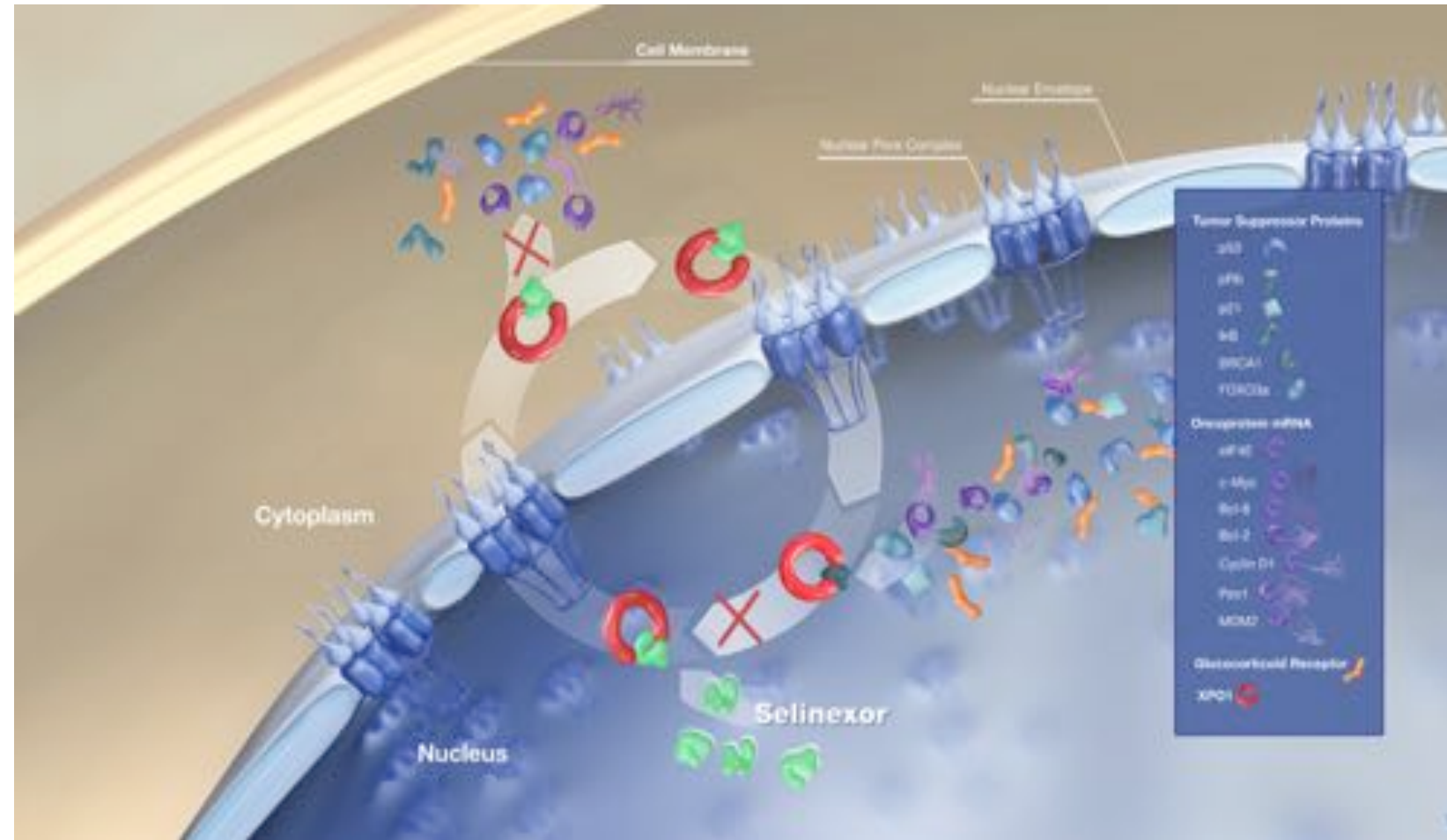


Phase 2 Results of Selinexor in Advanced De-Differentiated (DDLs) Liposarcoma (SEAL) Study: A Phase 2/3, Randomized, Double Blind, Placebo Controlled Cross-Over Study

