, both MRD negative
  - 1 was in second relapse, 1 had refractory disease



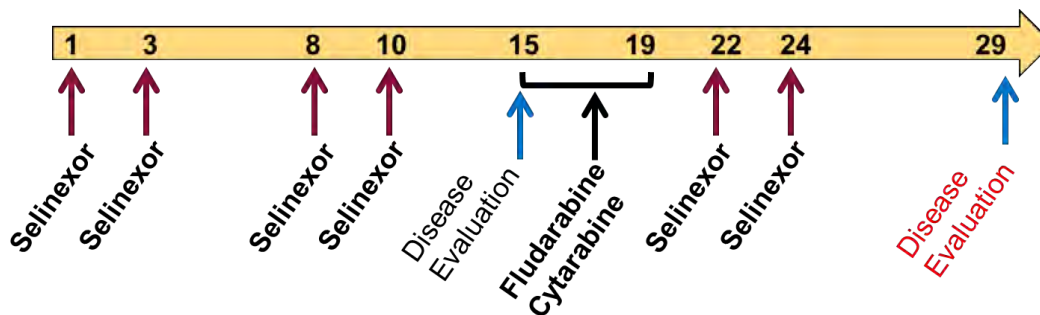
# MRD negative complete responses observed at day 15 and end of course 1

## Single Agent Response (Day 15)

- 2 patients with CR, both MRD negative
  - 1 was in second relapse, 1 had refractory disease

## Combination Response (End of course 1)

- 7/15 with CR or CRi
- 5 of responses were MRD negative



Can we predict responses?

# Summary

Selinexor in combination with fludarabine cytarabine:

1. Cerebellar toxicity is the dose limiting toxicity
2. PK / PD results show expected concentration, half life and on target effects
3. MRD negative complete responses were observed and response rate will be further explored in a Phase II study
4. The search for predictive markers continues...



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# References

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