ANTI-TUMOR ACTIVITY OF SELINEXOR (KPT-330), AN ORAL SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE), ± DEXAMETHASONE IN MULTIPLE MYELOMA PRECLINICAL MODELS & TRANSLATION IN PATIENTS WITH MULTIPLE MYELOMA

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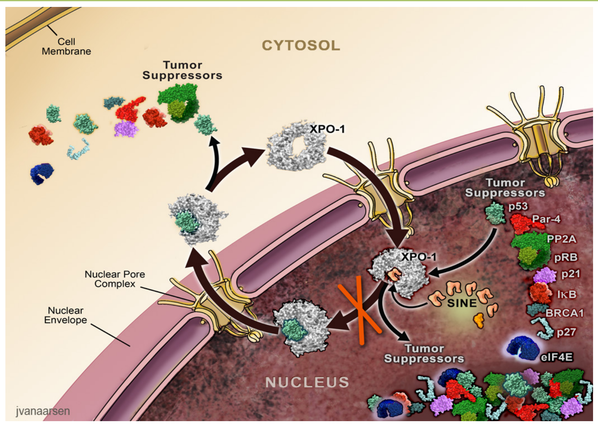
Abstract P953

Karyopharm Therapeutics

Selinexor Mechanism of Action



Pathway Affected	Effect of XPO1 Inhibition
p53 mutation	p73 activation, p21 activation
p53 and/or pRb destabilization	Nuclear p53 and pRB retention and stabilization
MDM2 activation	Nuclear p53 retention and activation
Decreased pRB signaling	Decreased pRB phosphorylation and increased nuclear pRB
NF-κB activation	IκB nuclear retention and activation
PIK3 or AKT activation	FOXO1, -3, -4 activation
Survivin-cytoplasmic	Survivin nuclear retention

- XPO1 is overexpressed in myeloma cells and other hematological malignancies and its levels often correlate with poor outcomes
- XPO1 mediates nuclear export of the majority of nuclear receptors including the glucocorticoid receptor
- Selinexor (KPT-330) is a covalent, oral selective inhibitor of nuclear export (SINE) that inhibits XPO1
- Selinexor forces nuclear restoration and reactivation of tumor suppressor proteins (TSP) leading to selective induction of apoptosis of cancer cells
- Selinexor treatment reduces proto-oncogene proteins including MDM2, MYC, Cyclin D and survivin and elevates IκB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in xenograft models of myeloma
- **Selinexor shows synergetic activity with dexamethasone in preclinical models**
- Summary data from ongoing first in human phase 1 study of oral selinexor in patients with advanced hematological malignancies (NCT01607892)

Phase 1 Study of Selinexor in Patients with Advanced Hematological Malignancies (Arm 1 Only) - NCT01607892

Objectives (modified 3+3 design)

- Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of selinexor;
- Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response; conformation of RP2D of KPT-330

Selinexor dosing

- Dose escalation and expansion 1: 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly); Doses 3mg/m^2 – 60mg/m^2
- Dose escalation and expansion 1: selinexor 45 mg/m^2 twice weekly with dexamethasone 20 mgs with each selinexor dose

Dose Escalation Cohort	Dose Expansion Cohorts in MM
Relapsed/Refractory B-Cell	EXP 1: 35mg/m^2
MM/WM, NHL, CLL	EXP 2: 45mg/m^2 + Dexamethasone (Dex) 20mgs with each Selinexor dose

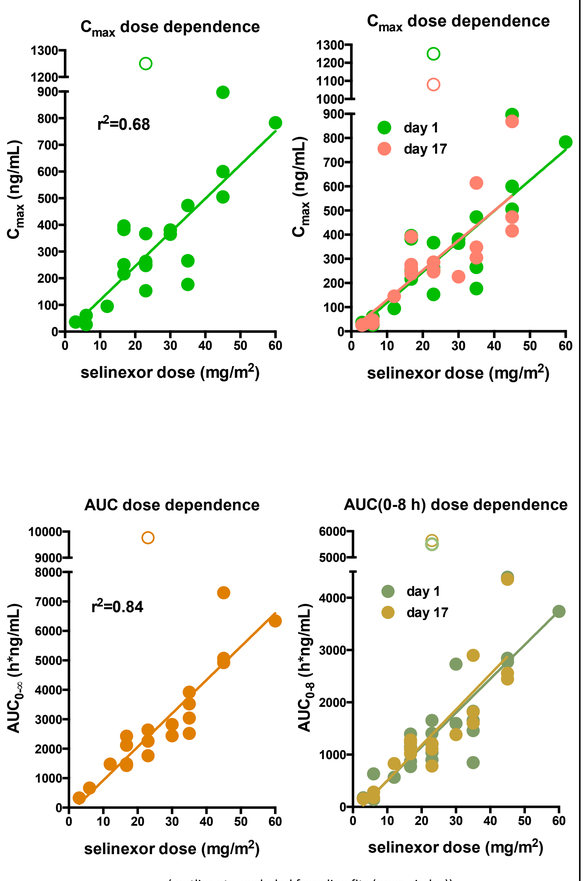
Patient Characteristics and Prior Treatments