Mrinal Gounder¹, Neeta Somaiah², Steven Attia³, Sant Chawla⁴, Victor Villalobos⁵, Bartosz Chmielowski⁶, Melissa Burgess⁷, Gary K. Schwartz⁸, Richard F. Riedel⁹, Margaret von Mehren¹⁰, Andrew J. Wagner¹¹, Edwin Choy¹², Shailendra Verma¹³, Boyd Mudenda¹⁴, Mara Sadanowicz¹⁴, Jatin Shah¹⁴, Lingling Li¹⁴, Sharon Shacham¹⁴, Michael Kauffman¹⁴, Albiruni R. Abdul Razak¹⁵

(1) Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY (2) MD Anderson Cancer center, Houston, TX (3) Mayo Clinic Florida, Jacksonville, FL (4) Sarcoma Oncology Center, Santa Monica, CA (5) University of Colorado, Denver, Colorado (6) University of California, Los Angeles, California (7) University of Pittsburgh Medical Center, Pittsburgh, PA (8) Columbia University MC New York, NY (9) Duke Cancer Institute, Durham, NC (10) Fox Chase Cancer Center, Philadelphia, PA (11) Dana-Farber Cancer Institute, Boston, MA (12) Massachusetts General Hospital, Boston, MA (13) Ottawa Hospital Cancer Center, ON, Canada (14) Karyopharm Therapeutics, Newton, MA (15) Princess Margaret Cancer Centre, Toronto, Ontario

Selinexor Mechanism of Action



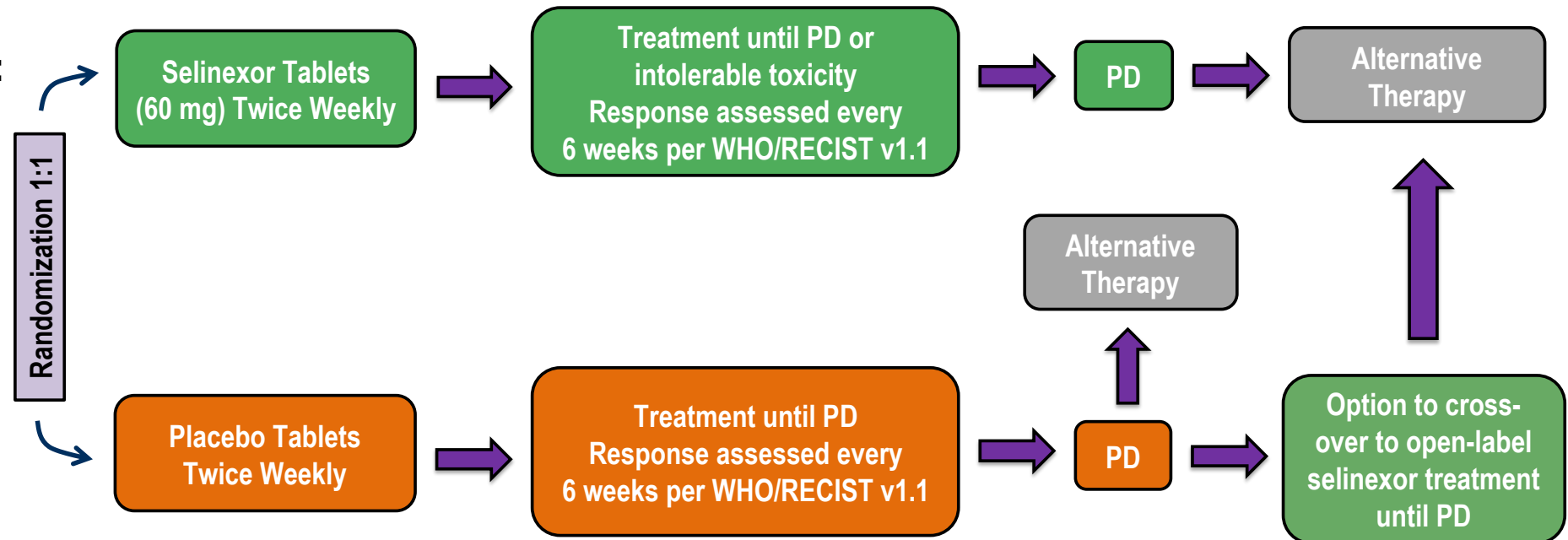
- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs) (e.g. p53, pRb, IκB, p27, p21) and eIF4E-bound oncoprotein mRNAs (e.g. c-Myc, MDM2, Bcl-2, Bcl-6, cyclin D)
- Selinexor, a selective inhibitor of XPO1-mediated nuclear export (SINE) compound, reactivates multiple TSPs including p53, IκB and FOXO, reduces c-Myc levels, and overcomes MDM2-mediated p53 degradation
- **Selinexor in liposarcoma:**
- CDK4 and MDM2 are amplified or overexpressed in dedifferentiated liposarcoma (DDLs) and contribute to active proliferation (*Thway 2016*)

