A PHASE 1 DOSE ESCALATION STUDY OF THE ORAL SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE) SELINEXOR (KPT-330) IN PATIENTS (PTS) WITH RELAPSED / REFRACTORY ACUTE MYELOID LEUKEMIA (AML)

Ramiro Garzon[1], Ian Flinn[2], Jesus Berdeja[2], Daniel DeAngelo[3], Martha Wadleigh[3], Karen Yee[4], Andre Schuh[4], Morten M Sorensen[5], Peter Brown[5], Jeffrey Lancet[6], Bijal Shah[6], Martin Gutierrez[7], Nashat Gabrail[8], Nina Wagner-Johnston[9], William Blum[1], Robert Carlson[10], Boris Klebanov[10], Jean-Richard Saint-Martin[10], Eran Shacham[10], John McCartney[10], Tracey Marshall[10], Dilara McCauley[10], Sasha Rebello[11], Tami Rashal[10], Michael Kauffman[10], Sharon Shacham[10], Mansoor Mirza[10], Richard Stone[3]

(1) The Ohio State University, Columbus, OH, USA;
(2) Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA;
(3) Dana-Farber Cancer Institute, Boston, MA, USA
(4) Princess Margaret Cancer Center, Toronto, Canada;
(5) Dept. of Oncology or Dept. of Hematology, Rigshospitalet, Copenhagen, Denmark;
(6) H. Lee Moffitt Cancer Center & Research Institute Inc., Tampa, FL, USA;
(7) Hackensack University Medical Center, Hackensack, NJ, USA;
(8) Gabrail Cancer Center, Canton, OH, USA;
(9) Washington University School of Medicine, St. Louis, MO, USA;
(10) Karyopharm Therapeutics Inc, Natick, MA, USA;
(11) Ozmosis Research Toronto, Ontario, Canada

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Presenter Disclosures

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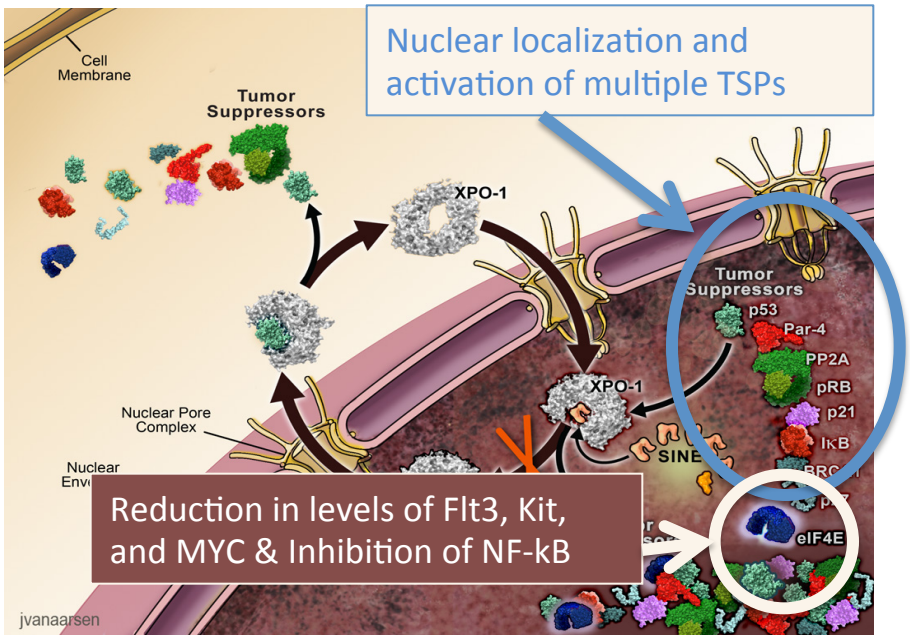
- **Consultant/Advisory Role:**
- **Stock Ownership:**
- **Honoraria:**
- **Research Funding:**
- **Expert Testimony:**
- **Other Remuneration:**

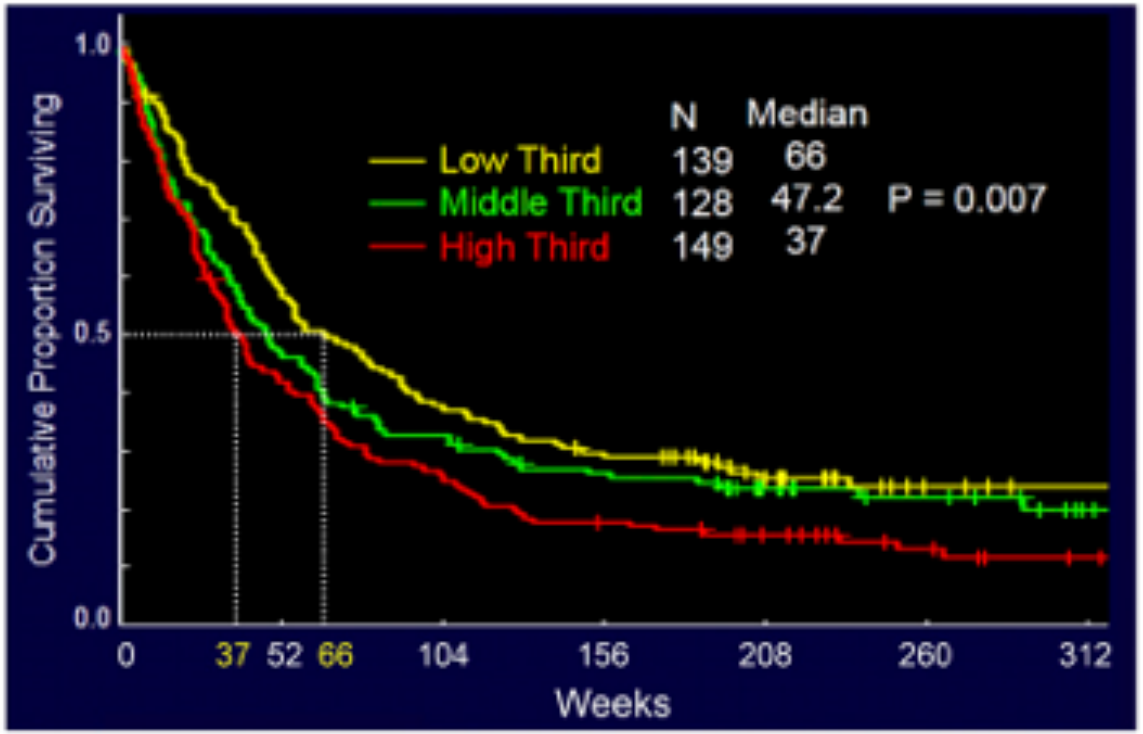
Selective Inhibitors of Nuclear Export (SINE)

- Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export
- XPO1 is elevated in Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), NHL and other malignancies
- Exportin 1 (XPO1, CRM1) is the *exclusive* nuclear exporter of most TSPs
- Selinexor (KPT-330) is a covalent, oral Selective Inhibitor of Nuclear Export (SINE) that blocks XPO1



- Selinexor forces the nuclear retention and activation of *multiple* TSPs
- Selinexor treatment reduces proto-oncogene proteins including Flt3, Kit and MYC and elevates IκB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in multiple preclinical models of AML and other hematologic malignancies, largely independent of cytogenetics
- We present summary data from ongoing first-in-human Phase 1 study of oral selinexor in hematological malignancies (NCT01607892)

XPO1 Elevation Predicts More Severe Disease and Poorer Survival in AML Patients



Higher levels of XPO1 were associated with:

- Higher marrow % blast (P< . 0.00001)
- White cell counts (P<0.0079)
- Peripheral blood % blast (P <0.00001)
- Absolute peripheral blood blast count (P<.0.0002)

Expression was lower in favorable cytogenetics compared with intermediate or unfavorable cytogenetics (P<0.029)

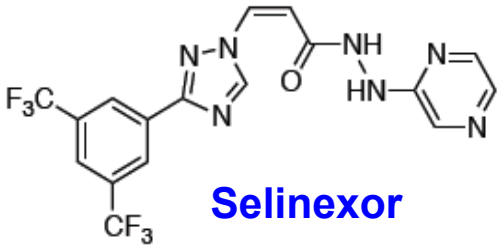
XPO1 levels were higher in patients with FLT3 mutations (P<0.003)

- Kaplan-Meier curves of multivariate analysis for overall survival in patients with AML
- High XPO1 expression is an independent predictor of overall survival in AML

Kojima et al, Blood, 2013

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)

- Novel, small molecule selective inhibitor of XPO1
- Oral drug given 2-3 times per week
- No known drug-drug interactions through CYP450s
- Potent anti-leukemic effects in vitro and in vivo in AML models
- Anti-tumor activity in ongoing Phase I and II studies in advanced hematologic and solid tumors



Selinexor

Selinexor Shows Marked Cytotoxicity Against AML and ALL Cell lines and Patients Cells

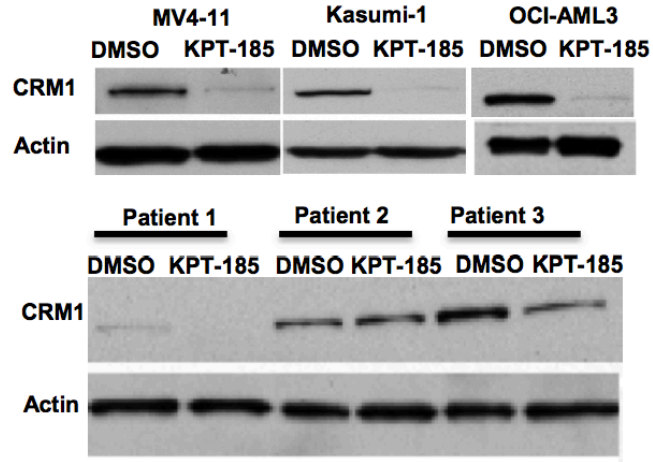
Origin	Cell Line	IC_{50} (nM)
Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)¥	MOLM-13	21
	OCI-AML2	41
	MV4-11	46
	SKNO-1	63
	SKM-1	88
	OCI-AML3	47
	HPB-ALL	55
	DND-41	203
	Jurkat	40
	MOLT-4	34
	SKW-3	123
	KOPTK-1	71
	HAL-01	115
	UOCB-1	85
Normal Cells*	**HEK293**	**1047**
	COS	**552**
	CHO	**1329**

Patient	Age	WHO	WBC*	Cytogenetics	NPM1	FLT3	IC50
1	27	Acute myelomonocytic leukemia	39	46,XX(20)	Mut (A)	WT	100nM
2	42	AML with maturation	26	46,XY(20)	Mut (A)	WT	100nM
3	62	AML without maturation	199	46,XX(20)	Mut (A)	WT	100nM
4	77	AML with maturation	85	46,XY(20)	Mut (A)	WT	50nM
5	62	AML with MDS related changes	8.8	46,XY(20)	WT	WT	500nM
6	52	AML with maturation	75	46,XY(20)	WT	WT	500nM
7	45	Acute myelomonocytic leukemia	53	46,XX(20)	WT	WT	500nM
8	56	Acute myelomonocytic leukemia	69	46,XX(20)	WT	ITD+	500nM
9	20	AML with inv(16)	45	46,XX,**inv(16)**	WT	WT	500nM
10	53	Acute myelomonocytic leukemia	79	46,XX(20)	WT	ITD+	500nM
11	85	AML without maturation	66	46,XY(20)	WT	ITD+	500nM
12	52	AML with t(8;21)	2.9	45,X,-X,**t(8;21)**	WT	WT	500nM
13	50	AML with t(8;21)	15.6	45,X,-Y,**t(8;21)**	WT	WT	500nM

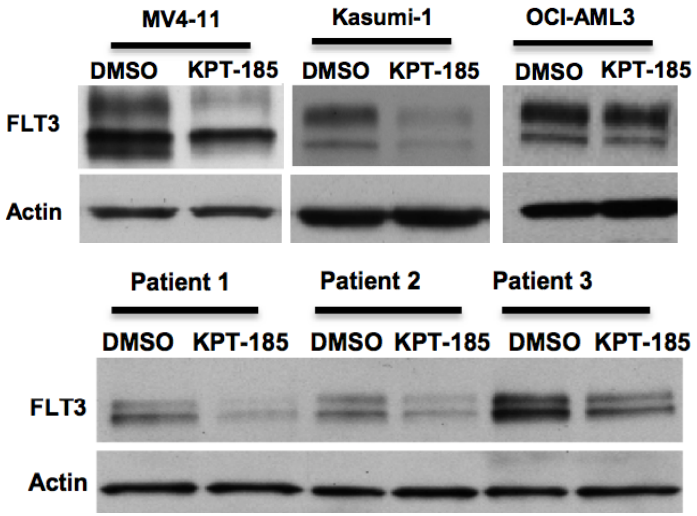
Ranganathan et al, Blood 2012
Etchin et al, Leukemia 2012

