A Phase 1b Study with Selinexor, a First In Class Selective Inhibitor of Nuclear Export (SINE) in Patients with Advanced Sarcomas: An Efficacy Analysis

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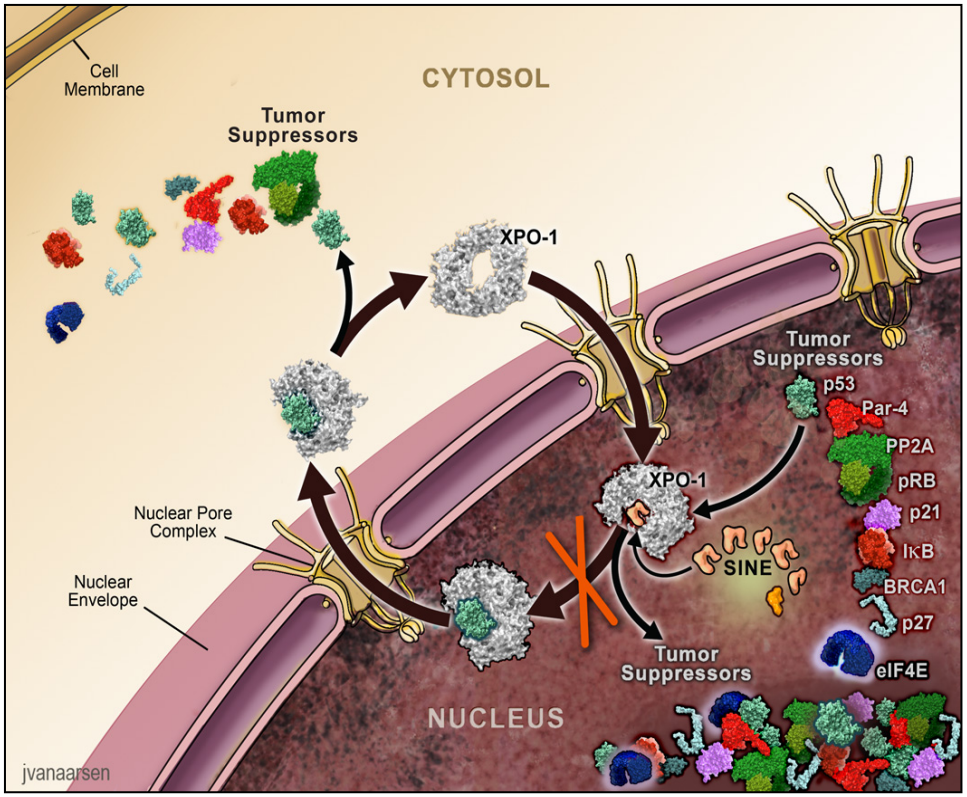
Selinexor – Mechanism of Action



- XPO1 is overexpressed in solid tumors and hematological malignancies and high levels often correlate with poor outcomes
- XPO1 is the sole nuclear exporter of 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 selectively induce apoptosis in cancer cells

- Selinexor reduces proto-oncogene protein expression, including MDM2, MYC, Cyclin D and survivin, and forces nuclear retention of 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

Study Design – NCT01896505

- **Phase 1b, open-label, randomized study in patients with metastatic, locally advanced, unresectable or locally recurrent sarcoma**
- **Approximately 53 patients enrolled in three groups**
  - **ARM 1, 2** (PK Group 1)
    - ~20 patients treated with 30 mg/m^2 selinexor twice weekly QOD (8 doses / 28 day cycle)
  - **ARM 3** (Non-PK Group)
    - ~15 patients treated with 50 mg/m^2 selinexor twice weekly QOD (8 doses / 28 day cycle)
  - **ARM 4, 5, 6 (**PK Group 2)
    - ~18 patients treated in Cycle 1 with 60 mg (flat dose) selinexor 2X wkly QOD (6 doses / 28 day)
    - For Cycles ≥ 2, selinexor is escalated to 80 mg (flat dose, 2X wkly QOD, 6 doses / 28 day)
- **Primary Objectives**
  - **ARM 1, 2**
    - Determine the effects of food on the pharmacokinetics of 30 mg/m^2 oral selinexor capsules and tablets.
  - **ARM 3**
    - Evaluate tumor response in sarcoma patients according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1 criteria)
  - **ARM 4, 5, 6**
    - Compare the PK of 2nd generation tablet formulation and suspension formula.
- **Exploratory Objective**
  - Assess the effects of selinexor on cellular morphology and biomarker changes on sarcoma biopsy specimens
- **Main Inclusion Criteria**
  - Patients ≥ 18 years old with histologically confirmed soft tissue or bone/cartilage sarcoma
  - Documented progression at study entry