- Selinexor reactivates p53 by increasing its protein levels, locking it in the nucleus and protecting it from MDM2-dependent-degradation
- Selinexor increases p21 protein levels. p21 binds to and inhibits the kinase activity of the cyclin D – CDK4
- Selinexor inhibits XPO1 mediated export of eIF4E and reduces the translation of eIF4E-dependent-protooncogenes among them cyclin D

SEAL – Study Design

- **Selinexor in Advanced Liposarcoma (SEAL)** is a phase 2-3, double-blind, randomized, placebo controlled, study comparing selinexor versus placebo in patients with dedifferentiated liposarcoma.
 - Patients ≥ 18 years with relapsed/refractory locally advanced or metastatic DDLS are randomized (1:1) to receive selinexor (60 mg) or placebo twice weekly per 42 day cycle
 - Randomization Stratifications: prior systemic therapies (1 vs. ≥ 2) and prior eribulin use (prior eribulin vs. no prior eribulin)
 - Main Inclusion/Exclusion Criteria: Histologically confirmed DDLS (using FISH or IHC), Refractory/relapsed, Measurable disease (by CT or MRI) per RECIST v1.1. Patients with brain metastases excluded
- **Phase II Primary Endpoint:** Progression free survival (PFS) as determined by an independent central imaging panel using WHO criteria. Pre-specified analysis using RECIST v1.1 was also included.
 - Secondary Endpoints: Overall response rate (ORR) and Duration of response (DOR) for each arm independently according to RECIST v1.1, safety for each arm

STUDY SCHEMATIC:



SEAL Patient Characteristics

SEAL Patient Characteristics	Selinexor	Placebo	All Patients
Enrolled¹	26	30	56
Median Age, Years (range)	55 (25 – 78)	64 (41-79)	61 (25-79)
Males : Females	14 M : 12 F	19 M : 11 F	33 M : 23 F
Cross-Over to Open Label Selinexor ²	2 (8%)	24 (80%)	26 (46%)
Median Number of Prior Regimens (range)	2 (1 – 7)	2 (1-9)	2 (1-9)
- Doxorubicin	18 (69%)	24 (80%)	42 (75%)
- Gemcitabine	12 (46%)	15 (50%)	27 (48%)
- CDK Inhibitor	8 (31%)	8 (27%)	16 (29%)
- Eribulin	8 (31%)	6 (20%)	14 (25%)
- Trabectedin	6 (23%)	5 (17%)	11 (20%)
- MDM2 Inhibitor	5 (19%)	9 (30%)	14 (25%)
- Surgery	23 (88%)	28 (93%)	51 (91%)
- Radiation	9 (35%)	14 (47%)	23 (41%)

¹Fifty-seven total patients enrolled however, one patient was deemed ineligible per protocol and was never unblinded

²Two patients on blinded selinexor crossed over to open-label selinexor due to progression based on WHO criteria, however treating PI believed these patients were deriving clinical benefit and kept treating patients with selinexor