Characteristic	N=42
Mean Age (range)	60 years (42–78)
Male / Female	23 Males : 19 Females
Mean Prior Treatment Regiments (range)	5.7 (2–13)
ECOG Performance Status, 0/1/2	8 / 33 / 01

Treatment	N	Steroid	Alkylator	Any IMID	Thalidomide	Lenalidomide	Pomalidomide	Proteasome Inhibitor - Any	Velcade	Carfilzomib	ASCT	Bendamustine	Anthracycline	Vinca	Other chemo	HDAC-Inhibitor
Selinexor Alone	34	100%	97%	100%	44%	97%	53%	100%	100%	26%	59%	9%	41%	12%	29%	21%
Selinexor + Low Dex	8	100%	100%	100%	25%	75%	62%	100%	87%	87%	87%	0%	25%	38%	38%	12%

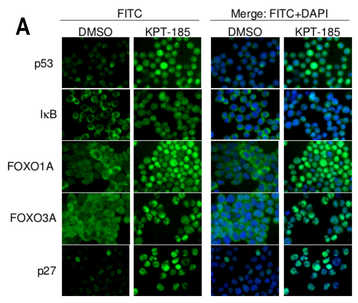
Drug Related Adverse Events ≥ 2 Patients & Pharmacokinetics

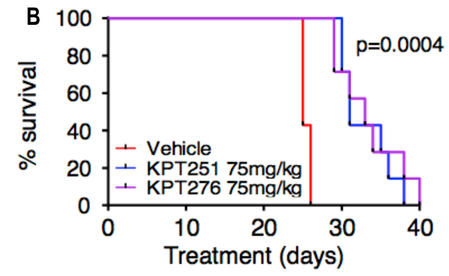
AE NAME	GRADE	Selinexor Low Doses ≤30mg/m^2 (N=17)	Selinexor HIgh Doses ≥35mg/m^2 (N=17)	Selinexor 45mg/m^2 + Dex 20mg (N=6)
Gastrointestinal, Constitutional, and Others				
Nausea	GRADE 1	7 (41%)	3 (18%)	1 (17%)
	GRADE 2	6 (35%)	12 (71%)	--
Anorexia	GRADE 1	1 (6%)	3 (18%)	--
	GRADE 2	9 (53%)	5 (29%)	--
Fatigue	GRADE 1	4 (24%)	3 (18%)	--
	GRADE 2	6 (35%)	7 (41%)	--
	GRADE 3	--	1 (6%)	--
Diarrhea	GRADE 1	4 (24%)	1 (6%)	--
	GRADE 2	2 (12%)	1 (6%)	--
	GRADE 3		1 (6%)	--
Weight Loss	GRADE 1	2 (12%)	4 (24%)	--
	GRADE 2	1 (6%)	1 (6%)	--
Dehydration	GRADE 1	--	1 (6%)	--
	GRADE 2	1 (6%)	1 (6%)	1 (17%)
	GRADE 3	1 (6%)	2 (12%)	--
Dizziness	GRADE 1	2 (12%)	--	--
Dyspnea	GRADE 1	1 (6%)	1 (6%)	--
	GRADE 2	2 (12%)	--	--
Hair Loss	GRADE 1	1 (6%)	2 (12%)	--
Vomiting	GRADE 1	6 (35%)	2 (12%)	--
	GRADE 2	1 (6%)	6 (35%)	--
Cataract	GRADE 2		1 (6%)	--
	GRADE 3	1 (6%)	--	--
Flashing Lights	GRADE 1	2 (12%)	--	--
Dry Mouth	GRADE 1	2 (12%)	--	--
Fever	GRADE 1	--	1 (6%)	--
	GRADE 3	--	1 (6%)	--
Taste Alteration	GRADE 1	3 (18%)	1 (6%)	--
	GRADE 2	--	--	--
Blurred Vision	GRADE 1	1 (6%)	3 (18%)	--
	GRADE 2	1 (6%)	1 (6%)	--
Hematological				
Thrombocytopenia	GRADE 1	1 (6%)	--	--
	GRADE 2	--	--	--
	GRADE 3	1 (6%)	--	--
	GRADE 4	4 (24%)	6 (35%)	--
Anemia	GRADE 1	2 (12%)	--	--
	GRADE 2	1 (6%)	1 (6%)	--
	GRADE 3	--	--	--
Neutropenia	GRADE 2	2 (12%)	1 (6%)	--
	GRADE 3	1 (6%)	--	--
	GRADE 4	2 (12%)	--	--
Leukopenia	GRADE 1	1 (6%)	1 (6%)	--
	GRADE 4	1 (6%)	--	--
Biochemical				
Hyponatremia	GRADE 1	--	1 (6%)	--
	GRADE 3	3 (18%)	3 (18%)	--
Creatinine Increased	GRADE 1	--	2 (12%)	--

