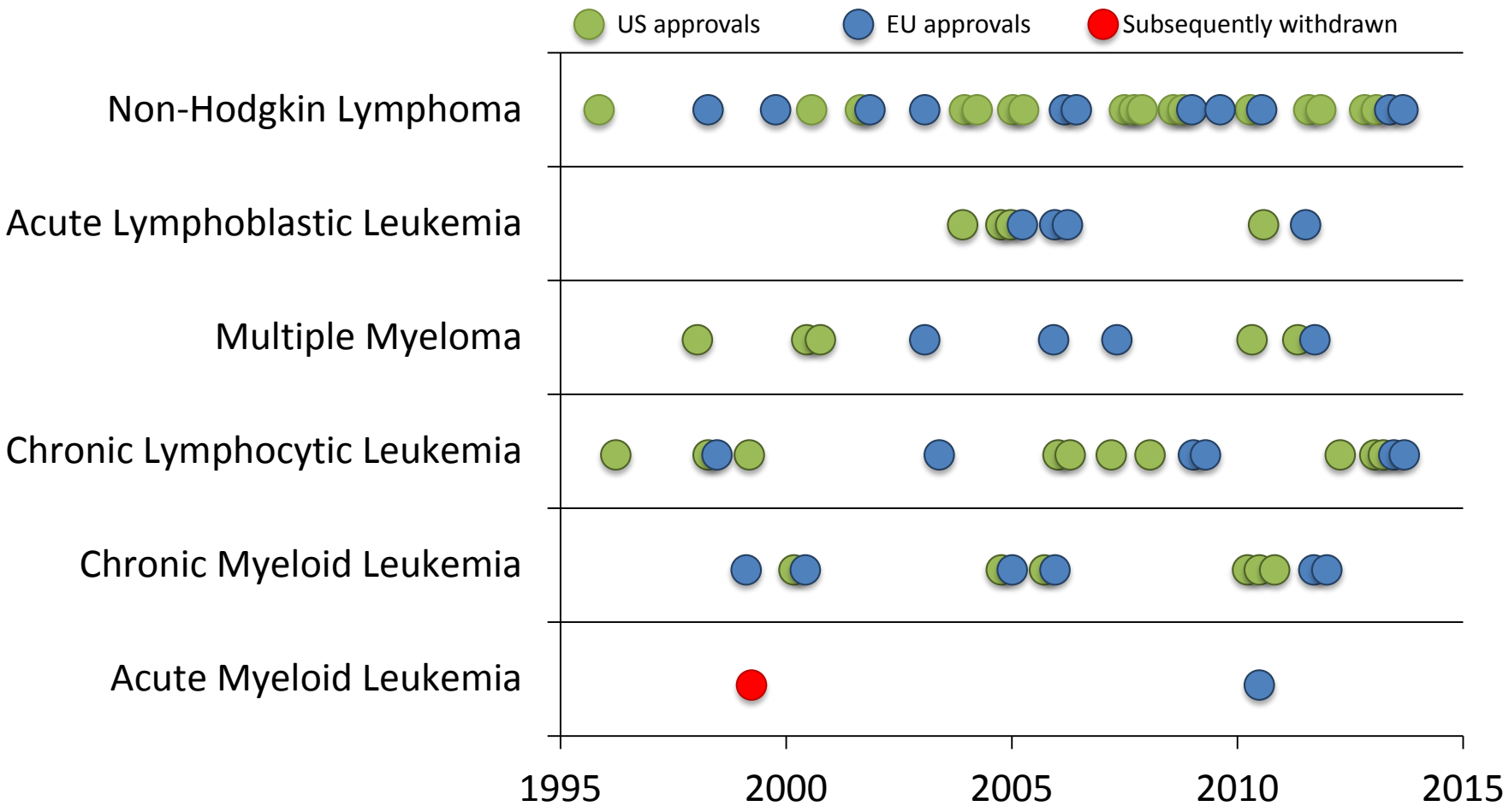
Targeting CRM1 in AML

Gert Ossenkoppele & colleagues
VU University Medical Center
Amsterdam

Approved Treatment Options for AML Compared to Other Hematologic Malignancies

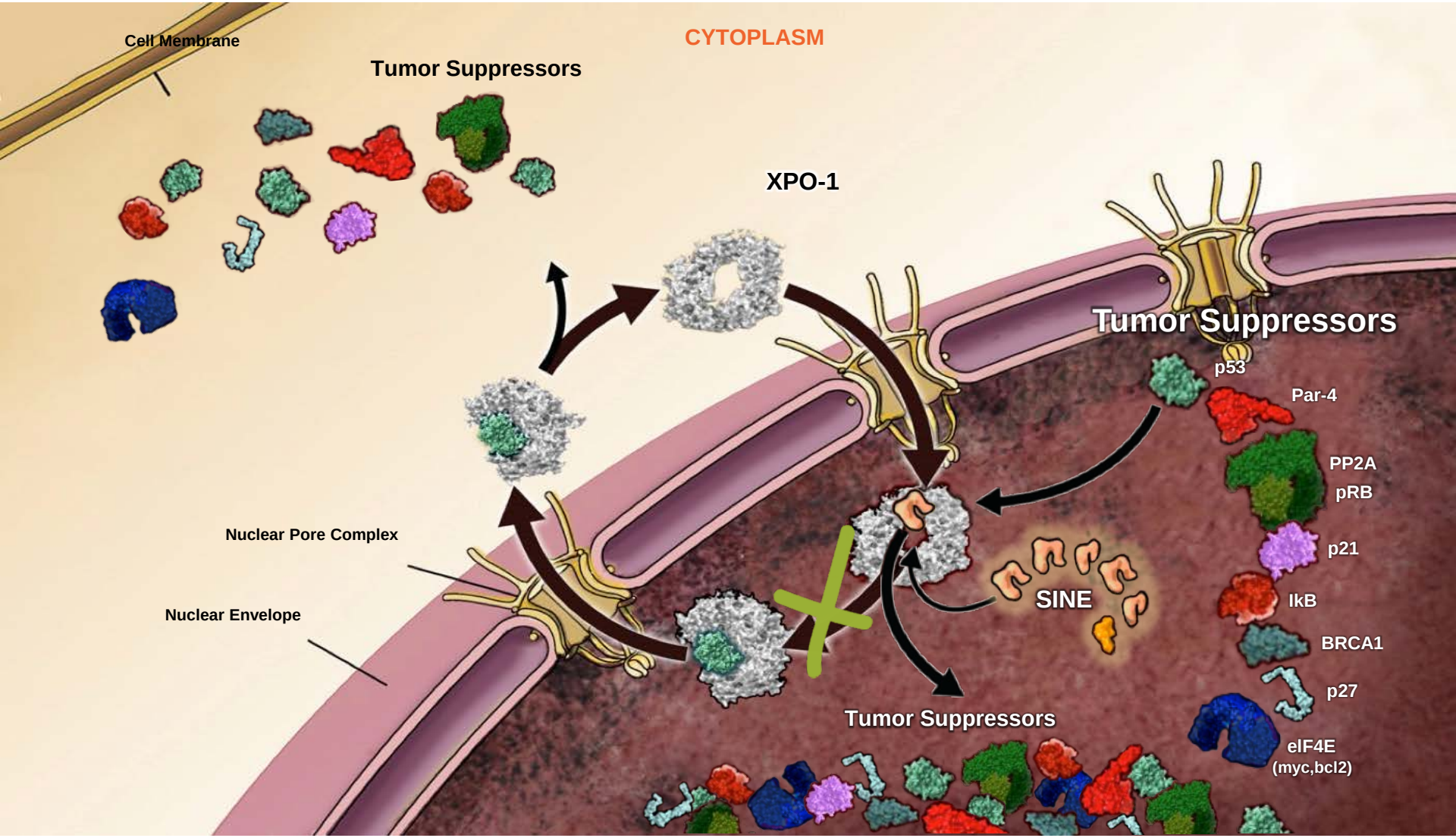


1. NCI Drug Info. http://www.cancer.gov/cancertopics/druginfo. 2. EMA Drug Approvals. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=. 3. FDA Drug Approvals. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.. 3. NCCN clinical practice guidelines in oncology: acute myeloid leukemia. National Comprehensive Cancer Network website. V.2.2014. http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf

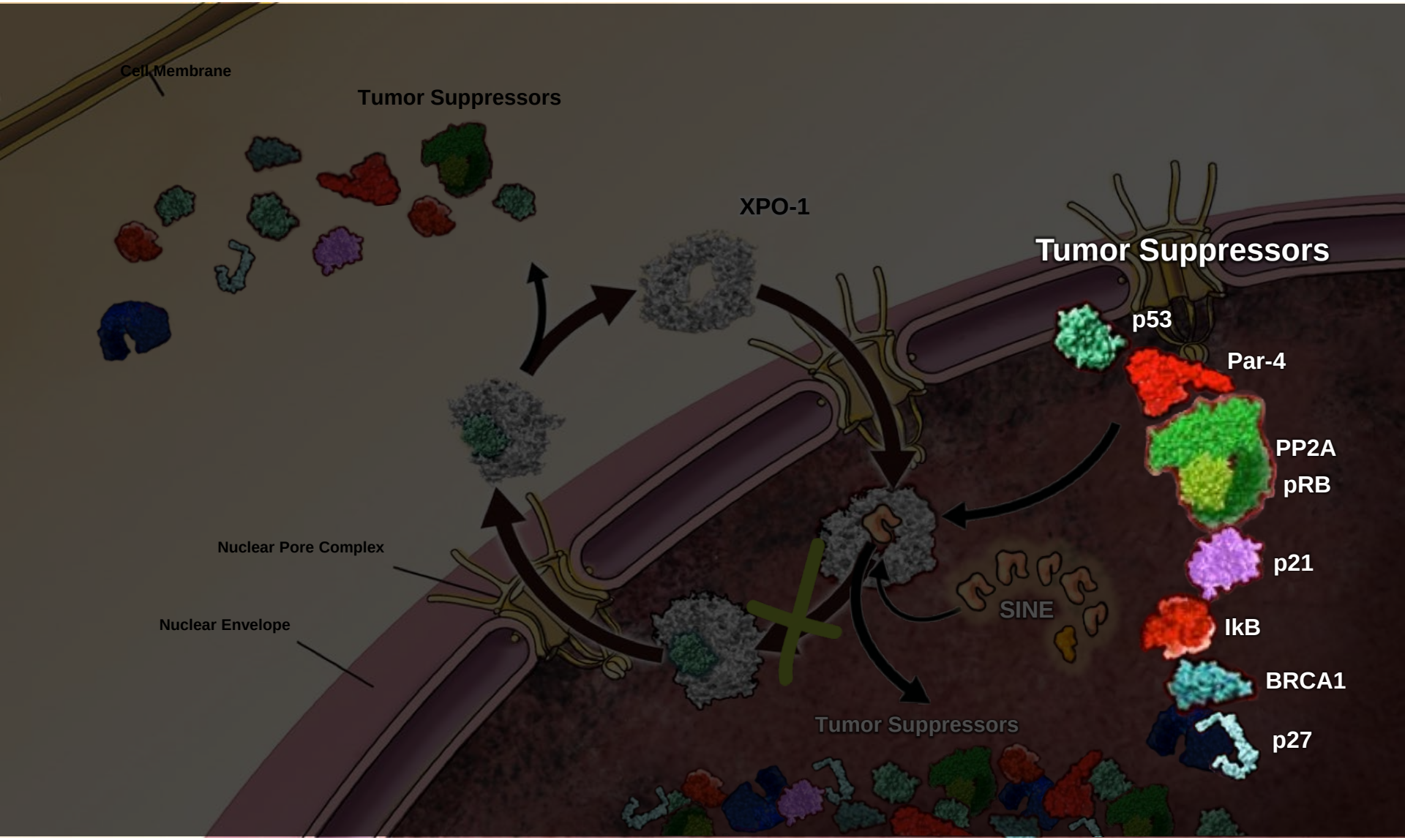
Selective Inhibitors of Nuclear Export(SINE)