SEAL Treatment Emergent Adverse Events by ARM ≥ 4 Patients

AE Term	Phase 2 - Blinded Selinexor (N=26)				Phase 2 - Blinded Placebo (N =30)		
	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)	Grade 1/2 (%)	Grade 3 (%)	Total (%)
Gastrointestinal							
Nausea	23 (88.5)	1 (3.8)	--	24 (92.3)	11 (36.7)	--	11 (36.7)
Anorexia	16 (61.5)	--	--	16 (61.5)	4 (13.3)	--	4 (13.3)
Vomiting	15 (57.7)	--	--	15 (57.7)	5 (16.7)	--	5 (16.7)
Altered Taste	11 (42.3)	--	--	11 (42.3)	2 (6.7)	--	2 (6.7)
Diarrhea	8 (30.8)	--	--	8 (30.8)	5 (16.7)	--	5 (16.7)
Abdominal pain	6 (23.1)	--	--	6 (23.1)	8 (26.7)	1 (3.3)	9 (30.0)
Constipation	5 (19.2)	--	--	5 (19.2)	8 (26.7)	--	8 (26.7)
Constitutional							
Fatigue	15 (57.7)	1 (3.8)	--	16 (61.5)	14 (46.7)	--	14 (46.7)
Weight loss	14 (53.8)	1 (3.8)	--	15 (57.7)	1 (3.3)	--	1 (3.3)
Dizziness	8 (30.8)	--	--	8 (30.8)	2 (6.7)	--	2 (6.7)
Edema	2 (7.7)	--	--	2 (7.7)	4 (13.3)	--	4 (13.3)
Metabolism							
Hyperglycemia	7 (26.9)	2 (7.7)	--	9 (34.6)	3 (10.0)	1 (3.3)	4 (13.3)
Hyponatremia	3 (11.5)	5 (19.2)	--	8 (30.8)	6 (20.0)	--	6 (20.0)
Alkaline Phosphatase Increase	5 (19.2)	--	--	5 (19.2)	5 (16.7)	--	5 (16.7)
Hypocalcemia	4 (15.4)	--	--	4 (15.4)	--	--	--
Hypokalemia	2 (7.7)	--	--	2 (7.7)	3 (10.0)	1 (3.3)	4 (13.3)
Other							
Vision Blurred	7 (26.9)	--	--	7 (26.9)	2 (6.7)	--	2 (6.7)
Hypertension	5 (19.2)	--	--	5 (19.2)	1 (3.3)	--	1 (3.3)
Headache	5 (19.2)	--	--	5 (19.2)	4 (13.3)	--	4 (13.3)
Cough	4 (15.4)	--	--	4 (15.4)	2 (6.7)	--	2 (6.7)
Hypotension	4 (15.4)	--	--	4 (15.4)	3 (10.0)	--	3 (10.0)
Fever	1 (3.8)	--	--	1 (3.8)	4 (13.3)	--	4 (13.3)
Hematologic							
Anemia	9 (34.6)	4 (15.4)	1 (3.8)	14 (53.8)	6 (20.0)	3 (10.0)	9 (30.0)
Thrombocytopenia	7 (26.9)	2 (7.7)	1 (3.8)	10 (38.5)	3 (10.0)	--	3 (10.0)
Leukopenia	7 (26.9)	1 (3.8)	--	8 (30.8)	1 (3.3)	--	1 (3.3)
Neutropenia	5 (19.2)	2 (7.7)	--	7 (26.9)	1 (3.3)	--	1 (3.3)

- 12 patients on selinexor had dose reductions due to AEs. No deaths occurred on blinded selinexor treatment. One death (colonic perforation) was reported on blinded placebo treatment.