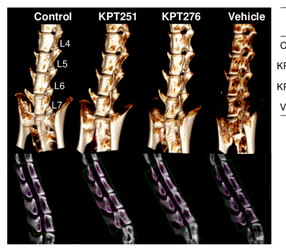


(outlier pts. excluded from line fits (open circles))

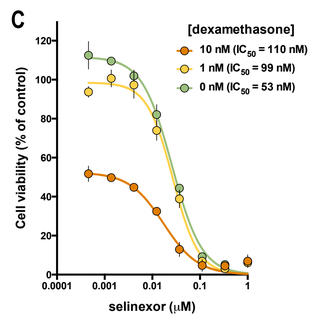
SINE Induced Nuclear Localization of TSPs in MM cells and Show Potent Anti-Myeloma Activity as Singe Agent in Combination or in Combination with Dexamethasone in Preclinical Myeloma Models

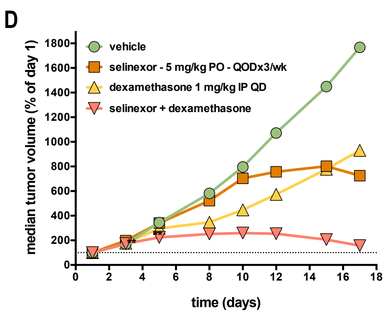






	BV /TV	BMD (mg/cc)
Control	58%	657
KPT251	55%	651
KPT276	54%	651
Vehicle	47%	521





(A) Selinexor induces nuclear localization of TSPs in MM cells
(B) SINEs induce significant anti-MM activity and inhibit MM-induced bone lysis in a disseminated murine model of human MM. SCID-beige mice were inoculated intravenously with MM1Sluc cells. KPT- 251 (75 mg/kg), KPT-276 (75 mg/kg) or vehicle were administered via oral gavage QoX3/Week
(C) The effect of combining selinexor with dexamethasone on in vitro survival of the MM.1s cell line
(D) Median tumor over time in MM1.S xenograft model. NOD-SCID mice were inoculated MM.1S cells suspended in Matrigel. When tumors reached ~100 mm^3, animals were randomized into treatment with vehicle, selinexor (5 mg/kg QODx3/wk PO), dexamethasone (1 mg/kg QD IP) or a combination of selinexor (5 mg/kg) and dexamethasone (1 mg/kg QD IP) over the duration of the experiment.

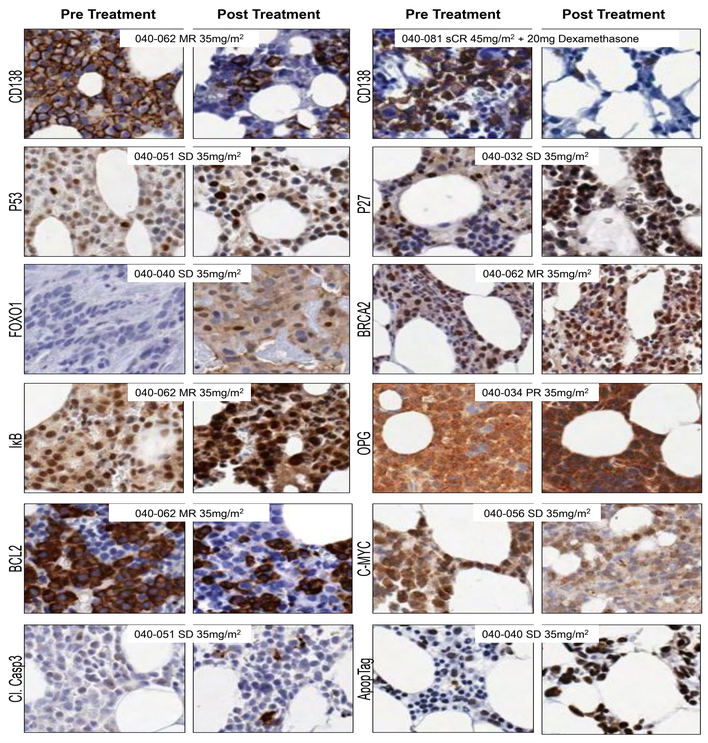
Selinexor Induced Nuclear Retention of Tumor Suppressor Proteins, Reduction of Pro-Survival Proteins, Induction of Apoptosis & Inhibition of Osteoclastogenesis

Bone marrow biopsies from multiple myeloma patients obtained prior and 3-4 weeks post selinexor treatment initiation were subjected to immunohistochemical analysis.