Selinexor Increases p53 levels and Reduces Flt3 and c-KIT Expression in AML cells

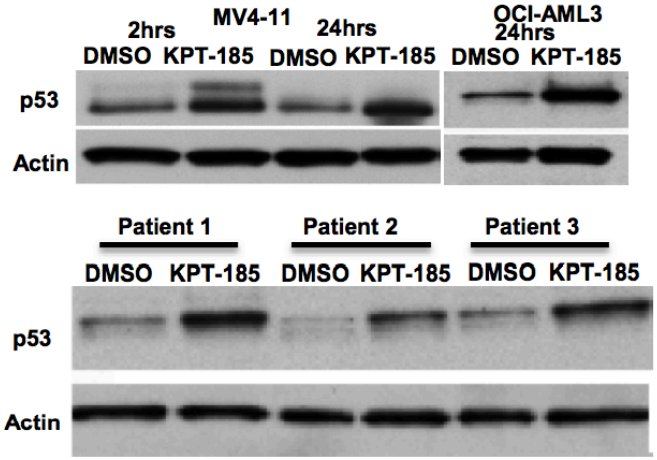
XPO1



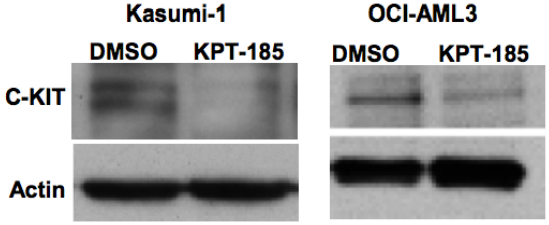
FLT3



p53



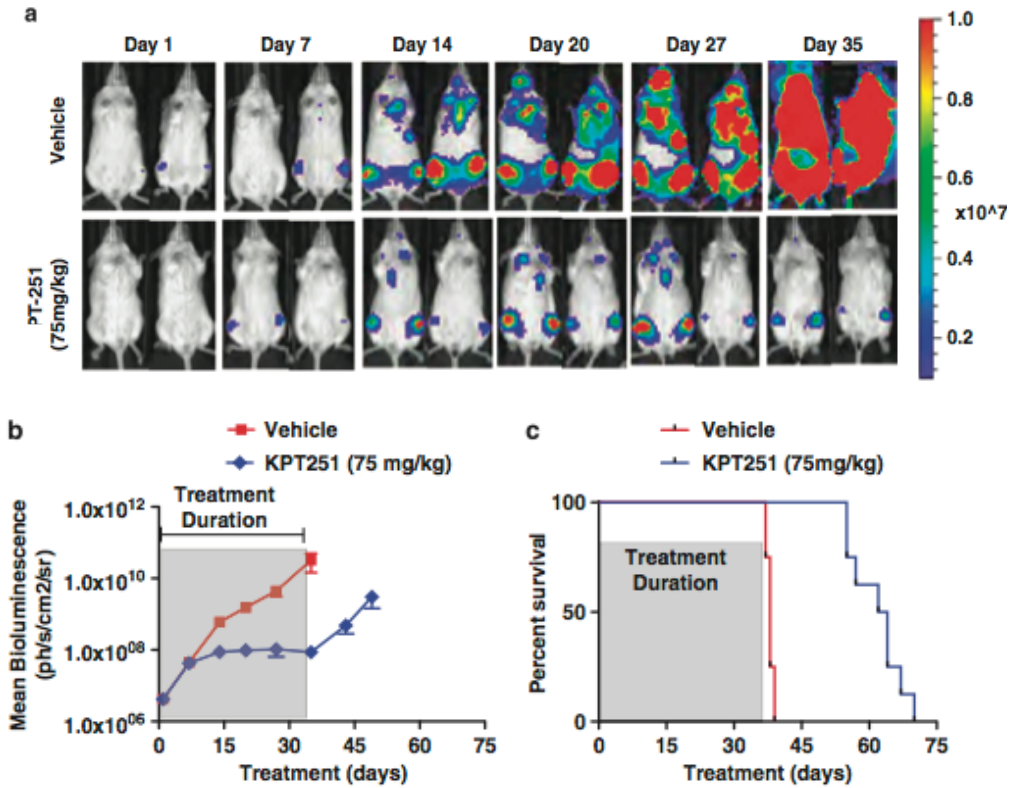
C-KIT



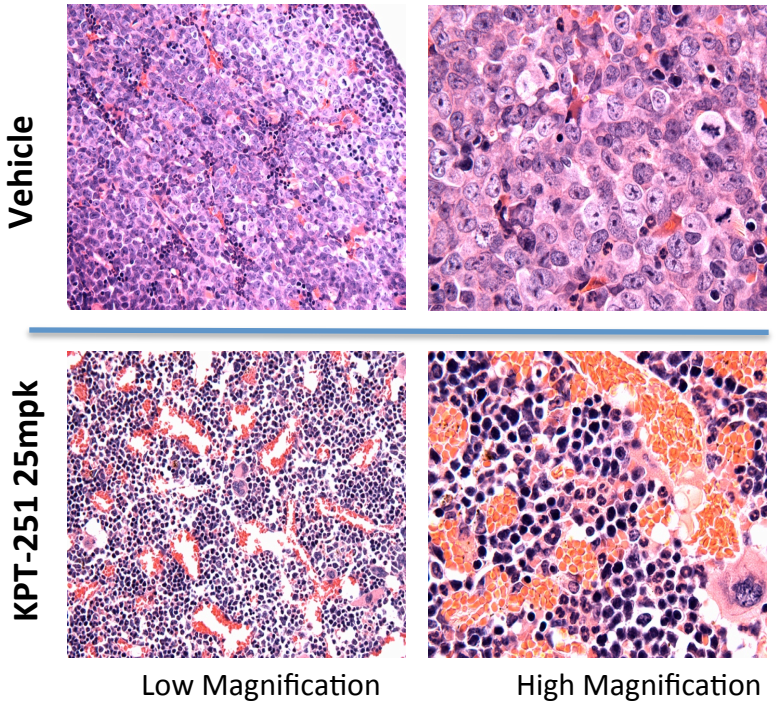
Ranganathan et al, Blood 2012

SINEs Kills AML but not Normal Hematopoietic Cells; Maintaining Near-Normal Bone Marrow