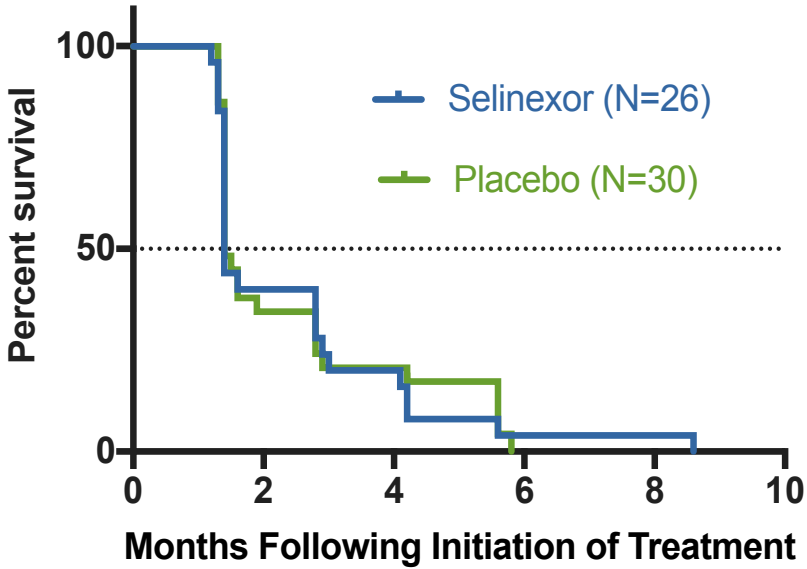
SEAL PFS: WHO v. RECIST v1.1 Criteria

Variable	WHO Criteria	RECIST v1.1 Criteria
Measurability at baseline	Bi-dimensional, any size, determine product of longest (LD) and shortest (SD) diameters	Uni-dimensional (LD only) with LD \geq 1 cm. Non-measurable: All other lesions, including small lesions (LD < 1 cm)
No. of Target Lesions Evaluated	All lesions are considered target lesions, including small (1 cm) lesions	Up to 5 total target lesions (maximum 2 per organ)
Progressive Disease	\geq 25% increase in product (LD x SD) of one or more isolated lesions or appearance of new lesions	\geq 20% increase over smallest SUM of LDs observed (absolute increase of at least 5 mm) or appearance of new lesions

Comparison of WHO to RECIST v1.1 revealed that the WHO criteria, which uses a bi-dimensional evaluation of each lesion, results in the premature determination of clinically asymptomatic progression events, typically involving small lesions, while overall tumor burden was stable. This phenomenon has already been observed in tumors such as sarcoma and melanoma, which are heterogenous and have irregularly shaped lesions. Numbers of patients with PD based on WHO criteria was 2-fold higher than the number of patients that had progressive disease using RECIST v1.1 criteria (*Therasse 2000, Mazumdar 2004*).

SEAL PFS: WHO vs. RECIST v1.1

WHO PFS - Selinexor v. Placebo

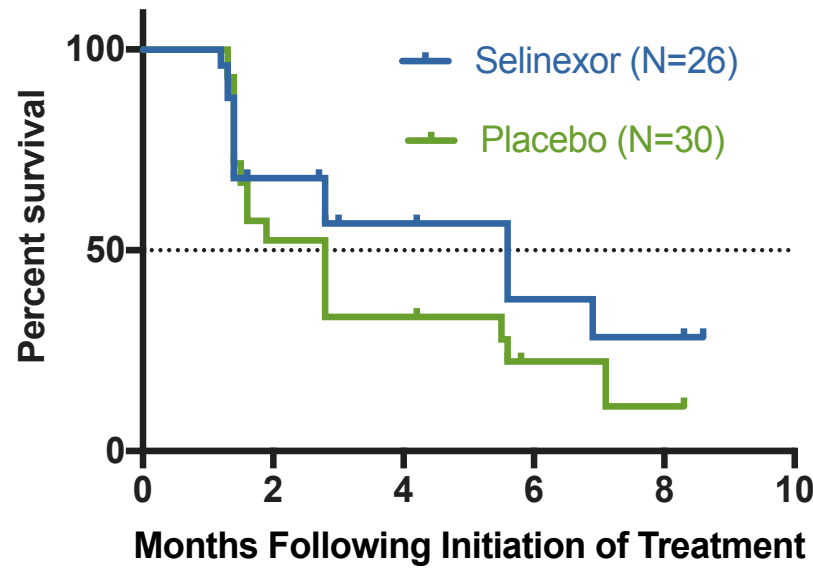


WHO Criteria

Median PFS= 1.4 Months, Selinexor and Placebo
Hazard Ratio (95% CI)= 1.02 (0.59, 1.77)
Progression Events= 25 Selinexor; 28 Placebo

