A Phase 1b Food Effect Study of the First-in-Class, Oral, Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Advanced Sarcomas

Abstract 10587

Mrinal Gounder[1], Herbert H Loong[2], Kjirsten Nyquist-Schultz[2], Stephanie Baker[2], Yelena Ustoyev[1], Lanier Tanner[1], Sharon Shacham[4], Dilara McCauley[4], Tami Rashal[4], Jean-Richard Saint-Martin[4], Sharon Tamir[4], Eran Shacham[4], Sharon Friedlander[4], Yosef Landesman[4], Tracey Marshall[4], Michael Kauffman[4], Sasha Rebello[5], Mansoor R Mirza[4], Gary Schwartz[3], Albiruni RA Razak[2]

(1) Memorial Sloan-Kettering Cancer Center, New York, USA; (2) Drug Development Program, Princess Margaret Cancer Center, Toronto, Canada; (3) Columbia University Medical Center, New York, USA (4) Karyopharm Therapeutics Inc, Natick, MA, USA; (5) Ozmosis Research Inc, Toronto, Canada;

ABSTRACT

Background: Sarcomas are heterogeneous diseases with multiple genetic abnormalities. XPO1 inhibition can restore the activity of multiple tumor suppressor proteins (TSP) including p53, Rb, and p27; and reduce cyclins and Akt. Selinexor is an oral XPO1 inhibitor that showed potent anti-sarcoma activity in preclinical ASPS, lipo- and bone sarcomas, and preliminary clinical activity in a phase 1 study.
Methods: Oral selinexor was given at 30 mg/m^2 twice weekly in capsule or tablet form based on an ongoing Phase 1. Appetite stimulants and anti-nausea agents were given. Pharmacokinetic (PK) analyses were performed under fasting and fed states (low vs high fat content). Paired tumor biopsies were obtained. Response evaluation was every 8 weeks (RECIST 1.1). All pts had documented progressive disease (PD) on study entry.
Results: 21 pts (9 M / 12 F; median age 53 yrs; median prior regimens: 3; ECOG PS 0/1: 12/9) including 6 leiomyo- (LMS), 4 lipo- (LPS), 2 chrondrosarcoma; 3 synovial (SS), and 6 other sarcomas. Grade 3-4 toxicities in cycle 1 included thrombocytopenia without bleeding (5%), hyponatremia (5%), vomiting (5%), and diarrhea (5%) . The most common Grade 1/2 AEs in cycle 1 were: nausea (76%), fatigue (76%), anorexia (43%) and vomiting (43%). PK in 12 patients showed similar exposures ($AUC_{0\text{-}inf}$ 3197 vs 3726 ng•hr/mL) of the drug in capsules or tablets; however, food (regardless of fat content) was associated with ~15% increased exposure versus fasted state. Analyses of tumor biopsies during treatment showed that Selinexor resulted in nuclear localization of p53 and FOXO1, reduced Ki67 index, increased apoptosis. Response was evaluable in 19 pts: (a) LMS: 3 SD, 2 PD; (b) LPS: 4 SD; (c) SS 3 PD; (d) chondrosarcoma: 1 SD, 1 PD; (e) chordoma: 1 SD; (f) spindle cell: 1 PD; (g) histiocytoma 1 SD; (h)1 SD aveolar soft part sarcoma; (i) osteogenic sarcoma 1 PD. 2 pts were not evauable for response. 5 of the 21 pts remain on study (61-211 days). **Conclusions:** Selinexor should be taken with food and is generally well tolerated in pts with supportive care. Tumor shrinkage and disease stabilization was observed in a variety of soft tissue sarcomas leading to expansion of the study. Additional studies of Selinexor in soft tissue sarcomas are planned.

Study Objectives

Primary: Determine the pharmacokinetic effects of high & low fat food and formulation of selinexor administered orally at 30mg/m^2 twice weekly.

Secondary:
- Safety and tolerability of oral selinexor
- Tumor response in sarcoma patients (RECIST v1.1 criteria)
- Stable disease will be measured as time to progression (duration of stable disease as TTP)

Major Eligibility Criteria:
- ECOG 0-1
- Documented progression at study entry
- Stable brain metastases permissible
- Liver metastases ineligible

Study Methods

Study Design:
- Phase 1b, open-label, randomized, four-week, four-period, study conducted at 2 sites in US and Canada in patients who have metastatic, locally advanced, un-resectable or locally recurrent sarcoma
- Approximately 35 patients will be enrolled in two groups: PK group (Arms 1 & 2, N= ~20) and Non-PK group (Arm 3, N= ~15). Arm 3 was added as early clinical benefit was seen in Arms 1 & 2.