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

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



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



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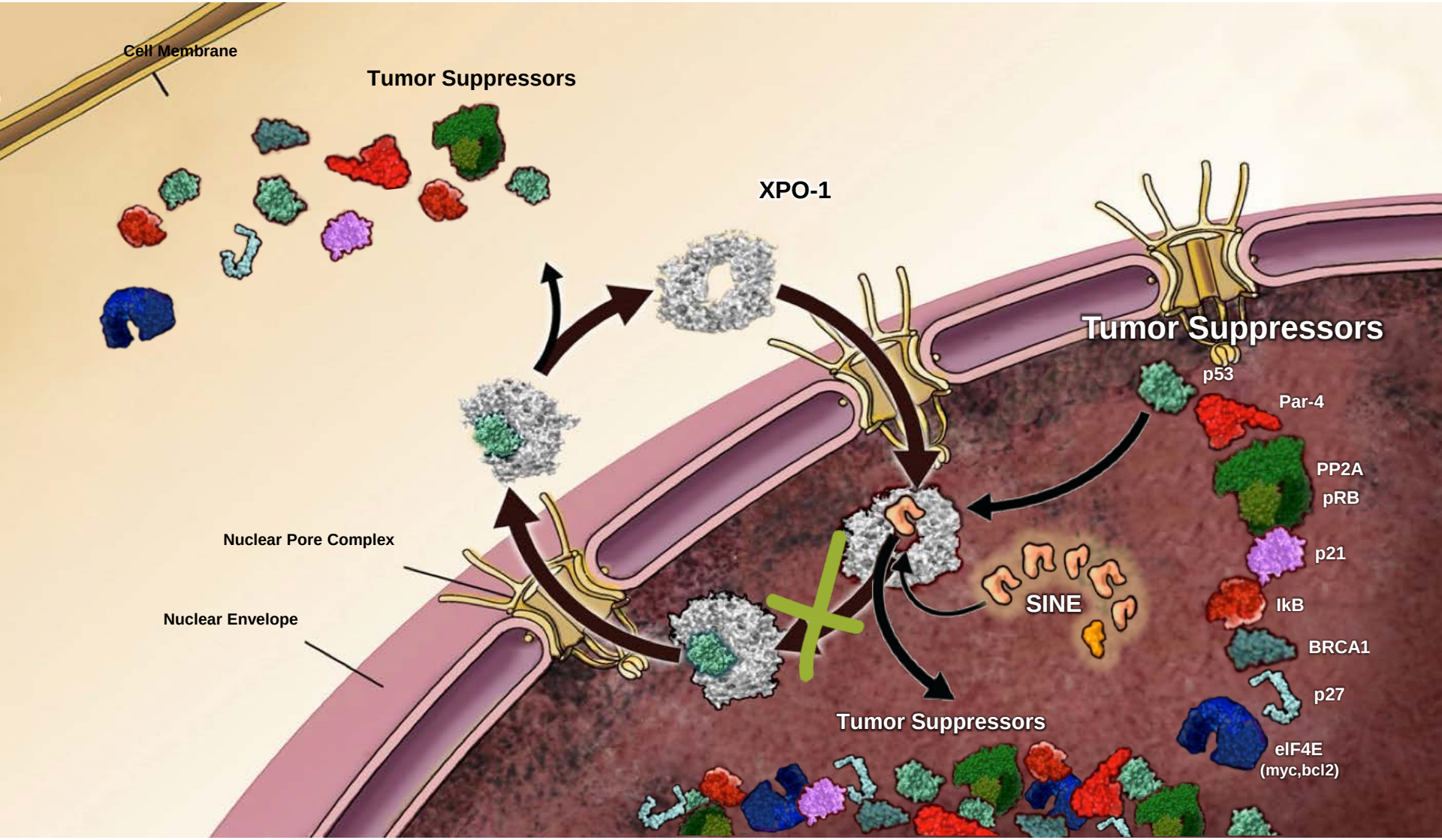
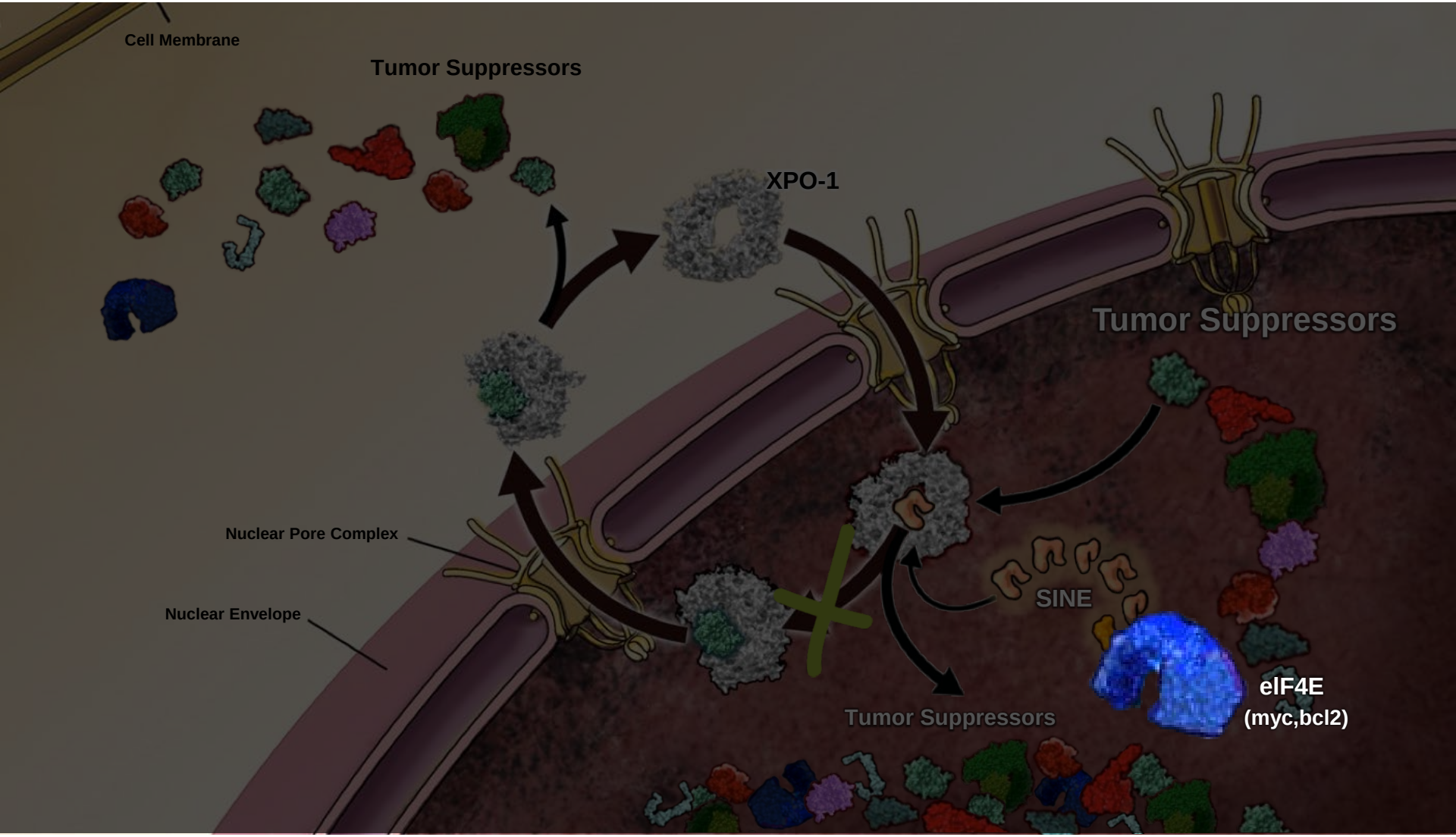
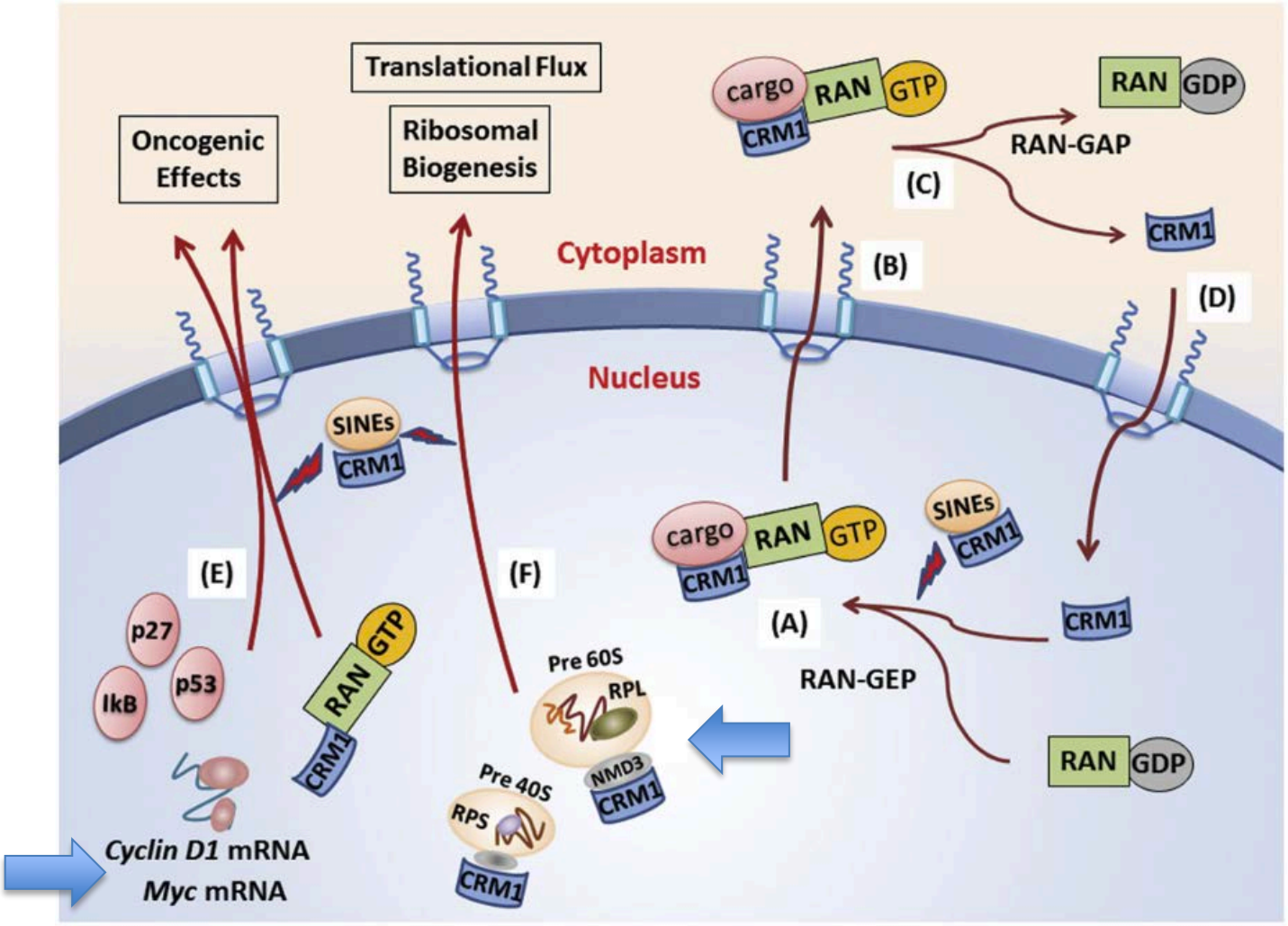


Selinexor: Novel Anti-Cancer Agent: Restores Tumor Suppressors & Reduces Oncoproteins