MOLT-4 (FLT3 ITD) AML Leukemograft Mice

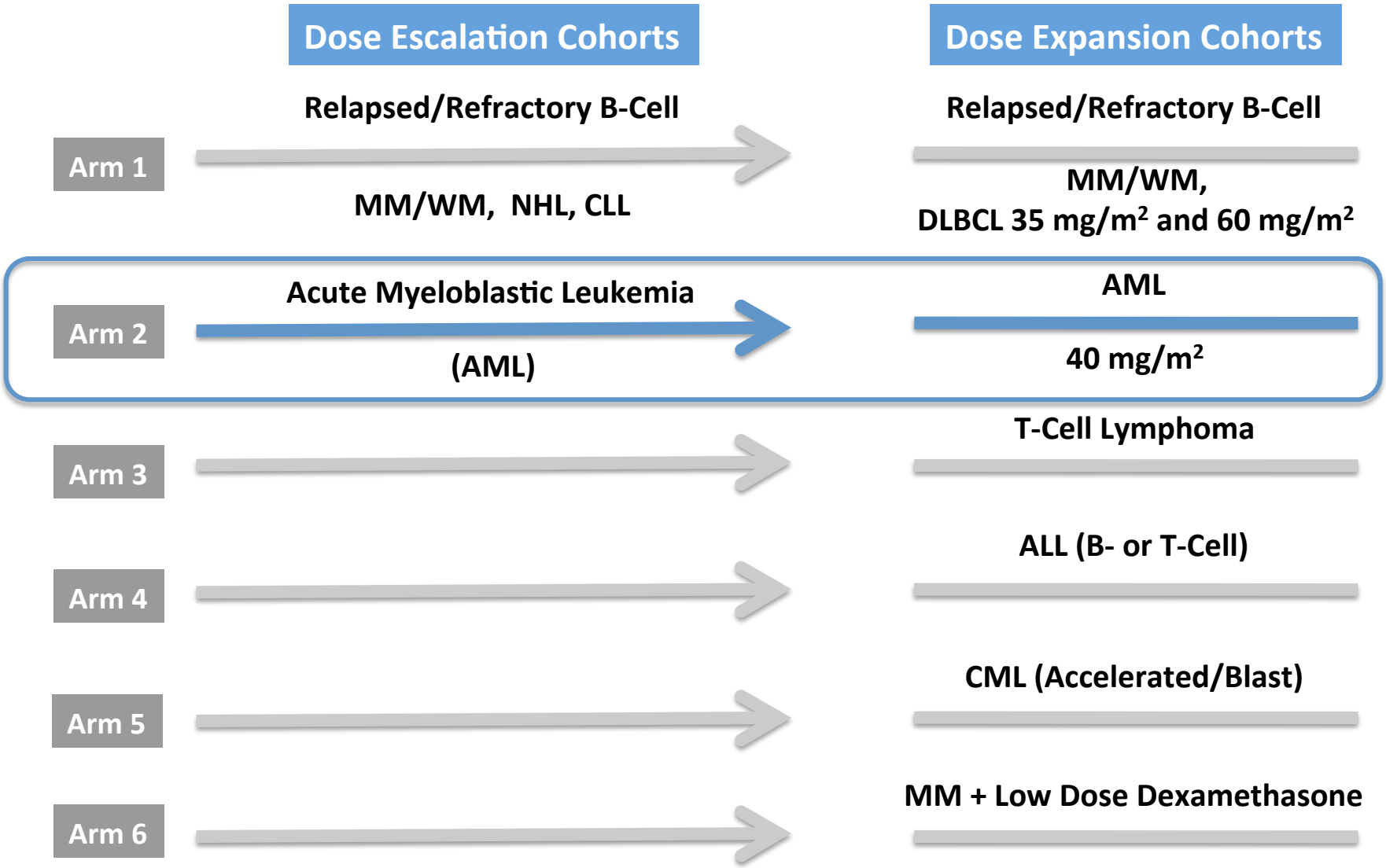


Bone Marrow: H&E Stain



Etchin et al, Leukemia 2012

Selinexor (KPT-330) Phase 1 Haematological Malignancies Study (NCT01607892)



Selinexor Phase 1 Study

- Objectives (modified 3+3 design)
  - Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of selinexor;
  - Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response; confirmation of RP2D of KPT-330

- Selinexor Dosing
  - Doses 16.8–70mg/m^2
  - Doses 16.8-30mg/m^2: 10 doses/cycle (2-3 doses/week)
  - Doses 35-70mg/m^2: 8 doses/cycle (twice weekly)
  - Also evaluating 4 doses/cycle (once weekly) at 70mg/m^2

- Major Eligibility Criteria:
  - Patients (ECOG ≤1) with relapsed/refractory hematologic tumors with no available standard treatments
  - Documented AML progression at study entry

Selinexor AML Phase 1 Study: Patient Characteristics

Characteristic	N=65
Mean Age (range)	67 (24 – 89)
Male /Female	34 Males : 31 Females
Mean Prior Lines of Treatment (range)	3 (1 – 7)
ECOG performance status, 0/1	18 / 47

Therapy Line for Disease	
2nd Line AML	15 (23%)
3rd Line AML	13 (20%)
> 3rd Line AML	28 (43%)
Unknown	9 (14%)

AML Cytogenetic Risk	
Favorable	10 (15%)
Intermediate	28 (43%)
Adverse	23 (36%)
Unknown	4 (6%)