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Patient Characteristics

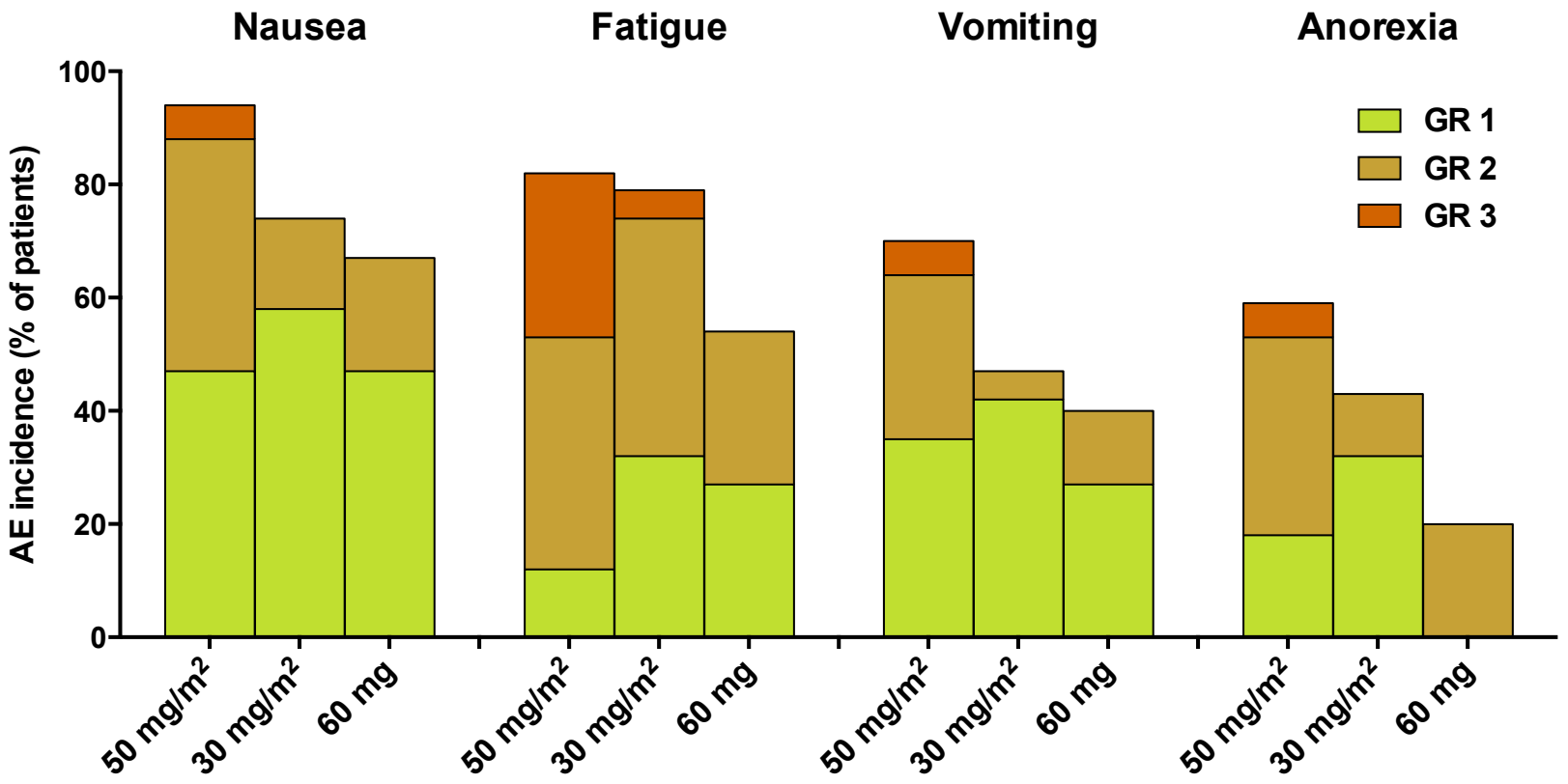
Characteristic	N=51
Median Age (Range)	55 (18 – 86)
Male / Female	21 Males / 30 Females
Median Prior Treatment Regimens – All Patients (Range)	3 (1 – 9)
Median Prior Treatment Regimens – Liposarcoma Patients (Range)	2 (1 – 9)
ECOG Performance Status (0:1)	13 : 38
PK Group, Patients Enrolled: ARM 1, 2	19
Non–PK Group, Patients Enrolled: ARM 3	17
PK Group 2, Patients Enrolled: ARM 4, 5, 6	15