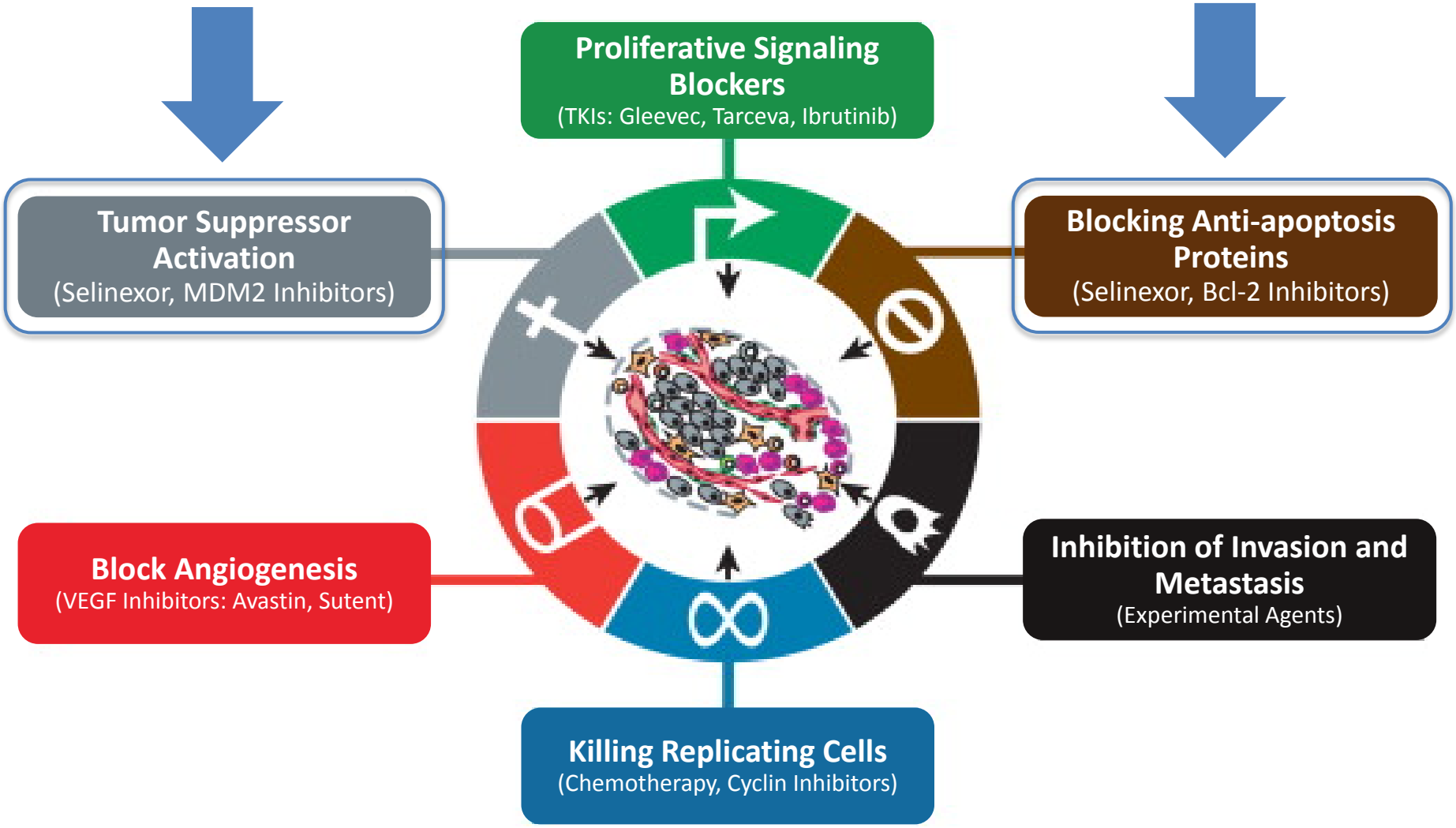


SINE Mechanisms of Action Beyond TSPs: Oncoproteins, Ribosomes



From Ishizawa et al., 2015. Pharmacol & Therap.

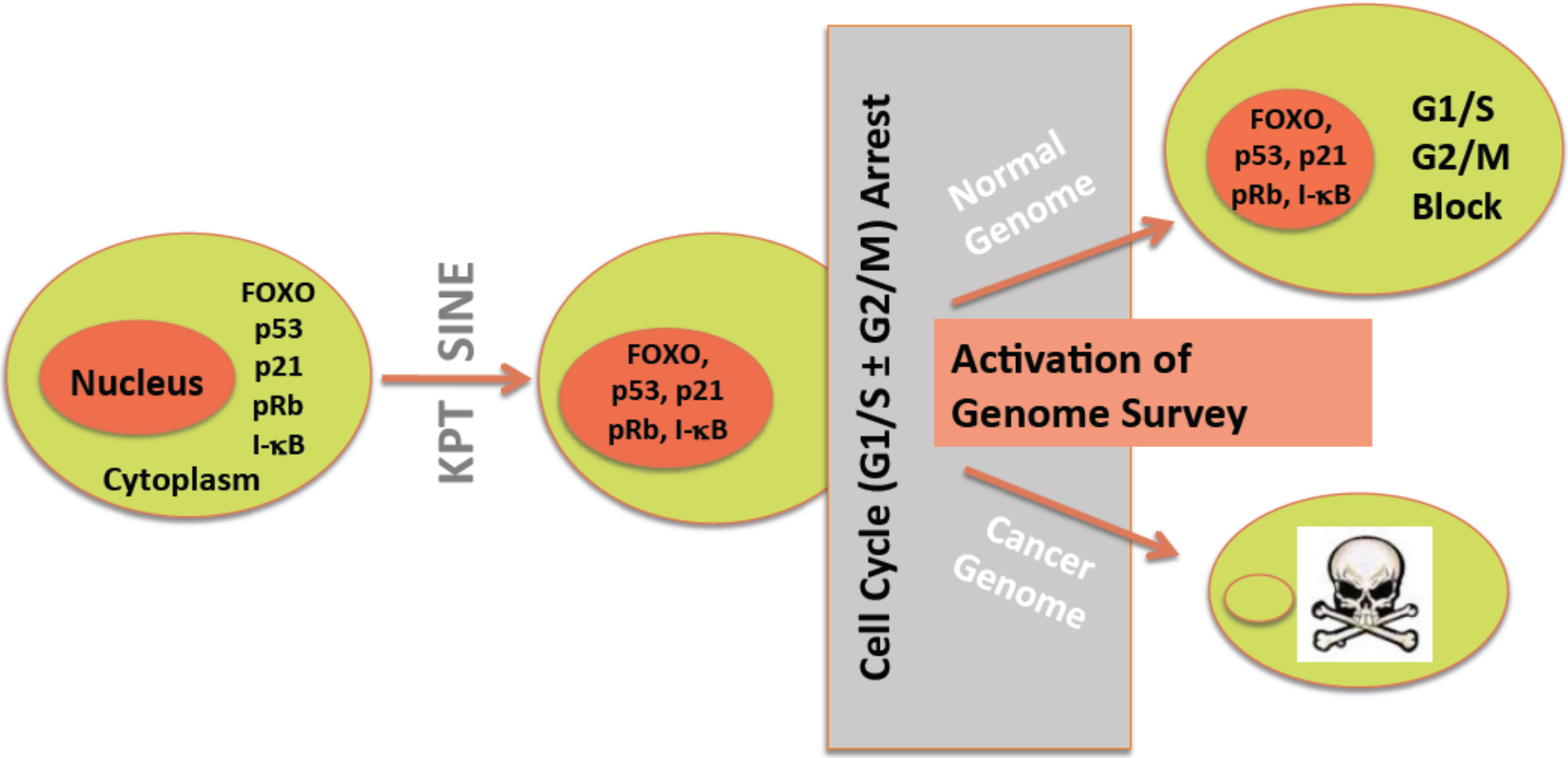
SINE Compounds Target the Hallmarks of Cancer Through Unique Dual Pathways



Modified from: Hanahan & Weinberg 2012, Cell, volume 144, issue 5 2011 646 - 674

SINE XPO1 Antagonists Kill Tumor Cells:

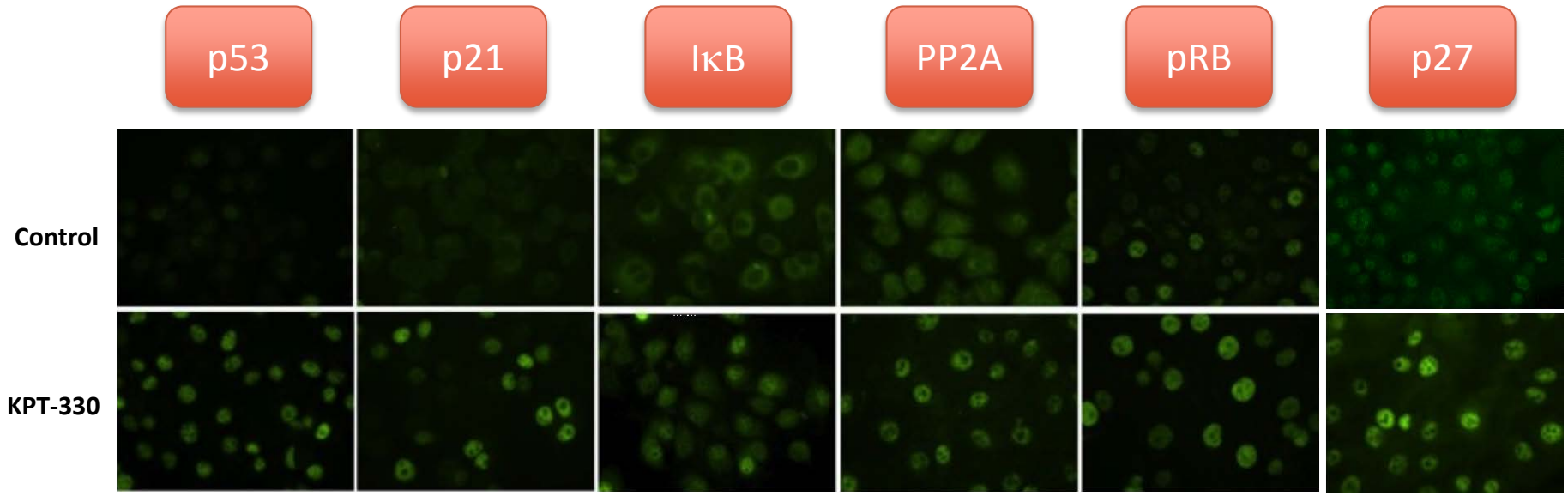
Normal cells undergo transient, reversible cell cycle block



Selinexor Forces Nuclear Retention, Increases Nuclear Levels of, and Activates Many TSPs

XPO1 Inhibition

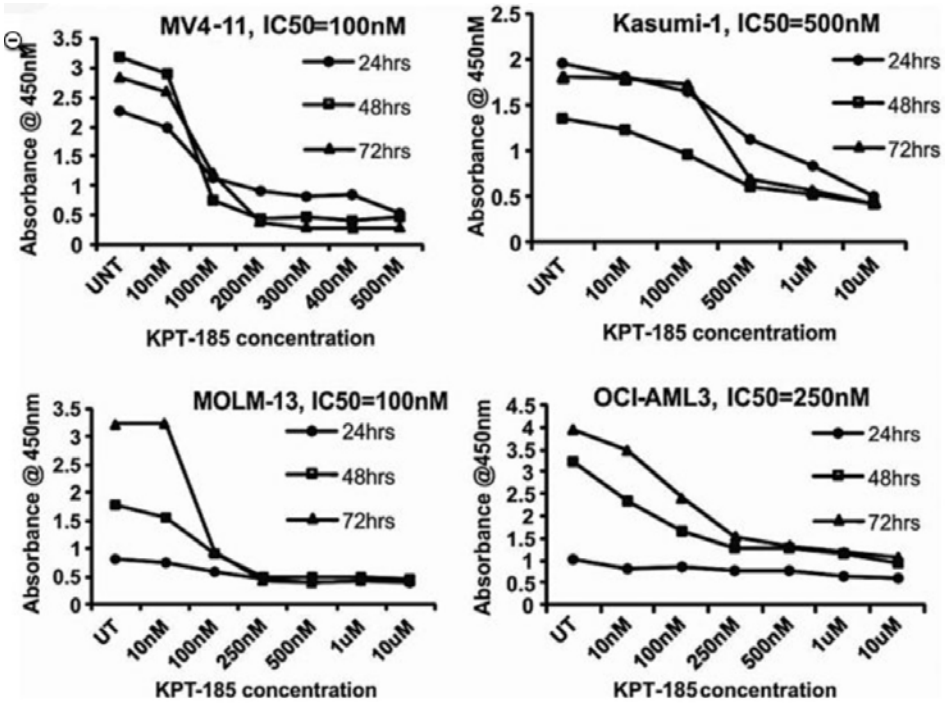
Forced Nuclear Retention & Activation by Blocking Nuclear Export