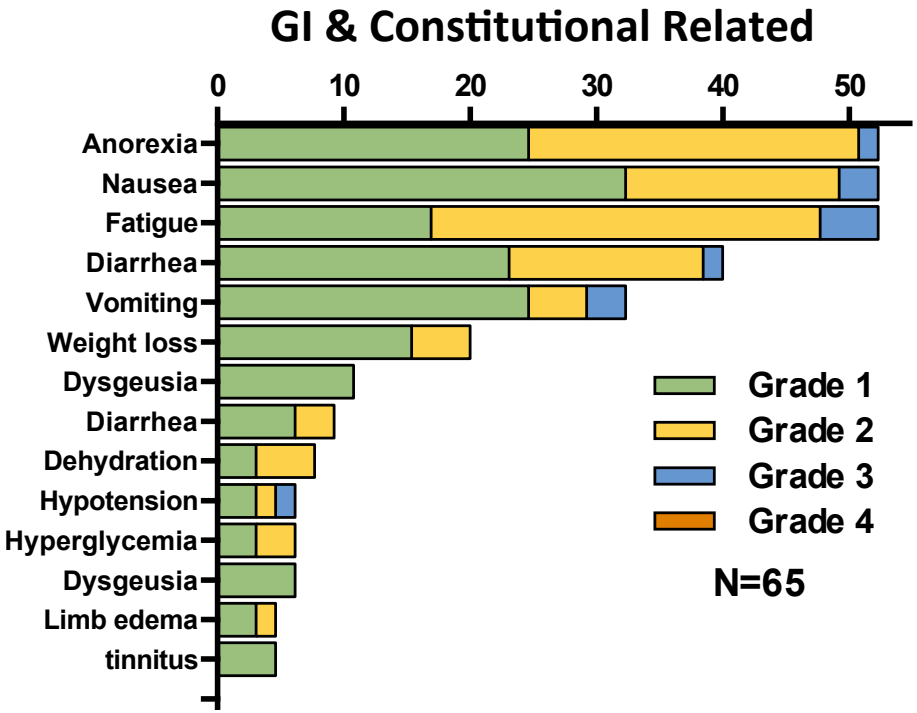
Selinexor AML Phase 1: DLT Criteria and Study Design

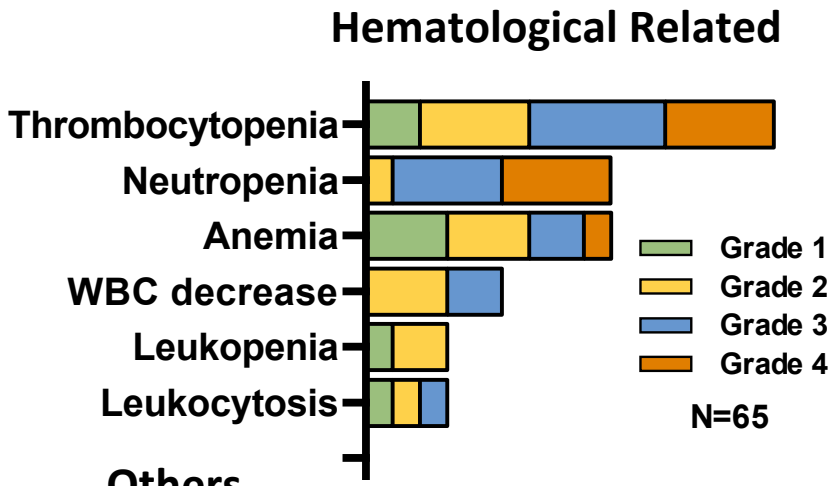
- ≥ 3 missed doses in 28 days at target dose
- Discontinuation of a patient due to a toxicity in Cycle 1
- Non Hematologic:
  - Grade ≥ 3 (nausea/ vomiting, electrolyte imbalances must be supported first and AST/ALT lasting more than 7 days)
  - Grade ≥ 3 fatigue lasting ≥5 days while taking supportive care

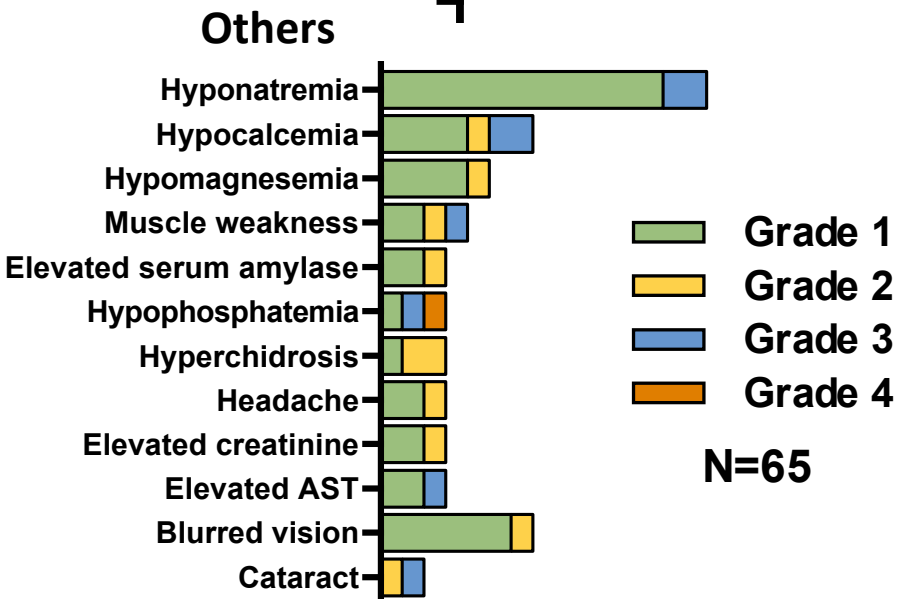
Cohort #	Dose Level (mg/m^2)	Doses per cycle	DLT Eval Patients	Patients with DLT
1	16.8	10	4	0
2	23	10	6	0
3	30	10	4	0
1	30	8	4	0
2	40	8	3	0
3	55	8	3	0
4	70	8	3	0
Expansion	40	8	--	–

- No DLT were observed up to doses of 70 mg/m^2
- Recommended Phase 2 Dose is 55-65 mg/m^2 based on results from ongoing Phase 1 in patients with solid tumors