Sarcoma Subtype	N
Liposarcoma	19
Leiomyosarcoma	10
Other Sarcoma	22

Adverse Events

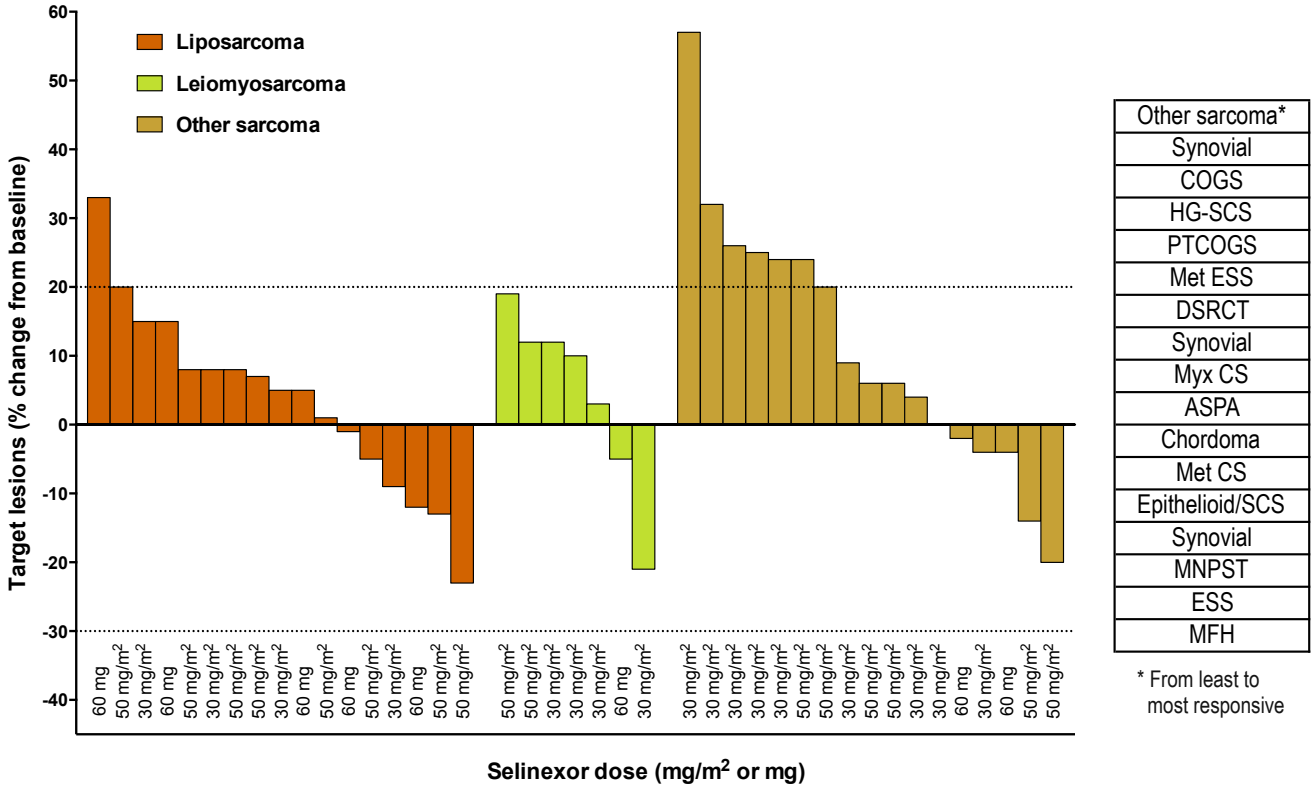
AE Term	Selinexor Dose – 50 mg/m^2 (~85 mg flat)			Selinexor Dose – 30 mg/m^2 (~50 mg flat)				Selinexor Dose – 60 mg (flat) (~35 mg/m^2)		
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Total**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total**	**Grade 1/2**	**Grade 3**	**Total**
Nausea	15 (88%)	1 (6%)	16 (94%)	14 (74%)	--	--	14 (74%)	10 (67%)	--	10 (67%)
Vomiting	11 (65%)	1 (6%)	12 (71%)	9 (47%)	--	--	9 (47%)	6 (40%)	--	6 (40%)
Anorexia	9 (53%)	1 (6%)	10 (59%)	8 (42%)	--	--	8 (42%)	3 (20%)	--	3 (20%)
Dysgeusia	8 (47%)	--	8 (47%)	8 (42%)	--	--	8 (42%)	3 (20%)	--	3 (20%)
Diarrhea	4 (24%)	--	4 (24%)	7 (37%)	1 (5%)	--	8 (42%)	1 (7%)	1 (7%)	2 (13%)
Constitutional										
Fatigue	9 (53%)	5 (29%)	14 (82%)	14 (74%)	1 (5%)	--	15 (79%)	8 (53%)	--	8 (53%)
Weight loss	6 (35%)	--	6 (35%)	3 (16%)	--	--	3 (16%)	4 (27%	--	4 (27%)
Metabolic										
Hyponatremia	5 (29%)	1 (6%)	6 (35%)	4 (21%)	2 (11%)	--	6 (32%)	7 (47%)	--	7 (47%)
Blood										
Thrombocytopenia	6 (35%)	2 (12%)	8 (47%)	8 (42%)	--	2 (11%)	10 (53%)	7 (47%)	1 (7%)	8 (53%)
Anemia	7 (41%)	3 (18%)	10 (59%)	5 (26%)	1 (5%)	--	6 (32%)	7 (47%)	1 (7%)	8 (53%)
Leukopenia	5 (29%)	1 (6%)	6 (35%)	6 (32%)	2 (11%)	--	8 (42%)	4 (27%	1 (7%)	5 (33%)
Neutropenia	4 (24%)	1 (6%)	5 (29%)	4 (21%)	2 (11%)	--	6 (32%)	1 (7%)	--	1 (7%)
Other										
Dizziness	10 (59%)	--	10 (59%)	2 (11%)	--	--	2 (11%)	1 (7%)	--	1 (7%)
Blurred vision	8 (47%)	--	8 (47%)	3 (16%)	--	--	3 (16%)	3 (20%)	--	3 (20%)