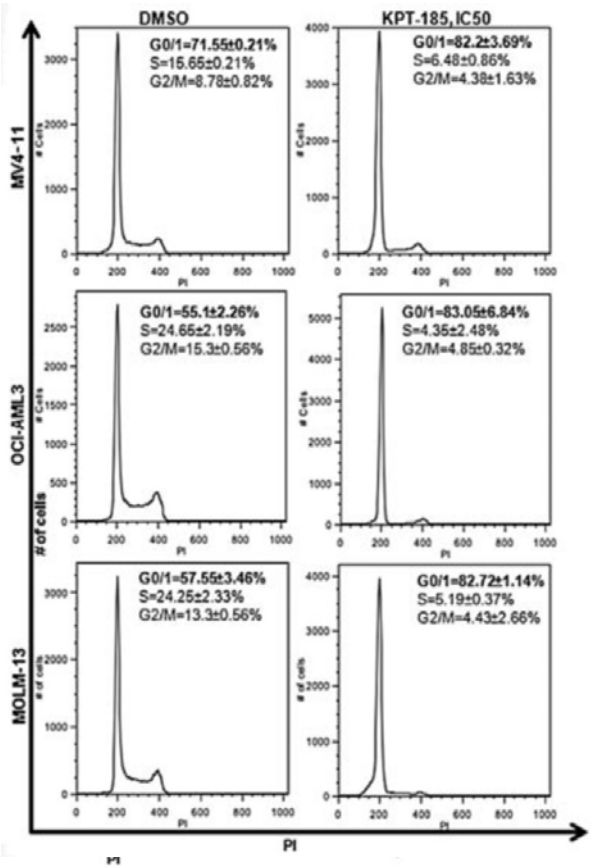


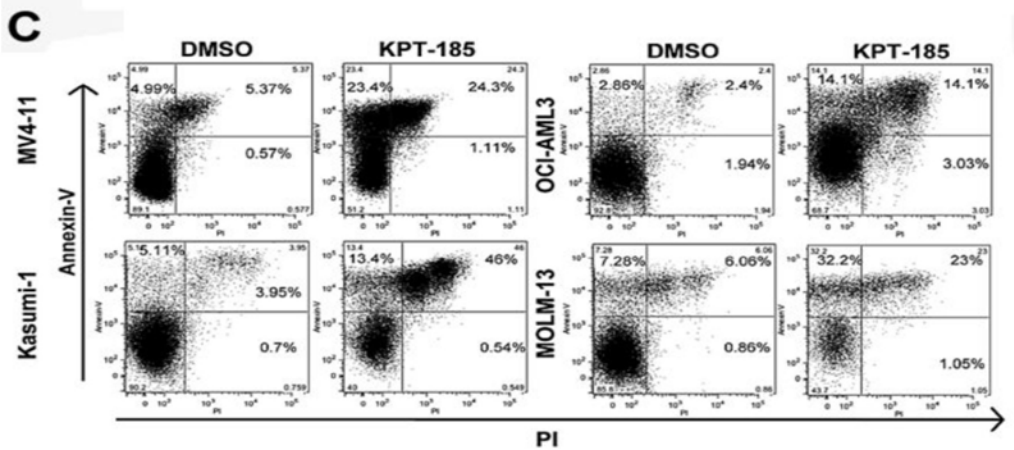
Tumor cells show very low levels and/or cytoplasmic location of their TSPs

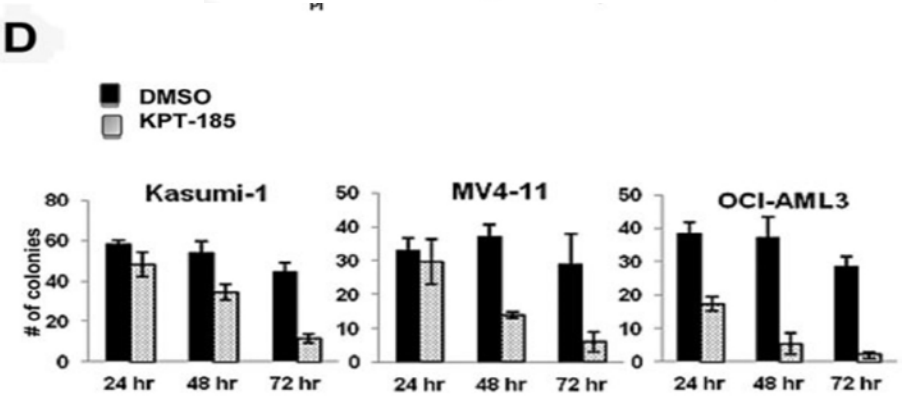
KPT-330 increases the total level *and* nuclear location of multiple TSPs

KPT-SINE significantly inhibits proliferation and induces cell-cycle arrest and apoptosis of AML cell lines



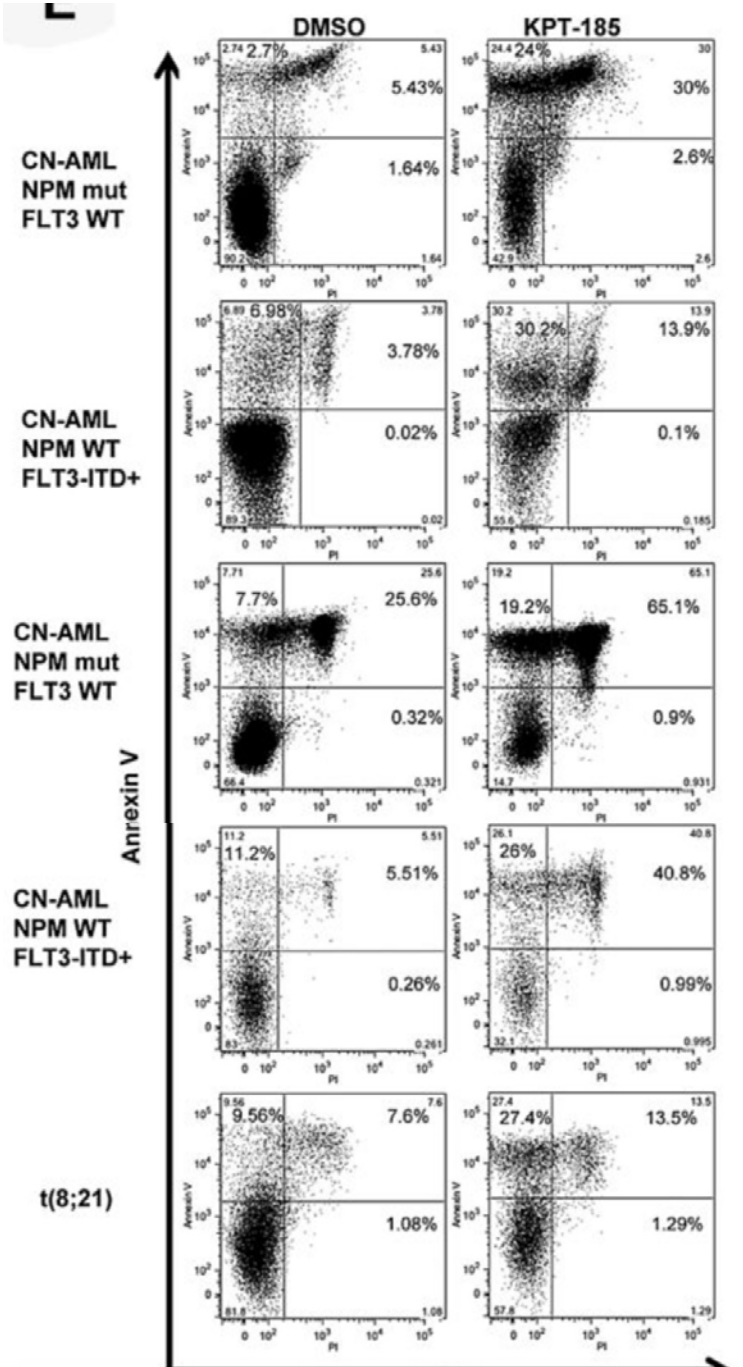


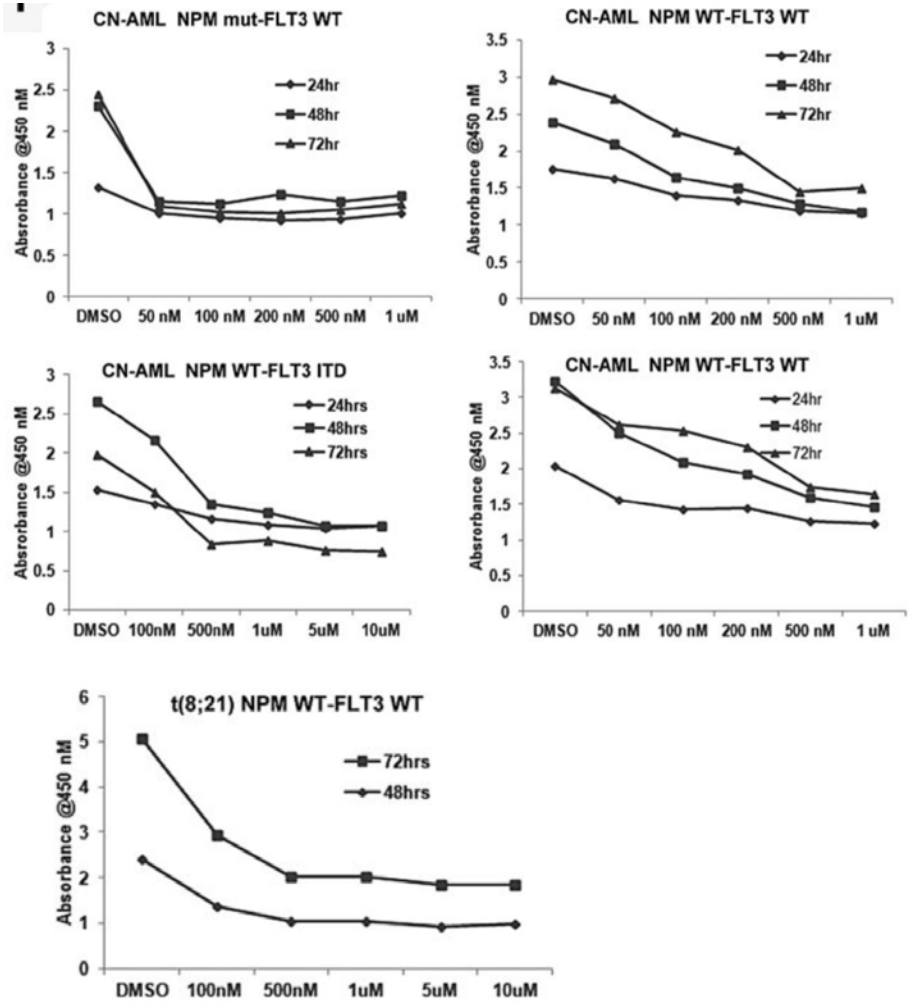




Ranganathan et al, Blood 2012

KPT-SINE significantly inhibits proliferation and induces cell-cycle arrest and apoptosis of primary AML blasts