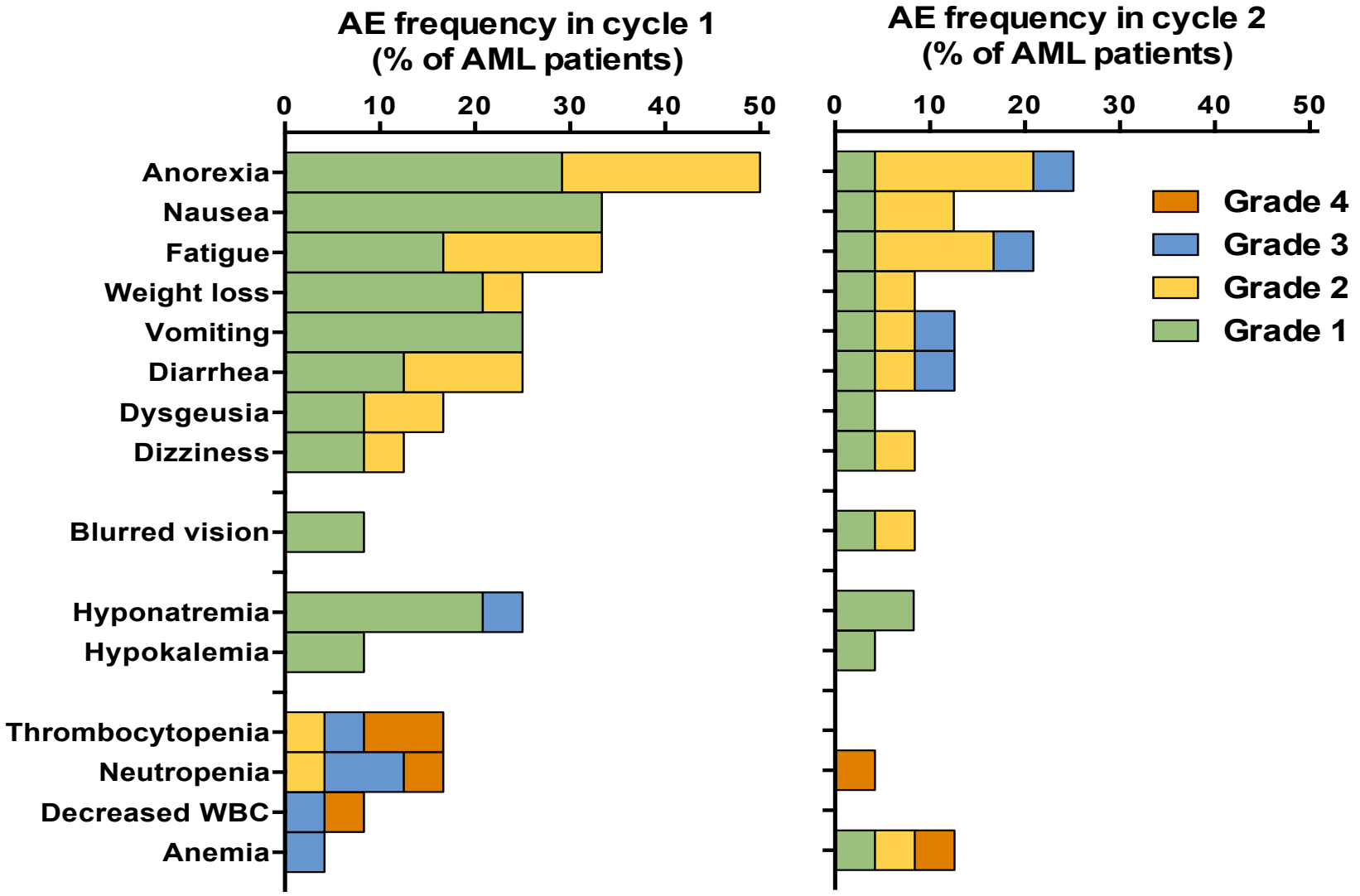
Selinexor AML Phase 1 Study: Drug Related Adverse Events



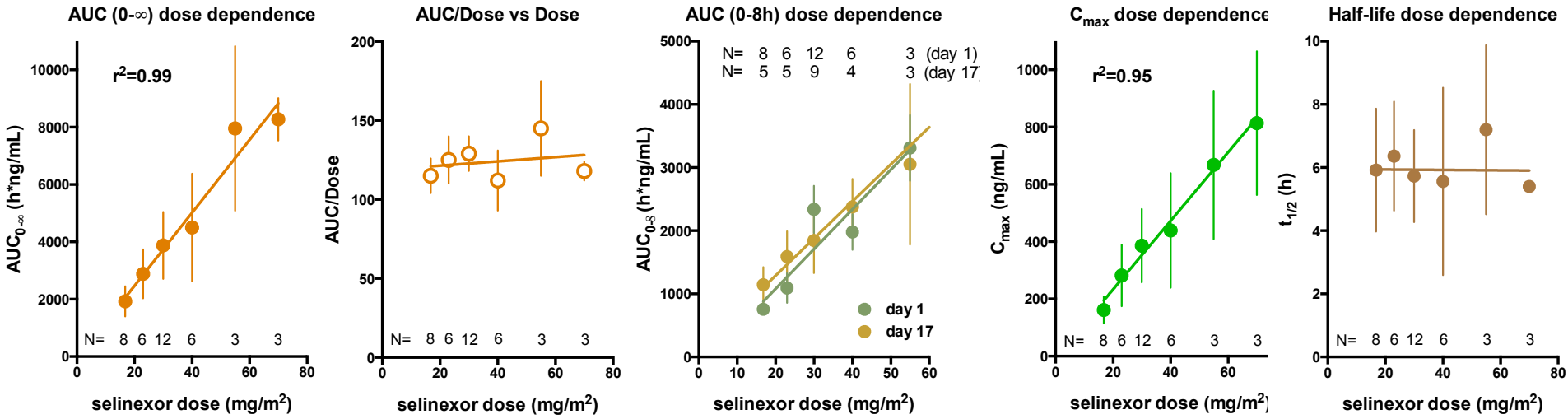




Selinexor AML Phase 1 Study: Common Adverse Events By Cycle



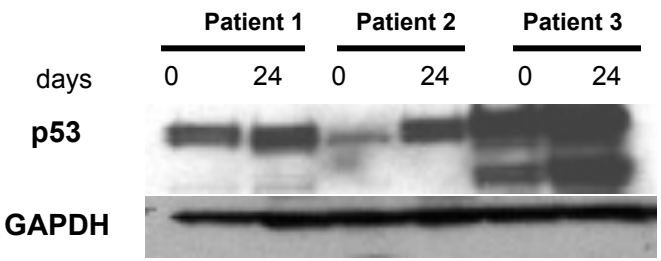
Selinexor AML Phase 1 Study: Pharmacokinetics



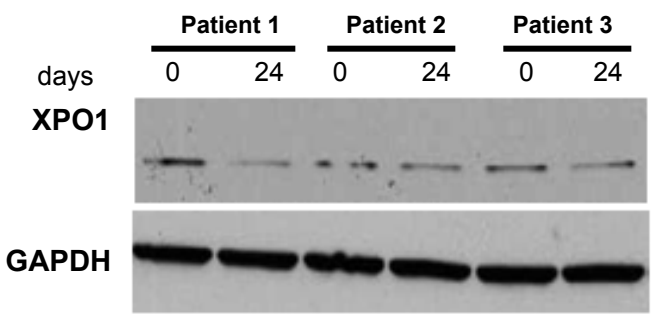
- Plasma selinexor exposure (AUC/Cmax) displayed dose proportionality in a linear fashion
- No evidence of accumulation was observed across all doses
- Terminal half life was ~5 –7 hours and independent of dose