Months	0	1.3	1.4	1.6	2.8	2.9	4.2	5.6	5.8	8.6
Selinexor	25	24	21	11	10	7	4	2	--	1
Placebo	29	29	25	13	10	7	6	4	1	--

RECIST v1.1 PFS - Selinexor v. Placebo

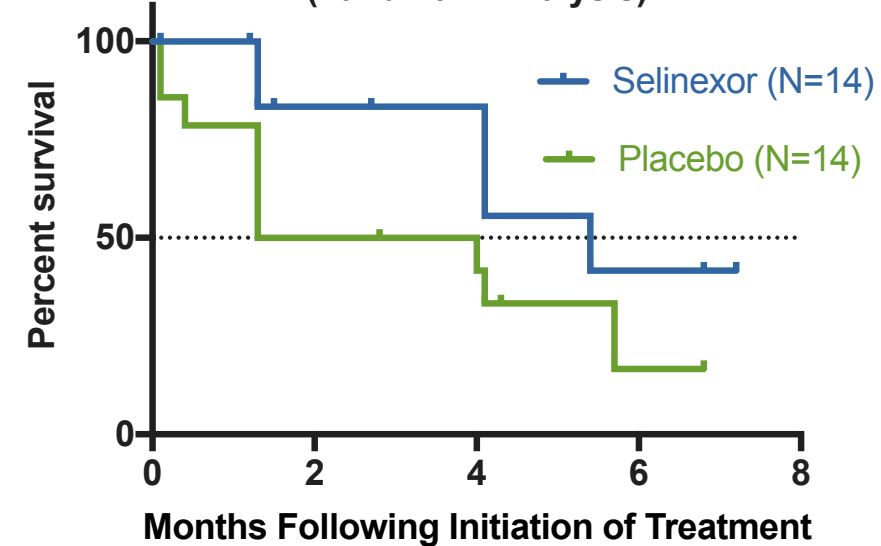


RECIST v1.1 Criteria

Selinexor Median PFS= 5.5 Months
Placebo Median PFS= 2.7 Months
Hazard Ratio (95% CI)= 0.67 (0.33, 1.37)
Progression Events= 13 Selinexor; 19 Placebo

Months	0	1.3	1.4	1.6	2.8	4.2	5.6	8.3	8.6
Selinexor	25	24	22	14	12	7	6	3	1
Placebo	29	29	26	14	11	7	5	1	--

RECIST v1.1 PFS - Selinexor v. Placebo (Landmark Analysis)