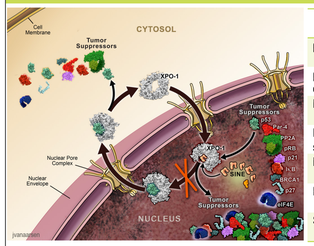
Pharmacokinetics Group (Arm 1 and Arm 2): 19 patients (Arm 1: 10pts, Arm 2: 9pts) were administered oral selinexor 30 mg/m^2 twice weekly, on days 1 and 3 of each week. For Day 1 of each of the first 4 weeks, patients were randomly allocated to one of the following arms:

Arm	Week 1	Week2	Week3	Week4
1	Tablet-**Fasted**	Tablet-high fat	Tablet-low fat	Capsule-low fat
2	Tablet-high fat	Tablet-**Fasted**	Capsule-low fat	Tablet-low fat

Blood sampling for PK drawn at baseline (time 0), 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 18 (only for hospitalized patient) and 24 hours post drug administration

Non PK Group (Arm 3): 2 patients have been enrolled and received selinexor 50 mg/m^2 twice weekly. Each cycle is 4 weeks with 8 doses of selinexor.

Selinexor's 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

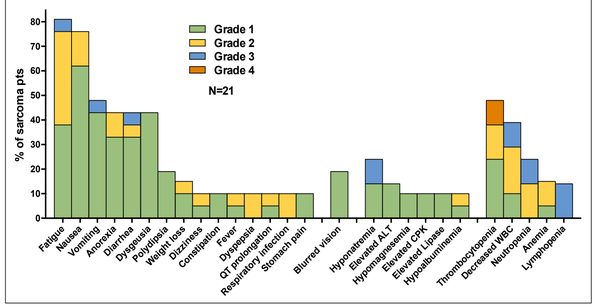
- XPO1 is overexpressed in solid tumors and hematological malignancies and its levels often correlate with poor outcomes.
- XPO1 is the sole nuclear exporter of the major tumor suppressor proteins (TSP).
- **Selinexor (KPT-330) is a covalent, slowly reversible, oral selective inhibitor of nuclear export (SINE) that inhibits XPO1**
- Selinexor forces nuclear restoration and reactivation of TSP leading to selective induction of apoptosis in 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 sarcoma including liposarcoma, alveolar soft part sarcoma (ASPS), rhabdomyosarcoma and Ewing's sarcoma
- Summary data from ongoing first in human phase 1 study of oral selinexor in patients with advanced sarcomas (NCT01896505)

Patients Characteristics

Characteristic	N=21
Mean age (range)	53 years (18-80)
Male /Female	9 Males : 12 Females
Mean prior treatment regiments (range)	3 (1-8)
ECOG performance status, 0/1	12 : 9

Subtype of Sarcoma	N
Leiomyosarcoma	6
Liposarcoma	4
Synovial sarcoma	3
Chondrosarcoma	2
Others	6

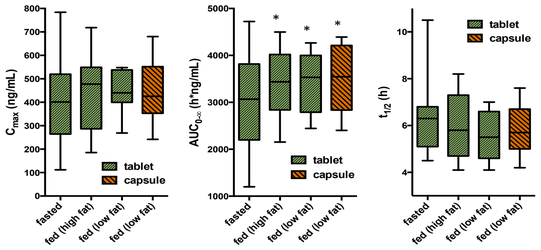
Selinexor Related Adverse Events Occurring in ≥2 Patients (N=21)



Pharmacokinetics Analysis

Treatment	Dose (mg/m^2)	Cmax (ng/mL)	Tmax (h)	AUC0-inf (ng*h/mL)	Vd/F (mL/kg)	t½ (h)
Fasted (tablet)	30	400	1.8	3197	2913	6.2
Fed, high-fat meal (tablet)	30	439	4	3643	2141	5.8
Fed, low-fat meal (tablet)	30	448	3.5	3647	1934	5.5
Fed, low-fat meal (capsule)	30	439	4	3726	2020	5.7

Mean plasma selinexor PK parameters following oral administration of selinexor at 30 mg/m^2 to fasted or fed patients with sarcoma (N=12*)
*Only 12 of 19 patients were eligible for full 4 week PK analysis