Selinexor-Induced Increase of p53 and Reduction in XPO1, Flt3 and KIT protein Levels

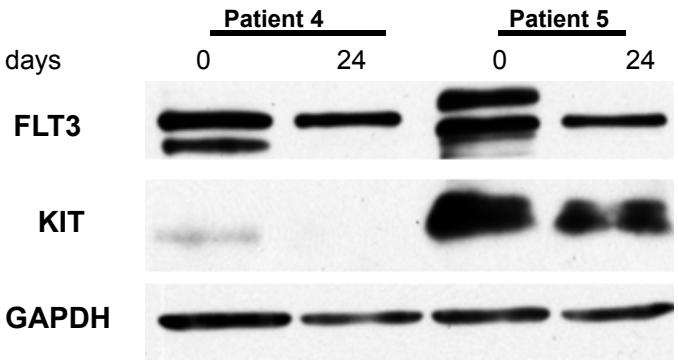
Increased P53 Levels



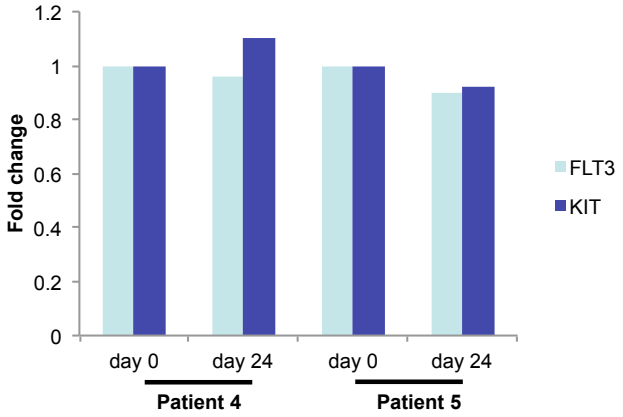
Reduced XPO1 Levels



Reduced Flt3 and KIT protein Levels



No Change in Flt3 and KIT mRNA Levels



Selinexor AML Phase 1 Study: Activity in Relapsed/ Refractory AML

Best Responses in Patients with AML as 10-June-2014									
N	**DCR**	**ORR**	**CR**	**CR(i)**	**PR**	**MLFS**	**SD**	**PD**	**NE**
65	32	10	5	2	1	2	22	16	17
%	49%	15%	8%	3%	2%	3%	34%	25%	26%

DCR=Disease Control Rate (CR+CR(i)+PR+MLFS+SD), **ORR**=Overall Response Rate (CR+CR(i)+PR+MLFS), **CR**=Complete Response, **CR(i)**=Complete Response Incomplete, **MLFS**=Morphological Leukemia Free State, **SD**=Stable Disease, **PD**=Progressive Disease, **NE**=Non Evaluable

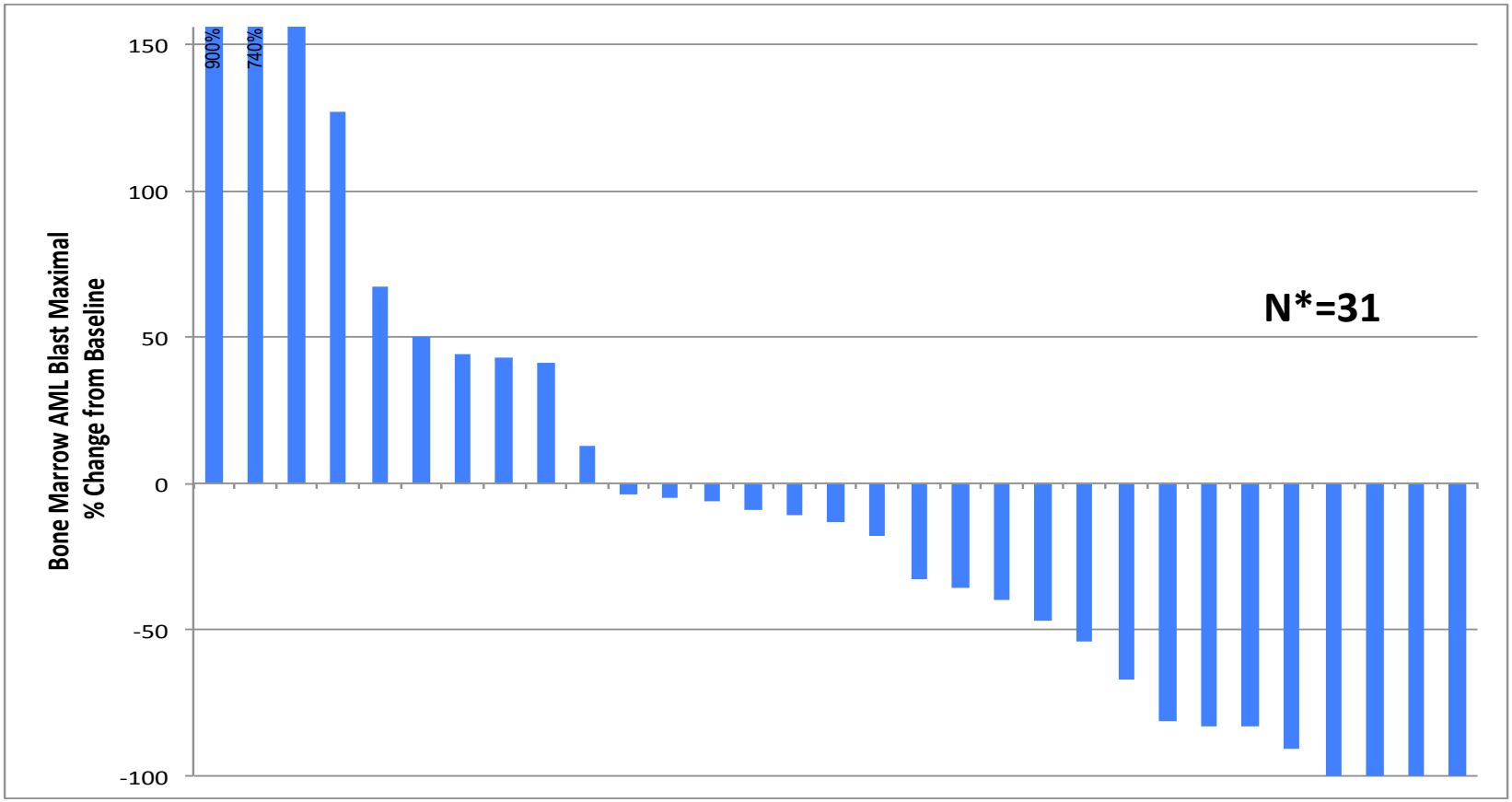
Selinexor AML Phase 1 Study: Patients with CR, MLFS, & PR Characteristics