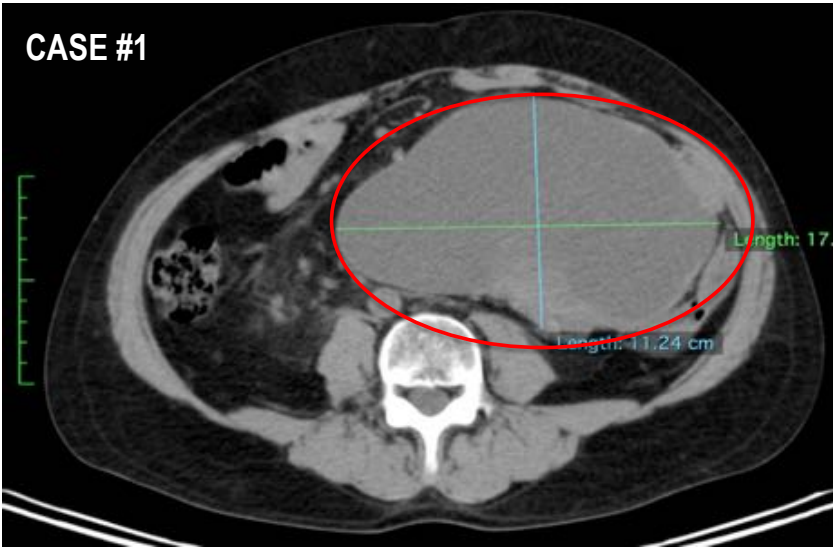


Landmark Analysis* RECIST v1.1 Criteria

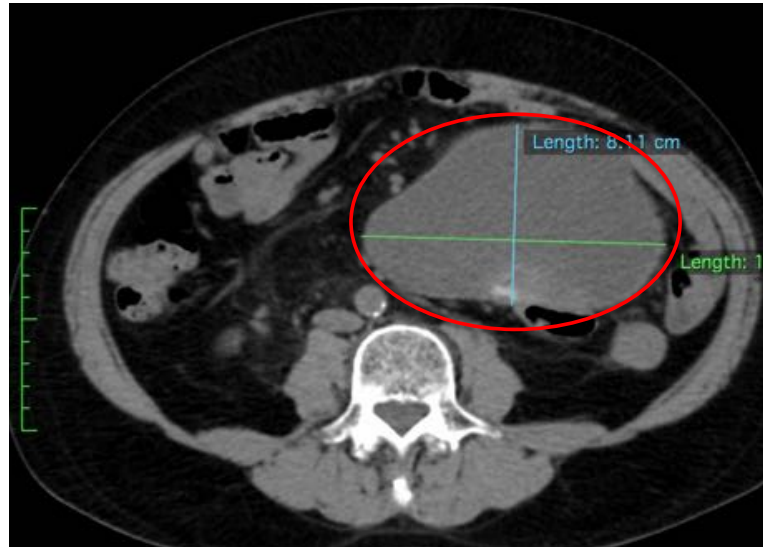
Selinexor Median PFS= 5.4 Months
Placebo Median PFS= 2.7 Months
Hazard Ratio (95% CI)= 0.43 (0.15, 1.26)
Progression Events= 5 Selinexor; 10 Placebo (*in patients on study ≥45 days)

Months	0	1.3	2.7	2.8	4.1	4.3	5.4	6.8	7.2
Selinexor	14	12	7	--	6	--	4	3	1
Placebo	14	11	--	7	5	3	--	1	--