Selinexor-related AEs by ARM/dose. Adverse events observed in at least 2 patients across all Arms. **ARM 3** - 50 mg/m^2 (N=17). **ARMS 1/2** - 30 mg/m^2 (N=19). **ARM 4-6** - 60 mg (flat dose, N=15). Most common related AEs were fatigue, anorexia, nausea, vomiting and thrombocytopenia. Doses below 50 mg/m^2 have generally better AE profiles.



Selinexor-related AEs by ARM/dose. Comparison of major GI and constitutional AEs as a function of dose. Doses below 50 mg/m^2 have generally better AE profiles.

A



Other sarcoma*
Synovial
COGS
HG-SCS
PTCOGS
Met ESS
DSRCT
Synovial
Myx CS
ASPA
Chordoma
Met CS
Epithelioid/SCS
Synovial
MNPST
ESS
MFH

* From least to most responsive

(A) Waterfall plot of best target lesion responses by sarcoma type. Changes in target lesion size from baseline are shown for all patients with pre- and post-treatment scans. The upper and lower dotted lines (+20% and -30%) mark the start boundaries of progressive disease and partial response. No apparent dose response was evident.

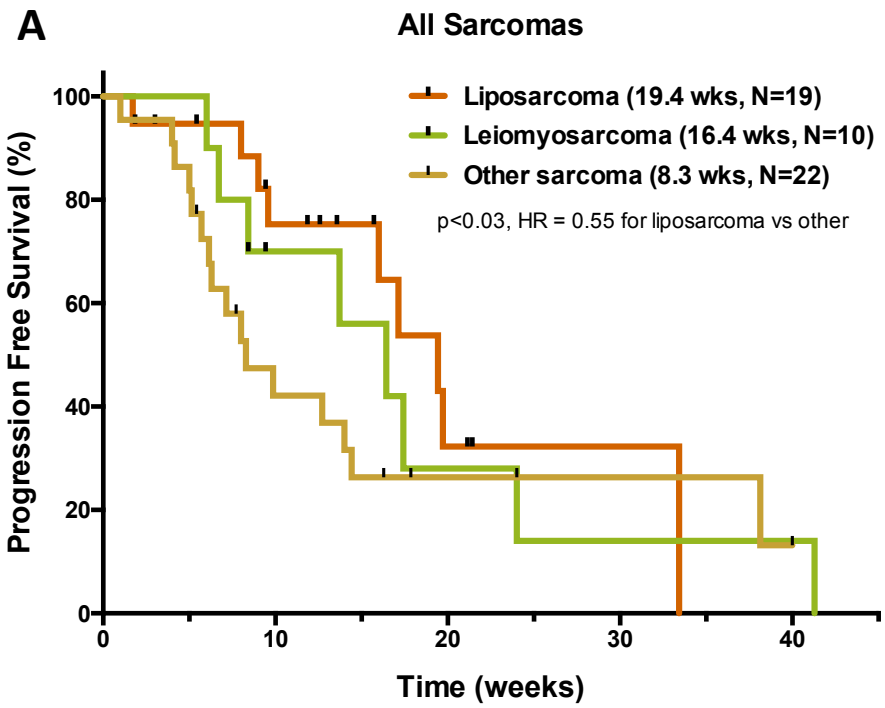
B

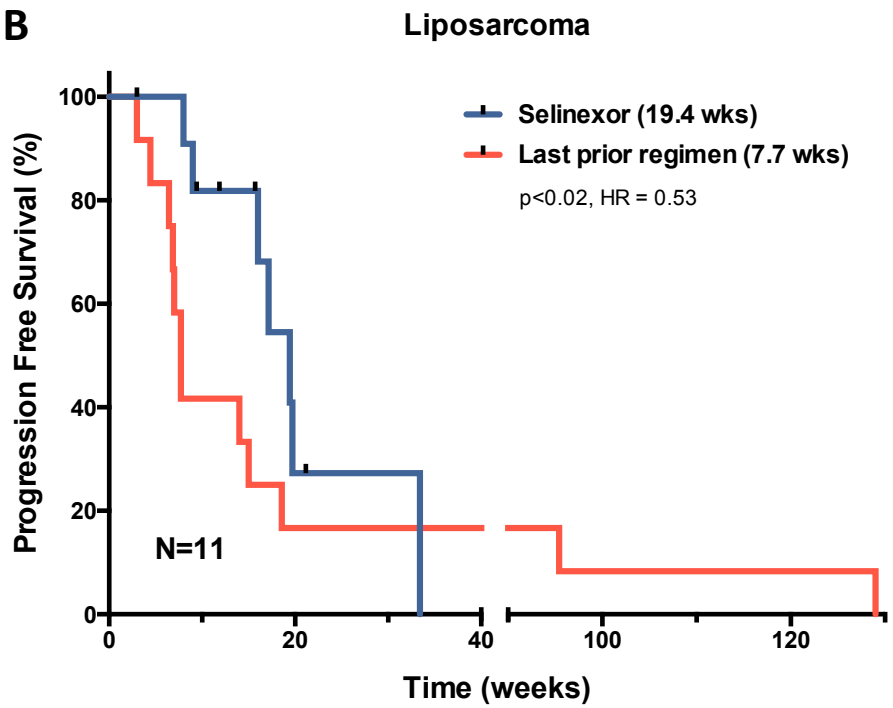
Best Responses in Evaluable* Patients by Subtype as of 10-May-2015				
Sarcoma Type	**N**	**SD – Total (%)**	**SD ≥4 Months**	**PD (%)**
Liposarcoma	18	14 (78%)	6 (43%)	4 (22%)
Leiomyosarcoma	8	5 (63%)	3 (60%)	3 (37%)
Other Sarcoma	19	8 (42%)	4 (50%)	11 (58%)
Total	**45**	**27 (60%)**	**13 (48%)**	**18 (40%)**

*Responses were adjudicated according to the *Response Evaluation Criteria in Solid Tumors (RECIST v1.1)* based on interim unaudited data – SD-Total=Stable Disease All Patients, SD≥4 Months= Patients with SD for at least 4 months
PD=Progressive Disease

(B) Response Table. Table of best tumor responses in evaluable patients by sarcoma type as of 10-May-2015.