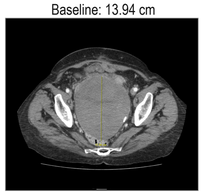
*p<0.02 vs fasted AUC

- A clear difference between fasted and fed treatments, regardless of fat content or formulation was observed
- Total exposure ($AUC_{0\text{-}inf}$) significantly greater (p <0.01) following oral selinexor administration with food. In addition, higher C_{max} and longer T_{max} were associated with fed treatments.
- There were no apparent differences related to the fat content of the meal
- There were no apparent differences related to selinexor formulation (tablet or capsule)
- Statistical significance was determined through paired t-test, comparing PK parameters for each fed condition versus fasted (*p<0.02)

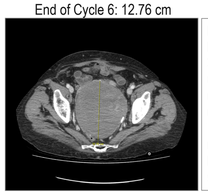
Patient Case Reports

Patient 050-016: Refractory Leiomyosarcoma (4th Line)

Baseline: 13.94 cm



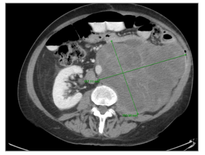
End of Cycle 6: 12.76 cm



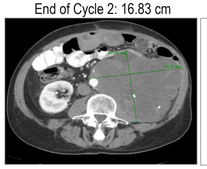
Patient 050-016: 67 year old F, leiomyosarcoma March 2011, Surgery x 1; 1st: Carboplatin-Doxorubicin (refractory), 2nd: Ifosfamide (relapsed); 3rd: Gemcitabine-Taxotere (treated for 2 months) refractory. Began 4th line therapy with selinexor, on study 196+ days.

Patient 050-005: Refractory Liposarcoma (3rd Line)

Baseline: 18.11 cm



End of Cycle 2: 16.83 cm



Patient 050-005: 66 year old M, liposarcoma, Sept 2009, surgery x 3, 1st: Gemcitabine-Radiation; 2nd: Doxil-Dacarbazine (treated for 2 months) refractory. Began 3rd line selinexor, on study 136 days with tumor shrinkage.

Clinical Activity

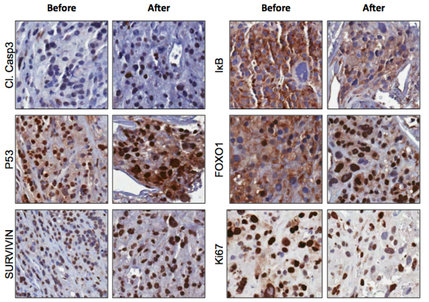
Best Responses in Patients with Sarcoma as 13-May-2014

N	SD	PD	NE
21	11	8	2
%	52%	38%	10%

Best Responses in Patients by Subtype as 13-May-2014

Sarcoma Type	N	SD (%)	PD (%)	NE (%)
Leiomyosarcoma	6	3 (50%)	2 (33%)	1 (17%)
Liposarcoma	4	4 (100%)	--	--
Synovial Sarcoma	3	--	3 (100%)	--
Chondrosarcoma	2	1 (50%)	1 (50%)	--
Others	6	3 (50%)	2 (33%)	1 (17%)
Total	**21**	**11 (52%)**	**8 (38%)**	**2 (10%)**

Selinexor Forces Nuclear Retention of XPO1 Cargos, Reduces Proliferation and Induces Apoptosis in a Lesion from a Patient with Leiomyosarcoma



Selinexor treatment reduced proliferation and induced nuclear localization of TSP and apoptosis in a kidney lesion from a patient with a refractory leiomyosarcoma. Immunohistochemical staining of the apoptosis maker cleaved caspase 3, the TSPs p53, Survivin, IκB, and FOXO1, and the proliferation marker Ki67. Biopsies were at screening and 3.5 weeks following the first dose of oral selinexor 30mg/m^2. Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification.

Conclusions

- Selinexor is generally well tolerated with supportive care for anorexia and nausea
- Selinexor is well absorbed in both fasted and fed states, independent of fat content of food. Fed stat has higher AUC.
- Single agent oral selinexor demonstrated durable stable disease in liposarcoma and leiomyosarcoma
- Post-treatment biopsies demonstrated p53 accumulation, increase in Caspase, Survivin, IκB, and FOXO1 and decrease in Ki67
- A larger study in liposarcoma and leiomyosarcoma are planned

Contact Information: Dr. Mrinal Gounder e-mail: gounderm@mskcc.org