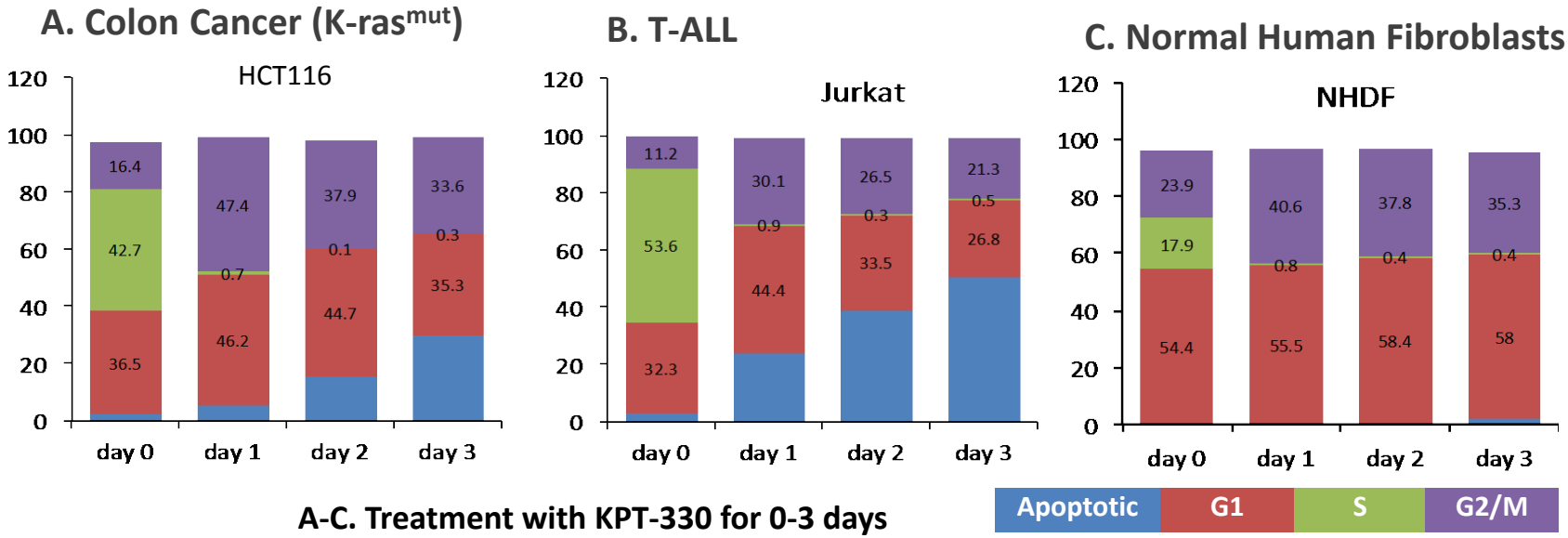




Ranganathan et al, Blood 2012

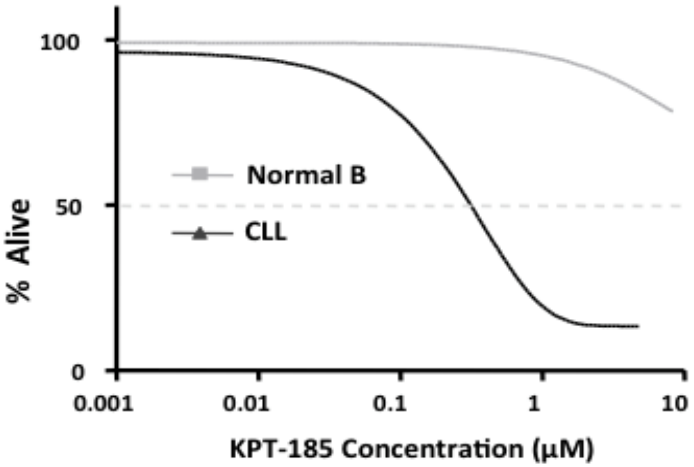
SINE Compounds Induce Cell Cycle Arrest in Multiple Cancer Cell Types

- ***Apotosis is induced in cancer cell lines, but not in normal cells***



A-C. Treatment with KPT-330 for 0-3 days

D. Human B-CLL and Normal Peripheral B Lymphocytes



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

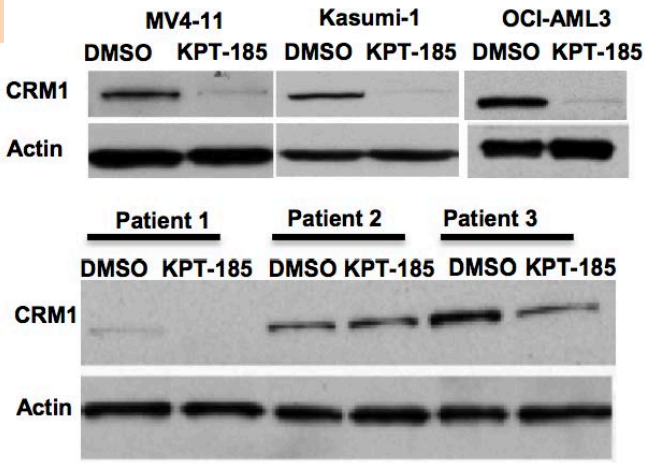
Patient	Age	WHO	WBX	Cytogenetics	NPM1	FLT3	IC_{50} (nM)
1	27	Acute Myelomonocytic Leukemia	39	46,XX(20)	Mut (A)	WT	100
2	42	AML with maturation	26	46,XY(20)	Mut (A)	WT	100
3	62	AML without maturation	199	46,XX(20)	Mut (A)	WT	100
4	77	AML with maturation	85	46,XY(20)	Mut (A)	WT	50
5	62	AML with MDS related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

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

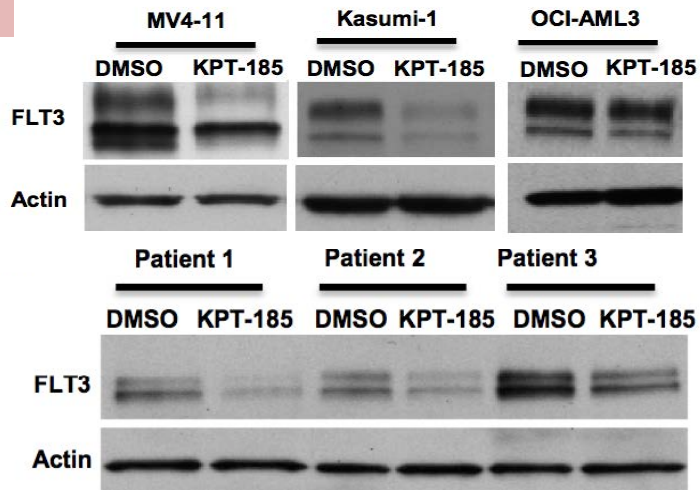
Grazon etal. EHA 2014 Annual Meeting

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

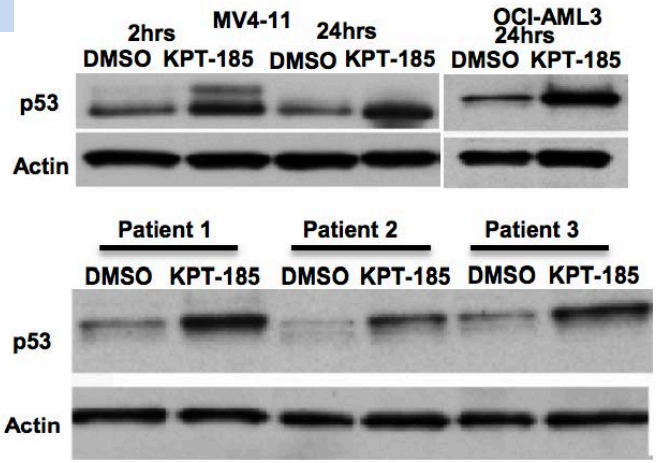
XPO1



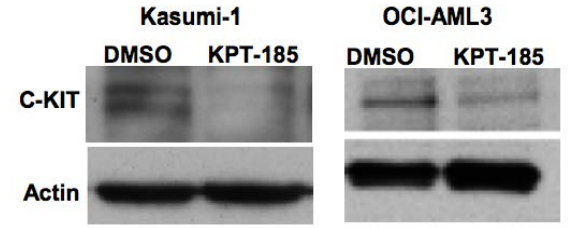
FLT3



p53



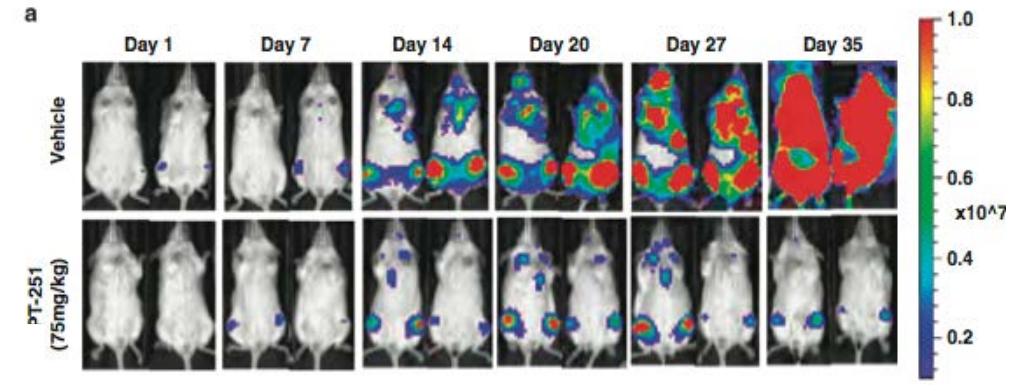
C-KIT

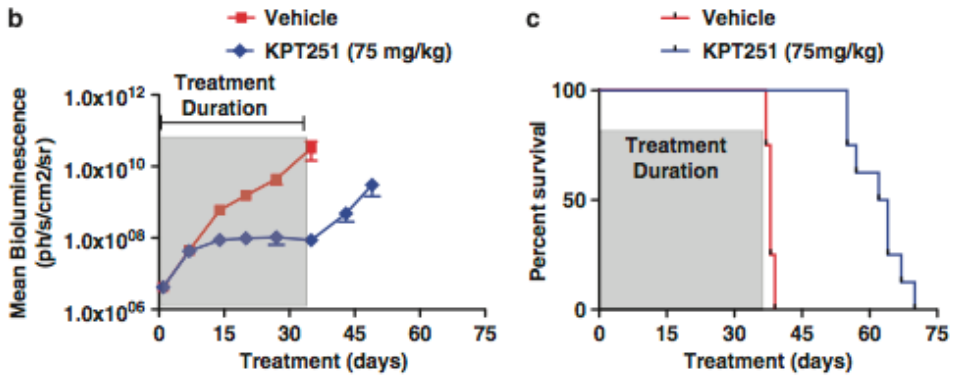


Ranganathan et al, Blood 2012
Grazon etal. EHA 2014 Annual Meeting

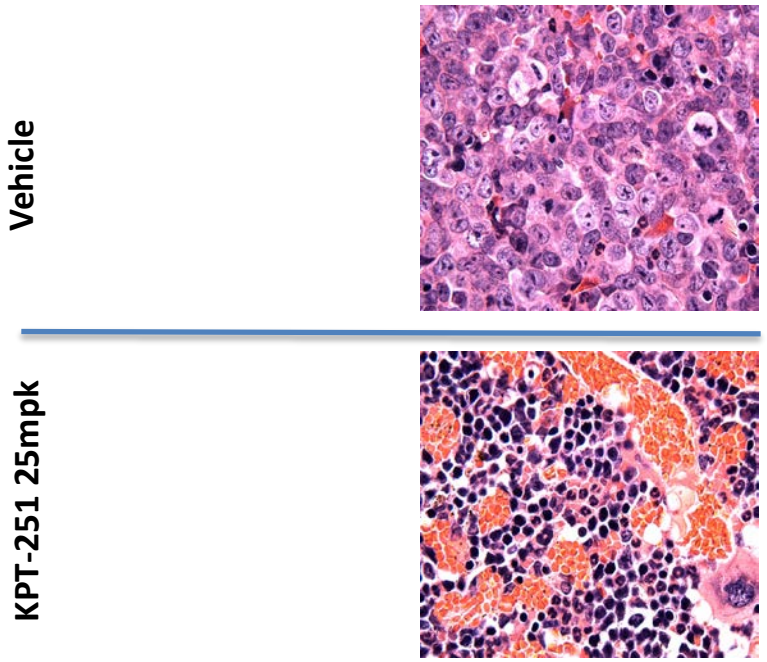
SINEs Kills AML But Not Normal Hematopoietic Cells; Maintaining Near-Normal Bone Marrow