Progression Free Survival (PFS) by Sarcoma Type





(A) Progression Free Survival (PFS) by sarcoma type and **(B)** Liposarcoma PFS for selinexor vs last prior regimen. Comparison of PFS vs last prior regimen is limited to liposarcoma patients with known time to progression for last prior regimen. Median PFS and N are listed in the legends in parentheses. P values and hazard ratios (by Gehan-Breslow-Wilcoxon and logrank respectively) are listed for statistically significant differences.

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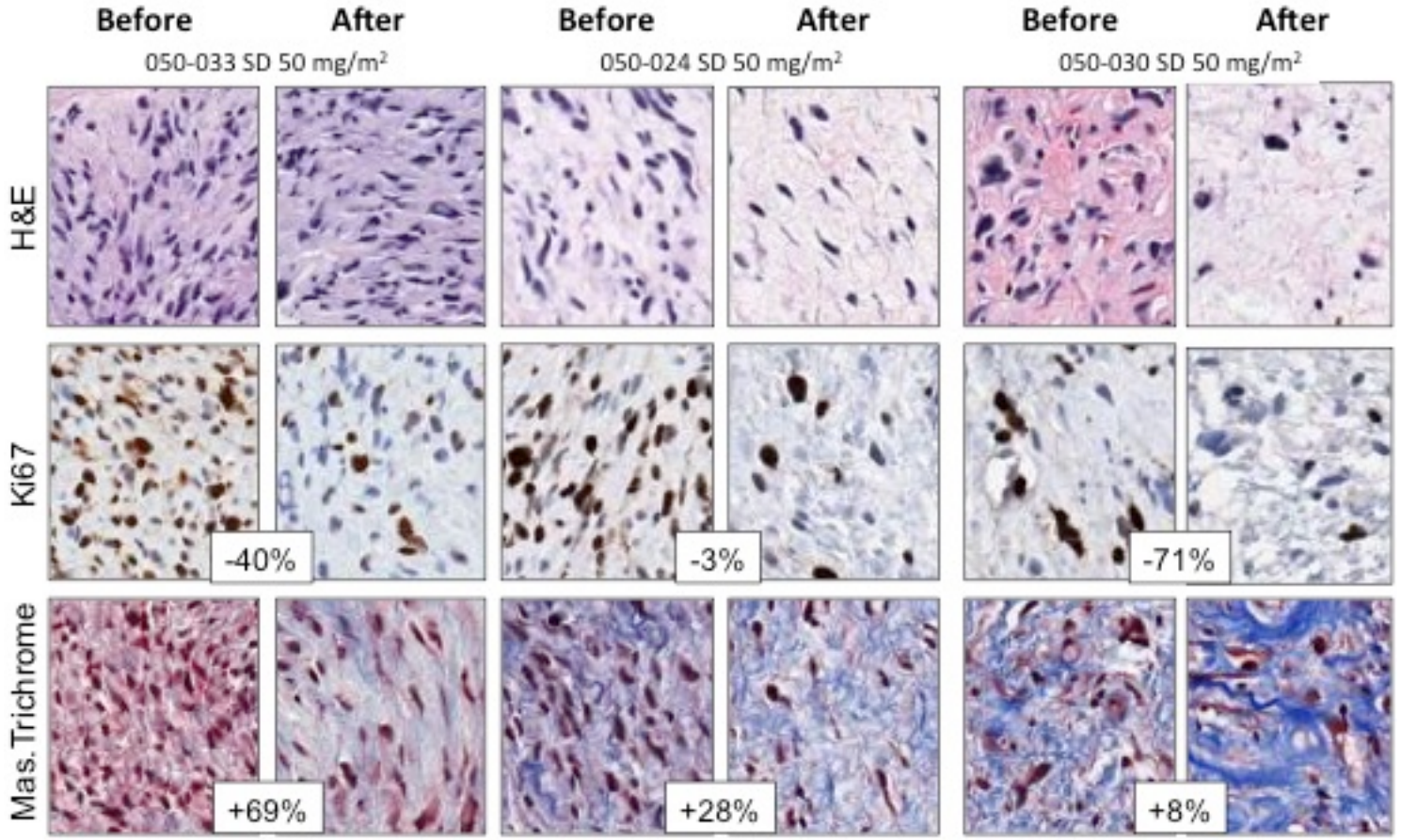
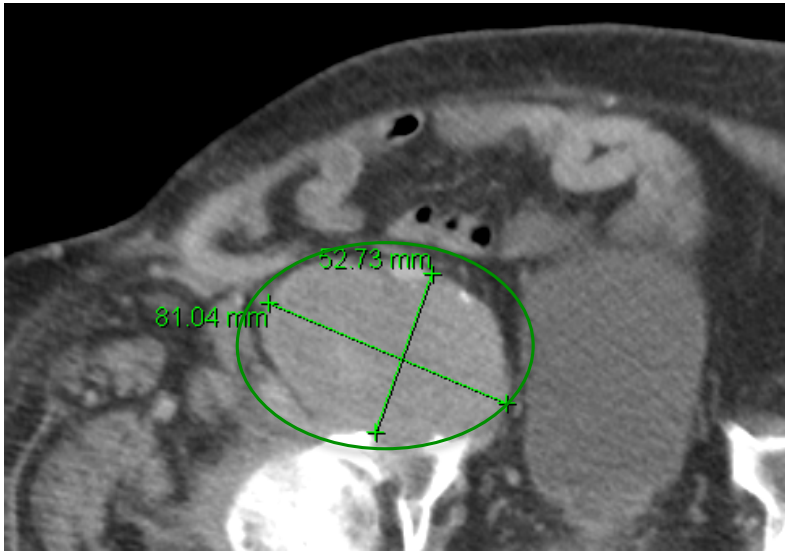
+ indicates patient still on selinexor treatment