Staining included the cell survival markers: CD138 and BCL2, the apoptosis markers: ApopTag and Cleaved Caspase3, XPO1 cargos and TSP: p53, FOXO1, IκB, p27 and BRCA2
the osteoclastogenesis inhibitory factor: Osteoprotegerin (OPG) and the c-MYC proto-oncogene.

Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification.

sCR = Stringent Complete Response
PR = Partial Response
MR = Minor Response
SD = Stable Disease

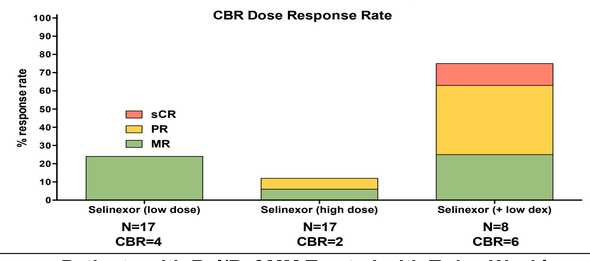


Clinical Activity

Best Responses in Patients with MM as 5-June-2014

Treatment	N	CBR	ORR	sCR	PR	MR	SD	PD	NE
Selinexor Low Dose	17	4 (24%)	--	--	--	4 (24%)	8 (47%)	3 (18%)	2 (12%)
Selinexor High Dose	17	2 (12%)	1 (6%)	--	1 (6%)	1 (6%)	8 (47%)	3 (18%)	4 (24%)
Selinexor + Low Dex	**8**	**6 (75%)**	**4 (50%)**	**1 (12%)**	**3 (38%)**	**2 (25%)**	**--**	**1 (12%)**	**1 (12%)**

CBR=Clinical Benefit Response (MR+PR+sCR), ORR=Overall Response Rate (sCR+PR), sCR= Stringent Complete Response MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, NE=Non Evaluable



Patients with Rel/Ref MM Treated with Twice Weekly Oral Selinexor 45mg/m^2 + Dexamethasone 20mg

Patient	Age	MM Type	Maximal Δ	Response	# Prior Tx	Prior Therapies	Study Days
076	63	IgG-κ	–73%	PR	7	Dox+Vinc+Dex, TD, Carfil-Dex, VRD, Cyclo-Pred-BCNU, Doxil-Carfil-Dex	122+
077	62	FLC-λ		NE	5	Len-Dex, ASCT, VRD,Carfil-Cyclo-Dex, Carfil-Cyclo-Dex-Len	15
079	65	FLC-κ	–53%	PR	3	TD-ASCT, CyBor-D,Len-Dex	45
081	55	FLC-κ	–98%	sCR	5	VAD-ASCT, ASCT, Cyclo-Pred, Pom-Carfil-Dex	107+
084	59	IgG-κ	–81%	PR	7	Vel-Dex, VD-ASCT, Len-Dex, Vel-dex, Carfil, Pom-Dex, Carfil, DT-PACE	81+
090	65	IgG-κ		PD	4	Vel-Lenalid-Dex, Cyclo-Bortez-Dex, Carfil-Dex - ASCT, Pom-Carfil-Dex	38
092	69	IgA-κ	–48%	MR	6	VRD-ASCT, Reolysin, TGO2, Carfil-Dex, Carfil-Cyclo-Dex, Carfil-Pom-Dex	51+
093	43	IgG-κ	–32%	MR	7	VAD, VTD+ASCT, Vel-Rev-Dex, Investigational, Carfil-Panob, Len-Elotu-Dex, Pom-Dex	46+

Conclusions

- XPO1 is overexpressed in myeloma (MM) cells with increasing levels from normal plasma cells to MGUS to frank MM
- XPO1 mediates nuclear export of the majority Tumor Suppressor Proteins (TSP) and of nuclear receptors including the glucocorticoid receptor
- Selinexor (KPT-330) is a covalent, oral selective inhibitor of nuclear export (SINE) XPO1 antagonist that forces nuclear restoration and reactivation of TSP leading to selective induction of apoptosis of cancer cells
- Selinexor treatment reduces proto-oncogene proteins including MDM2, MYC, Cyclin D and survivin and elevates IκB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in xenograft MM models with **synergistic activity with dexamethasone**
- First in human phase 1 study of oral selinexor in patients with advanced hematological malignancies (NCT01607892) includes Rel/Ref MM patients
- Main side effects: anorexia, nausea, fatigue reduced with supportive care
- Single agent activity with durable MR and SD at lower doses of selinexor; PR and durable MR/SD at higher doses
- Selinexor with low-dose dexamethasone shows marked activity with rapid M-protein reductions and good tolerability, even in patients with disease refractory to pomalidomide and/or carfilzomib
- Sel-Dex and other combination to be studied further in Rel/Ref MM

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