MOLT-4 (FLT3 ITD) AML Leukemograft Mice





Bone Marrow: H&E Stain

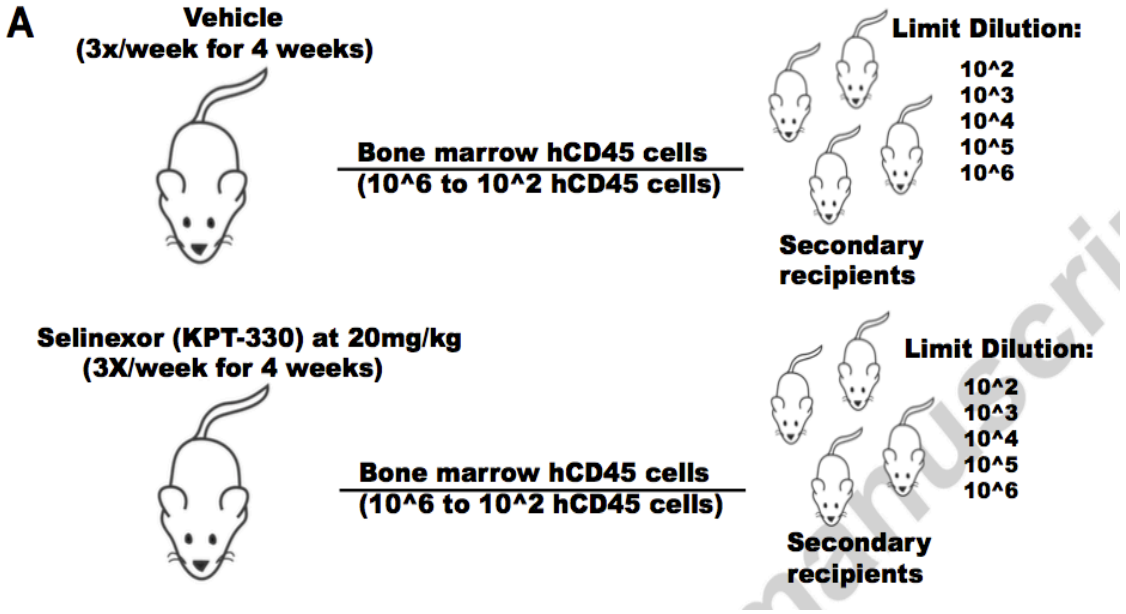


Etchin et al, Leukemia 2012

Grazon etal. EHA 2014 Annual Meeting

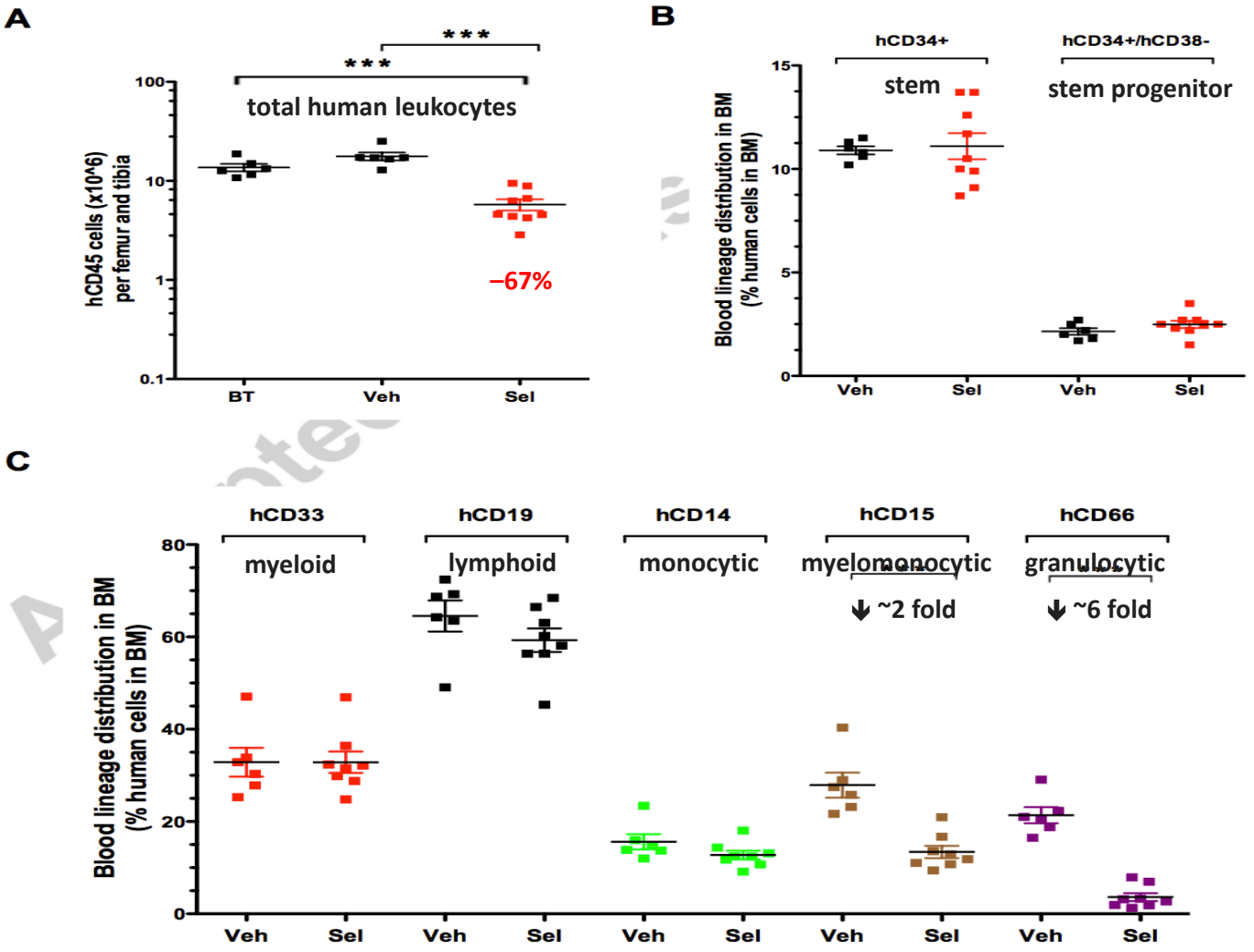
SINEs Target Leukemia Initiating Cells (LICs) in Three Primary AML Patient Samples

Xenograft	Genotype	Primary Tumor Effect	LIC Effect
AML-CK1	46,XX,dup(2)(q21q33), t(8;16)(p11;p13),psu dic(22;1)(p11;p11)[10]/ 46,XX,dup(1)(q32q42), t(8;16),psu dic(9;1)(q34;p11) [4]/ 46,XX,t(8;16),psu dic (19;1) (p13;p11)[4]/46,XX[2]; FLT3 WT	↓ ~80%	↓ ~6 fold
AML-CK2	46,XY,-2,der(5)t(2;5)(q3?1;q2?5), inv(11)(q21q23),add(15)(p11), del(20)(q12),+mar[19]/46, XY[1]; FLT3 WT	↓ ~40%	↓ >434 fold
AML-CN	46, XX; FLT3-ITD	↓ ~90%	↓ 171 fold



Etchin et al., Leukemia 2015

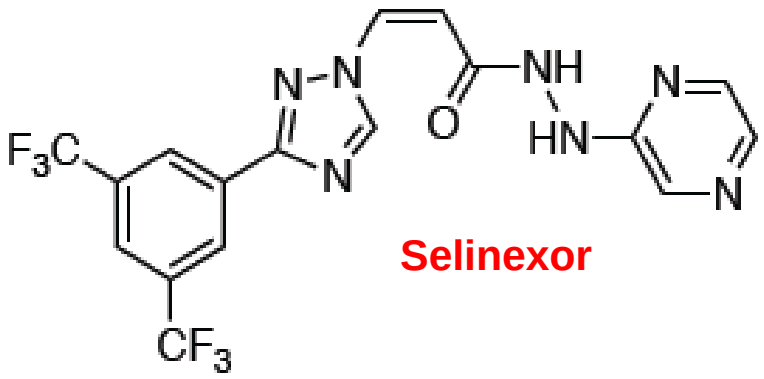
Selinexor Spares Most Normal Hematopoietic Cells in NSG Mice with Engrafted with Human Cord Blood (Normal) Cells



Etchin et al., Leukemia 2015

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

- Novel, small molecule selective inhibitor of XPO1
- Oral drug administered 1-2 times per week
- No known drug-drug interactions
- Potent anti-leukemic and anti-*vitro* and *in vivo* models



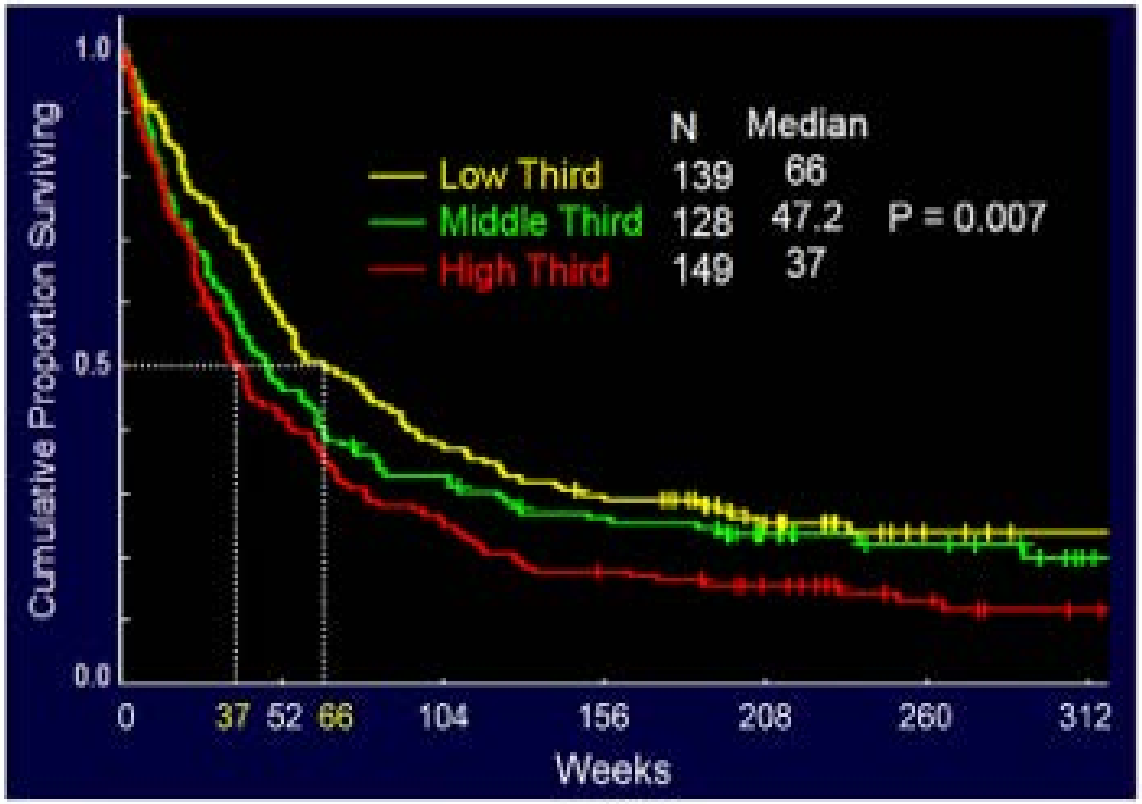
Selinexor

MW = 443 D

- Anti-tumor activity in ongoing Phase 1 and 2 studies in advanced hematologic and solid tumors
- Main side effects (anorexia, nausea, fatigue) manageable with standard supportive care, including steroids

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

- **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**



Higher levels of XPO1 associated with:

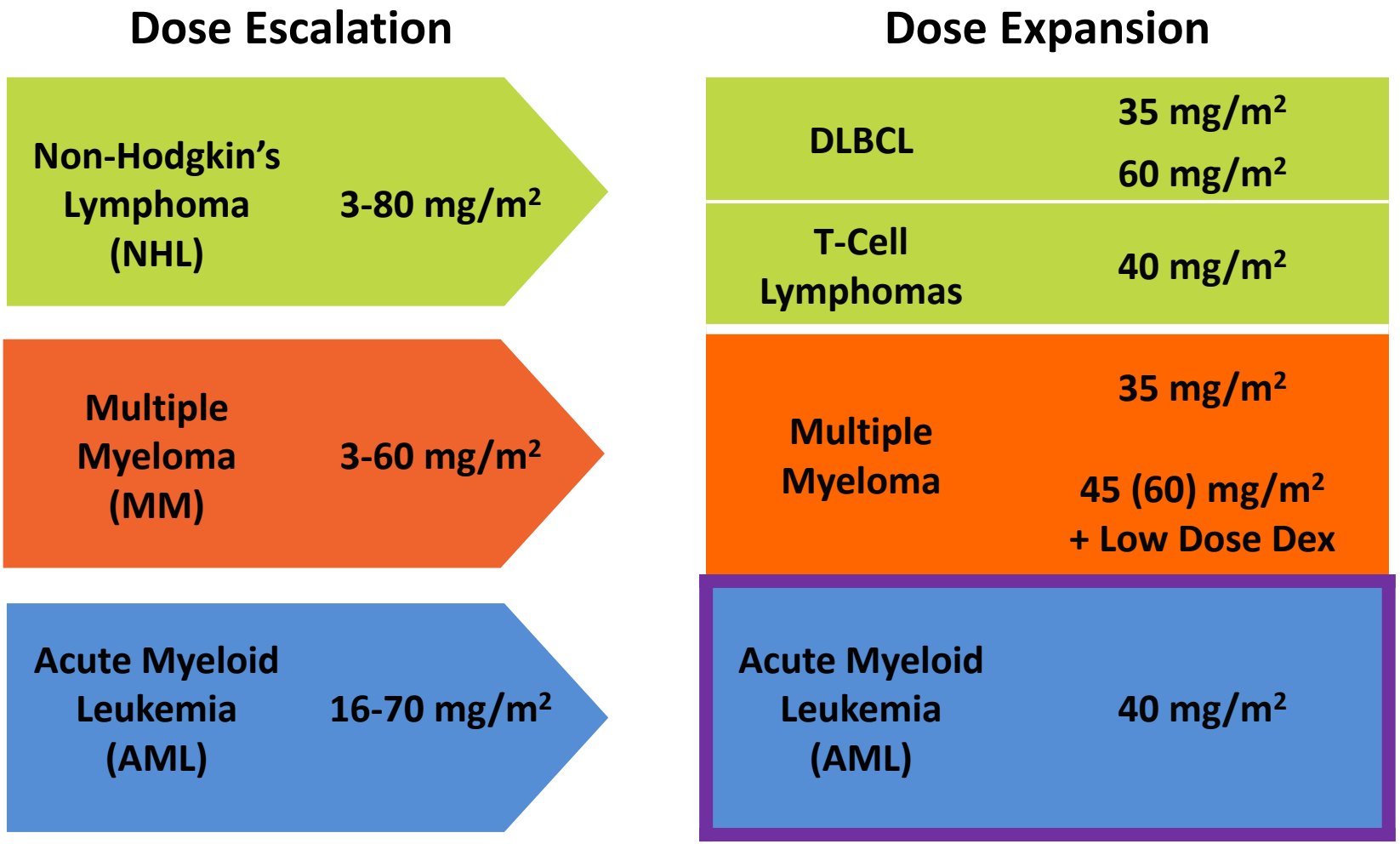
- Higher marrow % blast ($p < 0.00001$)
- White cell counts ($p<0.0079$)
- Peripheral blood % blast ($p<0.00001$)
- Absolute peripheral blood blast count ($p<0.0002$)

Expression lower in favorable cytogenetics compared with intermediate/unfavorable cytogenetics ($p<0.029$)

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

Kojima et al, Blood, 2013

Selinexor (KPT-330) Phase 1 Hematological Malignancies Study



clinicaltrials.gov: NCT01607892

A Phase 1 Dose Escalation Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-330 (Selinexor) in Patients (pts) with Relapsed / Refractory Acute Myeloid Leukemia (AML)

Yee et al EHA 2014

Phase 1, Open Label, Dose Escalation Study in Patients with Advanced, Hematological Malignancies

Study Design:

- Arm 2 included patients with AML.
- Doses 16, 23, 30, 40, 55 and 70 mg/m^2; 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)
- Modified "3+3" design

Major Eligibility Criteria:

- Patients with AML with no available standard treatments
- ECOG 0-1
- *Documented progression at study entry*

DLT Definition

- ≥ 3 missed doses in 28 days at target dose
- Discontinuation of a patient due to a toxicity in Cycle 1

***Non Hematologic**:*

- Grade ≥3 excluding nausea/vomiting or electrolyte imbalances amenable to supportive care and AST/ALT lasting less than 7 days
- Grade ≥3 fatigue lasting ≥5 days while taking supportive care

Yee et al EHA 2014

Selinexor Phase 1 Study in AML: Patient Demographics

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

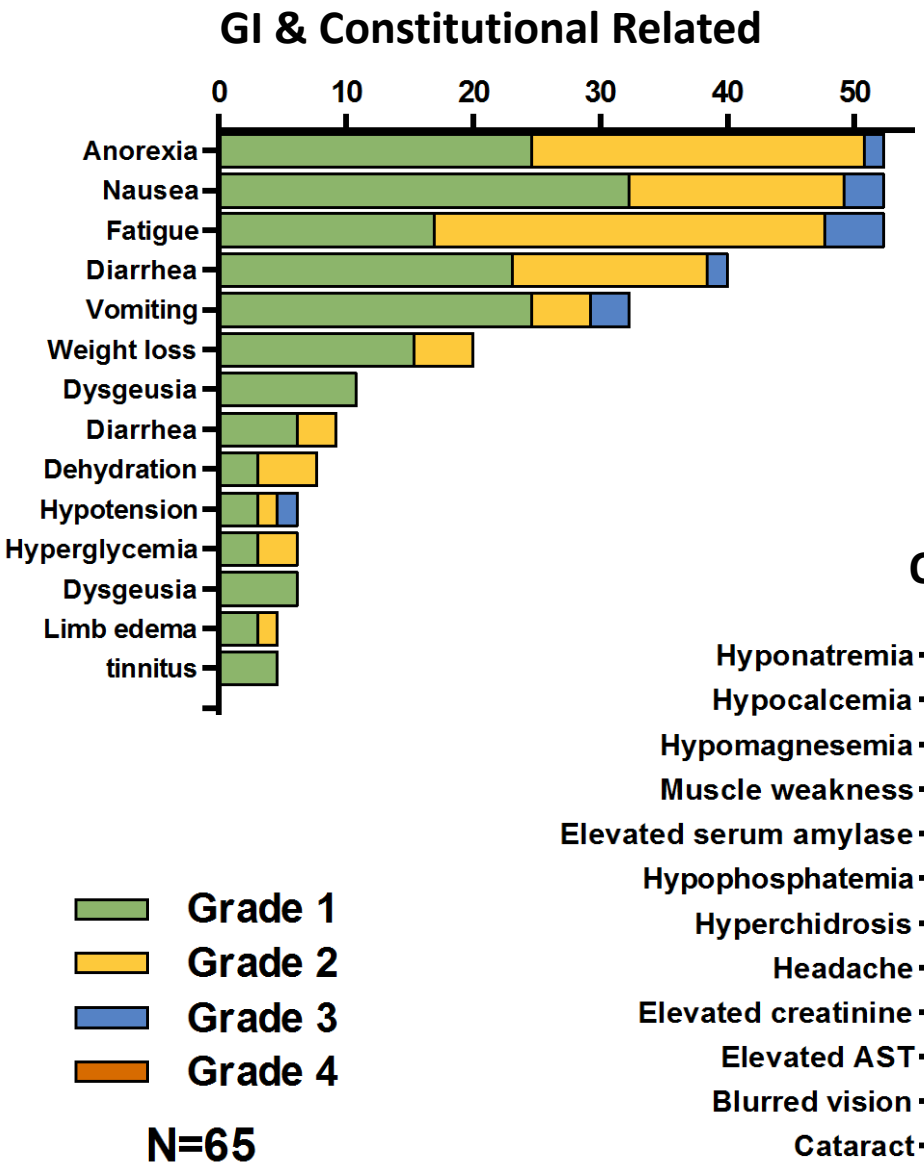
Therapy Line for Disease	
2nd Line AML	15 (23%)
3rd Line AML	13 (20%)
> 3rd Line AML	28 (43%)
Unknown	9 (14%)

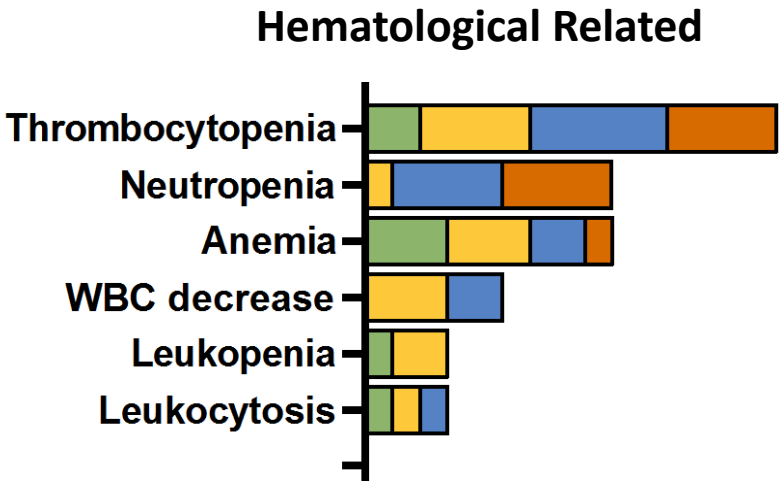
AML Cytogenetic Risk	
Favorable	10 (15%)
Intermediate	28 (43%)
Adverse	23 (35%)
Unknown	4 (6%)

Summary: Patients with AML enrolled in KCP-330-001 have heavily pretreated AML with disease that is progressing on study entry. The majority of patients have intermediate or poor cytogenetic risk >50% are over 67 years old.

Yee et al EHA 2014

Selinexor AML Phase 1 Study: Drug Related Adverse Events

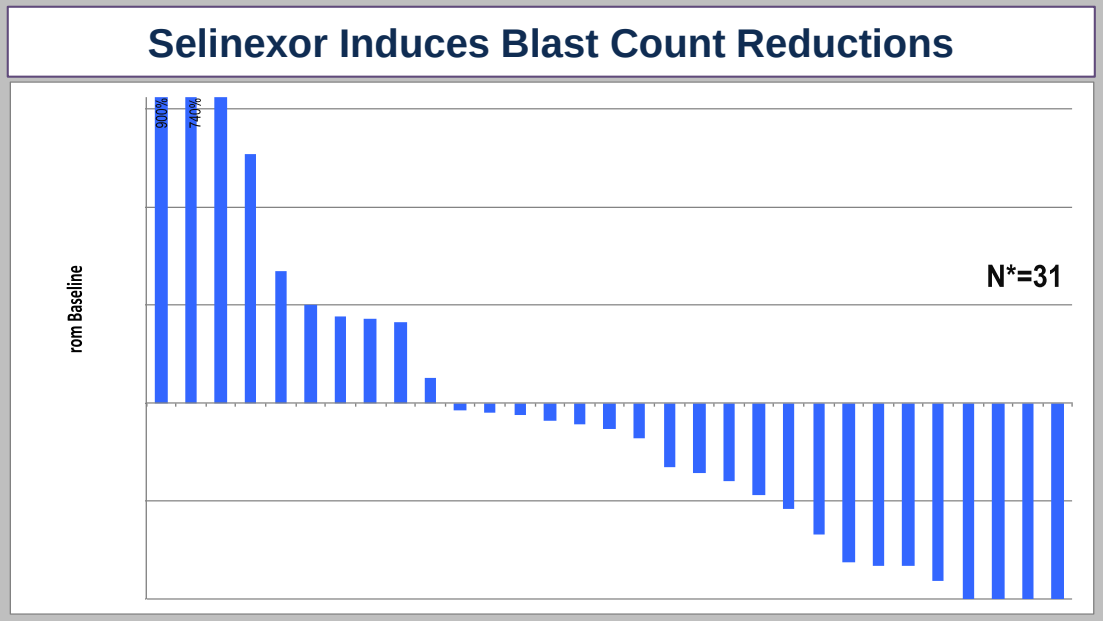




Yee et al EHA 2014

Selinexor Phase 1 Study: Efficacy and Conclusions

Best Responses in Patients with AML as 13-May-2014									
N	**DCR**	**ORR**	**CR**	**CR(i)**	**PR**	**MLFS**	**SD**	**PD**	**NE**
63	31	10	5	2	1	2	21	16	16
%	49%	16%	8%	3%	2%	3%	33%	25%	25%



- Selinexor (KPT-330) is a covalent, oral SINE XPO1 antagonist that forces nuclear restoration and reactivation of TSP and reduces proto-oncogenes leading to the selective apoptosis of AML cells.
- Common AEs are reversible nausea, anorexia and fatigue; extended dosing feasible with appetite stimulants and anti-nausea agents
- Objective Responses and reduction in BM blasts were observed in heavily pre-treated patients with AML