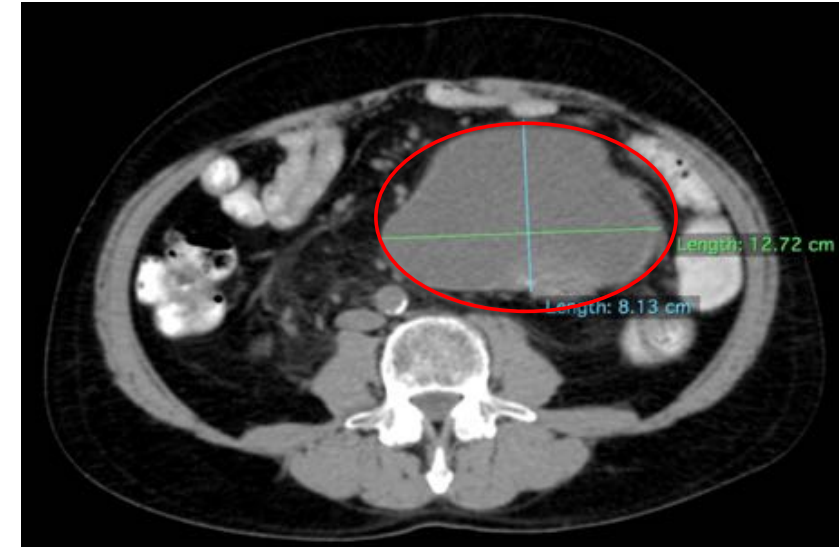
SEAL Patient Case #1 Study



Lesion at Baseline – LD 174.7 mm



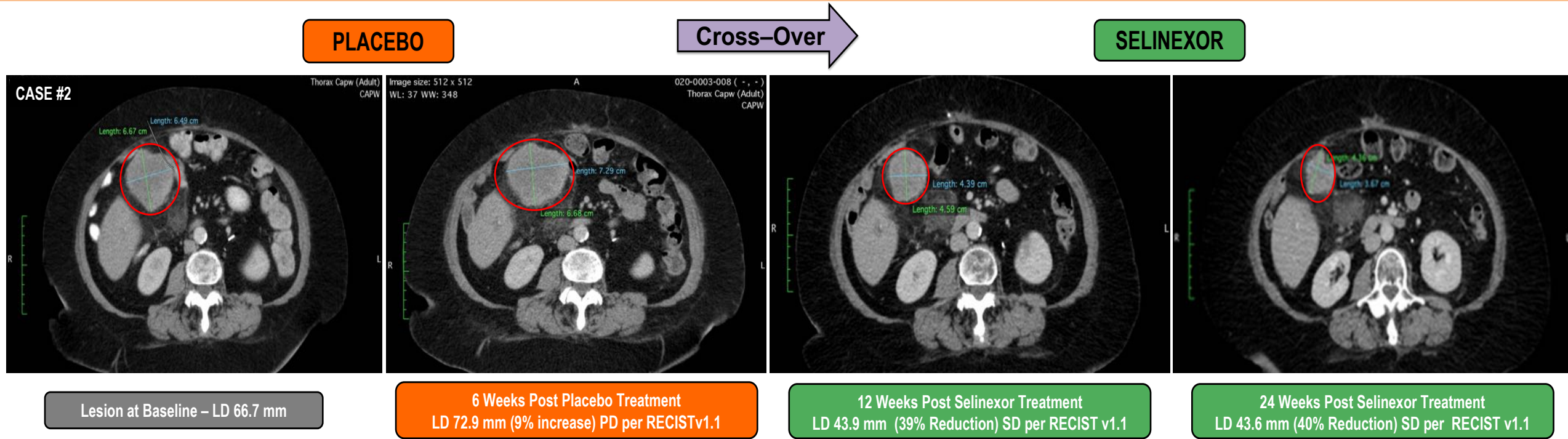
12 Weeks Post Selinexor Treatment
LD 135.3mm (23% Reduction) SD per RECIST v1.1



17 Weeks Post Selinexor Treatment
LD 127.2 mm (27% Reduction) SD per RECIST v1.1

Blinded Selinexor Case #1 Study: 65 y/o male originally diagnosed with retroperitoneal liposarcoma (MDM2 and CDK4 co-amplification), surgically resected. Recurrence was treated with four prior lines of therapy (¹gem/doc/dox, ²trabectedin, ³dacarbazine, ⁴ifosfamide). Randomized to selinexor. This patient remained on treatment until disease progression at 9 months.

SEAL Patient Case #2 Study



Placebo to Cross-Over Selinexor Case #2 Study: 61 y/o female originally diagnosed with metastatic MDM2 amplified liposarcoma in June 2008. Patient had several resections for recurrent disease and was treated with seven prior systemic therapies (¹ifosf/dox; ²gem/doc; ³valproic acid; ⁴trabectedin; ⁵palbociclib; ⁶nivolumab; ⁷pazopanib). Patient was randomized to placebo arm, and crossed over to selinexor upon progression. This patient remained on open label selinexor treatment until disease progression at 11 months.

Conclusions

- Phase 2 portion of the SEAL trial is now complete and the Phase 3 portion is ongoing
- The most common adverse events of selinexor treatment are: nausea, fatigue, anorexia, and weight loss (mostly Grade 1/2).
Hyponatremia and anemia are the most common Grade 3/4 adverse events.
- RECIST v1.1 may be better criteria than WHO to evaluate selinexor efficacy in DDLS; as WHO results in the premature determination of clinically asymptomatic progression events, typically involving small lesions, while overall tumor burden was stable
 - Hazard Ratios (95% CI) comparing Selinexor to Placebo of 0.67 (0.33, 1.37) using RECIST v1.1 criteria, as compared to 1.02 (0.59, 1.77) using WHO criteria
 - Median PFS for Selinexor and Placebo are – RECIST: 5.5 months vs. 2.7 months; WHO: 1.4 months for both
- Improvement of PFS (RECIST v1.1) is promising and supports continuation of the Phase 3 portion of selinexor in DDLS using RECIST v1.1 criteria only