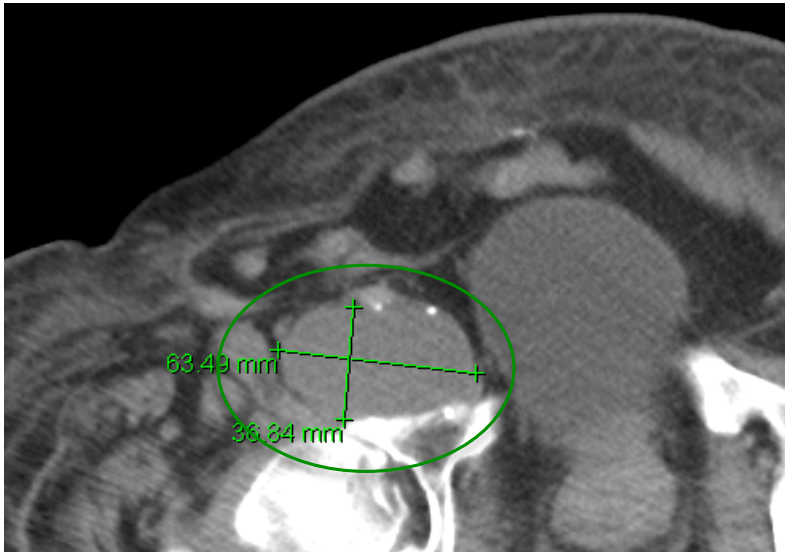


Reduced tumor cell number, proliferation and increase stroma post selinexor in liposarcoma biopsies. Immunohistochemistry and quantitative image analysis were performed on paired patients tumor biopsies obtained before and ~3.5 weeks after initiation of selinexor treatment. Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification. Nuclear Ki67 and Masson's Trichrome staining were quantified using Definiens™ Tissue Studio software. Hematoxylin and Eosin (H&E) staining revealed reduction in tumor cell number post treatment. Proliferative index marker Ki67 staining showed decreases in proliferative rate. Masson's Trichrome staining showed increased stromal connective tissue (blue) with corresponding decrease in tumor cell number.

BASELINE



CYCLE 2



CT scans of patient treated on ARM 3. 86 year old male diagnosed with differentiated liposarcoma in Jan 2012. Selinexor was preceded by separate regimens of gemcitabine-docetaxel, doxorubicin, and surgery. Selinexor monotherapy (50 mg/m^2) began in May 2014, leading to stable disease in Cycle 2 with a 23% reduction in tumor burden. This patient remained on study 138 days before progressing.

- Selinexor is generally well tolerated with supportive care for anorexia and nausea
- Selinexor (PO twice weekly) at 30 mg/m^2 or 60 mg flat dose is better tolerated than 50 mg/m^2
- Single agent oral selinexor demonstrated durable stable disease in liposarcoma, leiomyosarcoma and other sarcomas and with longer PFS than last prior regimen in liposarcoma patients
- Post-treatment biopsies demonstrated pharmacological activity based upon decreased tumor cell number, proliferative rate and increased stromal tissue
- Based on these data, additional studies in patients with liposarcoma, are planned with selinexor