Patient ID	Age	Dose (mg/m^2)	Doses/ Cycle	Prior MDS	Flt3	NPM	Cytogenic Risk	Prior Therapies	Response	Days on Study
138	**39**	40	8	N	N	N	Favorable	DAU, CYT, MITO,	**CR**	178
111	**70**	23	10	Y	N	N	Intermediate	DEC, CYT	**CR**	157
505	**82**	40	8	N	N	N	Adverse	CYT	**CR**	142
501	**71**	16.8	10	N	Y	Y	Intermediate	DAU, CYT	**CR**	113
133	**81**	40	8	N	N	N	Favorable	DEC	**CR**	78
102	**70**	16.8	10	N	N	N	Intermediate	VID, DEC	**CR(i)**	81
150	**61**	40	8	N	Unk	Unk	Intermediate	DAU, CYT	**CR(i)**	119+
121	**77**	30	8	N	N	N	Adverse	VID, CYT	**MLFS**	170
155	**83**	40	8	Y	N	N	Intermediate	VID, DEC	**MLFS**	92+
114	**70**	30	8	N	N	N	Intermediate	CYT, IDA	**PR**	87

Selinexor AML Phase 1 Study: Patients with Stable Disease Characteristics

Patient ID	Age	Dose (mg/m^2)	Doses/ Cycle	Prior MDS	Flt3	NPM	Cytogenic Risk	Prior Therapies	Days on Study
110	**73**	23	10	N	N	N	Favorable	CYT, FLU, IDA, FIL, VID, DAU, MIT	312
147	**79**	40	8	Y	N	N	Intermediate	No Priors	132+
149	**63**	70	8	N	N	N	Intermediate	DAU, CYT, EPO, MIT, ROS	120+
108	**67**	16.8	10	N	N	N	Intermediate	CYT, DAU, VID	93
113	**88**	23	10	N	N	N	Unk	VID	74
156	**49**	70	8	N	N	N	Adverse	CYT, DAU	90
126	**89**	30	10	N	N	N	Adverse	VID, DEC	65
507	**69**	70	8	Y	N	N	Intermediate	DAU, CYT	62
136	**49**	55	8	N	Unk	Unk	Adverse	LEN, IDA, CYT, DEC	58
148	**72**	40	8	Y	N	N	Intermediate	DAU, CYT	56
142	**37**	55	8	N	N	N	Favorable	DAU, CYT, VOS, FLU, IDA	56

Selinexor AML Phase 1 Study: Maximal % Change in Bone Marrow AML Blast Cells



BM Blast cells were evaluated at screening and at the end of each cycle

*Excludes 34 patients who did not have a post treatment bone marrow biopsy

Conclusions

- Selinexor (KPT-330) is a Novel, oral SINE that can safely be given as monotherapy to patients with relapsed/refractory AML
  - Main toxicities: fatigue, anorexia, nausea
  - Single agent Phase 2/3 Recommended Dose is 50-65 mg/m^2 PO BIW
  - Maximum Tolerated Dose: 70 mg/m^2 PO BIW
  - Appetite stimulants permit long term use of selinexor

- Selinexor has favorable PK and induces nuclear localization of Tumor Suppressor Proteins (TSPs) in patients' AML cells

- Selinexor demonstrates responses and durable stable disease in heavily pretreated AML patients, independent of underlying genetic abnormalities, including those with medium and high risk AML

- SOPRA is a Randomized Phase 2 study in patients ≥60 years old with relapsed/refractory AML that are unfit for intensive chemotherapy or transplantation is ongoing (NCT02088541)

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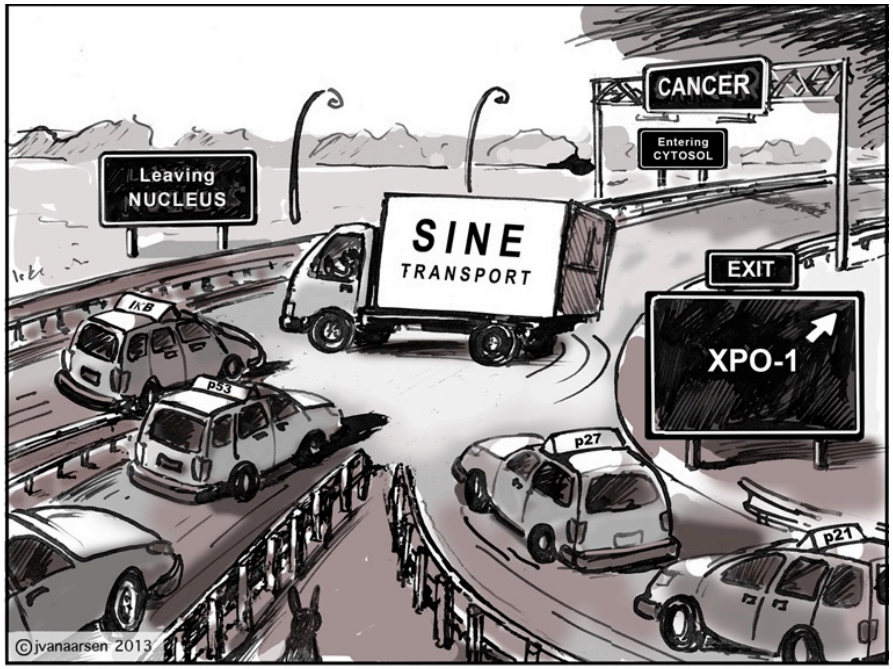
    - Dana Farber Cancer Institute
    - Gabrail Cancer Center Research
    - Sarah Cannon Research Institute
    - Tom Baker Cancer Centre
    - Washington University; St Louis, MO



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