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

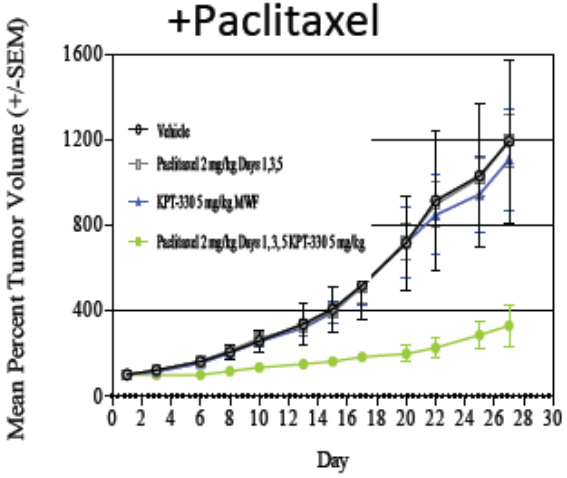
* Excludes 14 patients who withdrew consent & 18 patients who clinically progressed before post treatment bone marrow biopsy

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

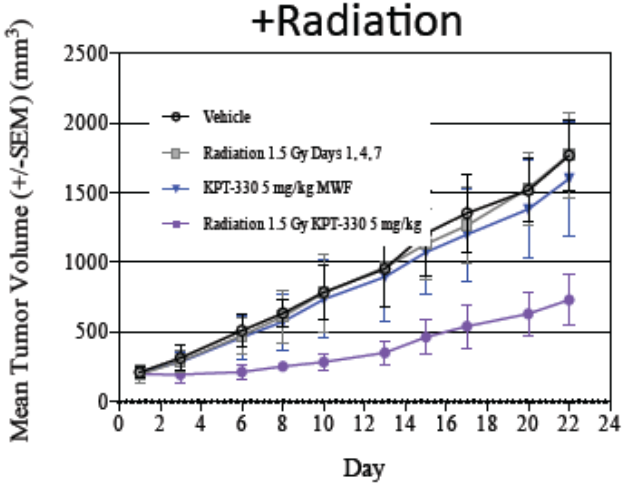
Yee et al EHA 2014

SINE Combination Studies

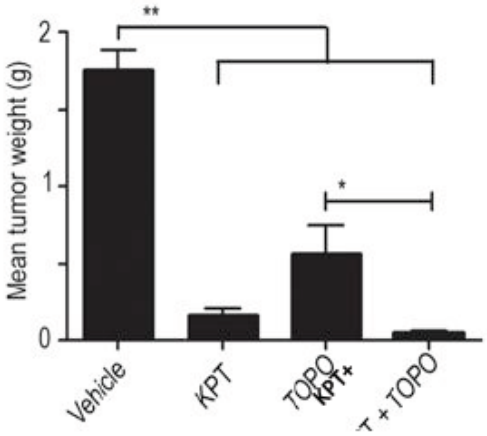
TNBC KPT-330 +Paclitaxel



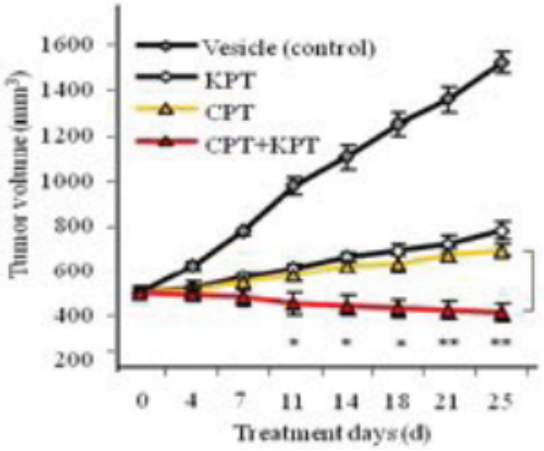
NSCLC KPT-330 +Radiation



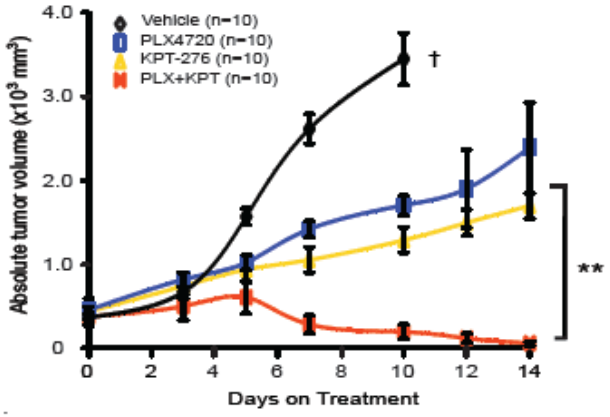
Ovarian Ca KPT-330 +Topotecan



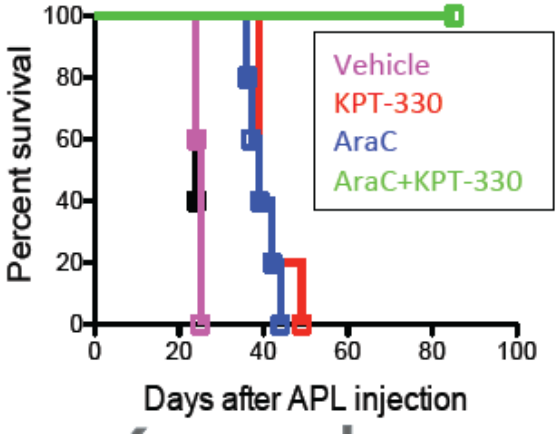
CRC KPT+Irinotecan (Cusack, MGH)



Melanoma KPT+Velboraf (Cusack, MGH)

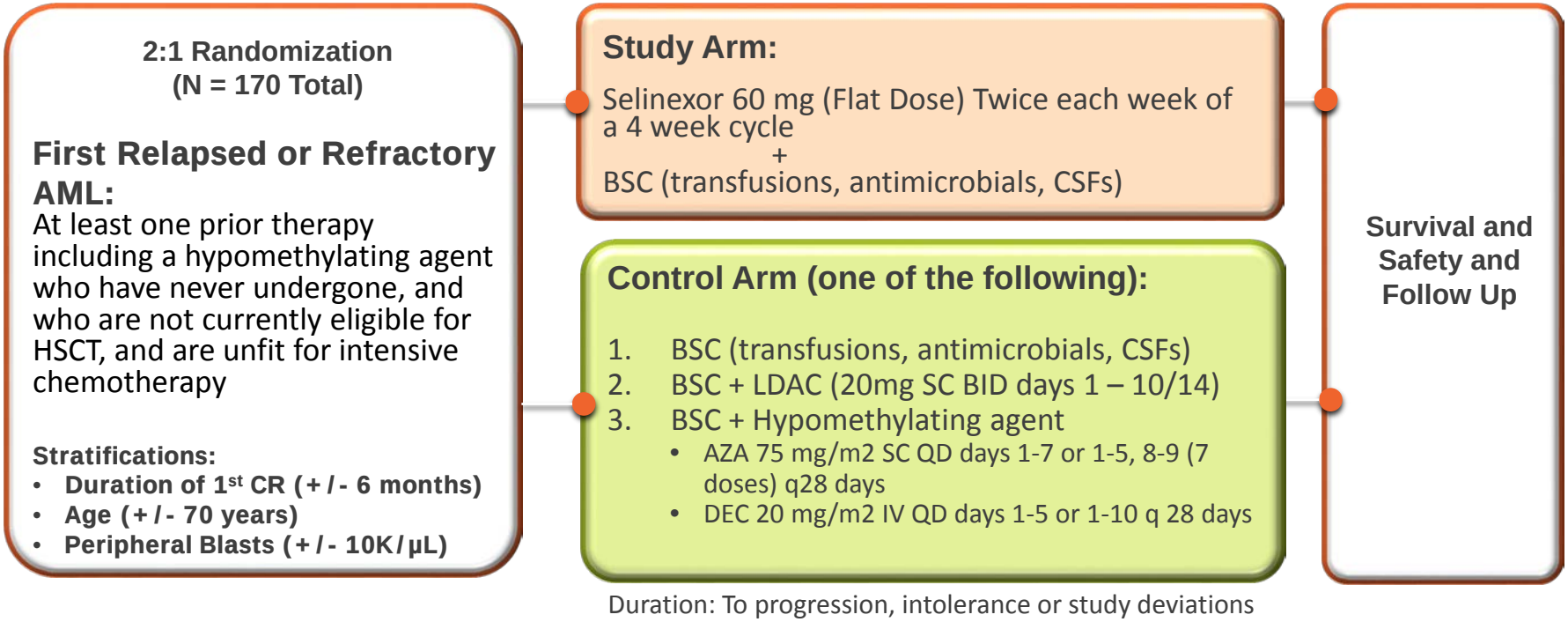


APL KPT-330+AraC (Rettig, Wash U)



KCP-330-008: SOPRA = Selinexor in Older Patients with Relapsed/refractory AML

- **A Randomized, Open-label, Phase 2 Study of the Selective Inhibitor of Nuclear Export Factor (SINE) Selinexor (KPT-330) , Versus Specified Physician Choice in Patients ≥ 60 Years Old With Relapsed/Refractory Acute Myeloid Leukemia (AML) Who are Ineligible for Intensive Chemotherapy or Transplantation (Amended)**



Duration: To progression, intolerance or study deviations

Objectives:

Primary: OS

Secondary: CRR (CR+CRi+CRp), DOR, DCR, Safety, QOL

Rationale for Recent Dose Reduction in SOPRA Study

- Periodic review of Serious Adverse Events (SAEs) on SOPRA trial revealed Sepsis Rates of 11% (8 of 70 pts) on selinexor 55mg/m^2 (~100mg) versus 6.7% (2 of 30 pts) on Physician's Choice
- Although this trend was not statistically significant, review of Phase 1 data indicated that higher doses of selinexor (>80mg) were associated with increased sepsis risk in AML only
- Phase 1 & 2 results across other hematologic and solid tumors showed no increase in sepsis
- Majority of the Phase 1 AML responses occurred at selinexor doses of <70mg
- Therefore, dose in SOPRA study was reduced to 60mg twice weekly (~35 mg/m^2) and accrual count restarting at N = 170

Percentage of Patients with Infectious SAEs Across All Indications (Single Agent Selinexor)

	KCP-330-											
	-008	-001	-001	-002	-003	-004	-005	-006	-007	-009	-010	-013
	Elderly AML	AML +ALL	Other Heme	Solid Tumors	Sarcoma	GBM	Gyn	Sq H&N/lung	Prostate	DLBCL	Richter's	TCL
	N=70	N=78	N=273	N=188	N=55	N=28	N=104	N=46	N=17	N=48	N=6	N=10
Total SAEs	**47**	**61**	**65**	**29**	**0**	**1**	**9**	**14**	**0**	**10**	**3**	**1**
% Patients with Any Infection SAE	67%	78%	24%	15%	0%	4%	9%	30%	0%	21%	50%	10%
% Patients with Sepsis	11%	15%	2%	4%	0%	0%	0%	2%	0%	0%	0%	0%
% Patients with Pneumonia / lung Infections	16%	21%	9%	7%	0%	0%	3%	20%	0%	8%	17%	0%

Sepsis Rates with Selinexor are Similar to Other Agents in Elderly AML Patients

	Decitabine 1st Line[1]	Azacytidine Rel/Ref[2]	Selinexor SOPRA	Selinexor Phase 1 AML	Physician's Choice SOPRA
Number	238	130	70	88	30
Febrile Neutropenia	32%	Not Reported	24%	25%	33%
Sepsis	12%	Not Reported	11%	15%	6.7%
Sepsis + Febrile Neutropenia	44%	62%	35%	40%	40%

1. Kantarjian et al., 2012. *J Clin Oncol.* 30(21):2670
2. Itykson et al. 2015. *Leuk Res.* 39(2015):124

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 now 60 mg flat dose (~35 mg/m^2) PO BIW
  - Maximum Tolerated Dose: 70 mg/m^2 PO BIW
  - Appetite stimulants permit long term use of selinexor
  - Individualized mitigation strategies for drug-associated toxicities is a top priority
- 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 with at least 1 prior therapy that are unfit for intensive chemotherapy or transplantation is ongoing (NCT02088541)