

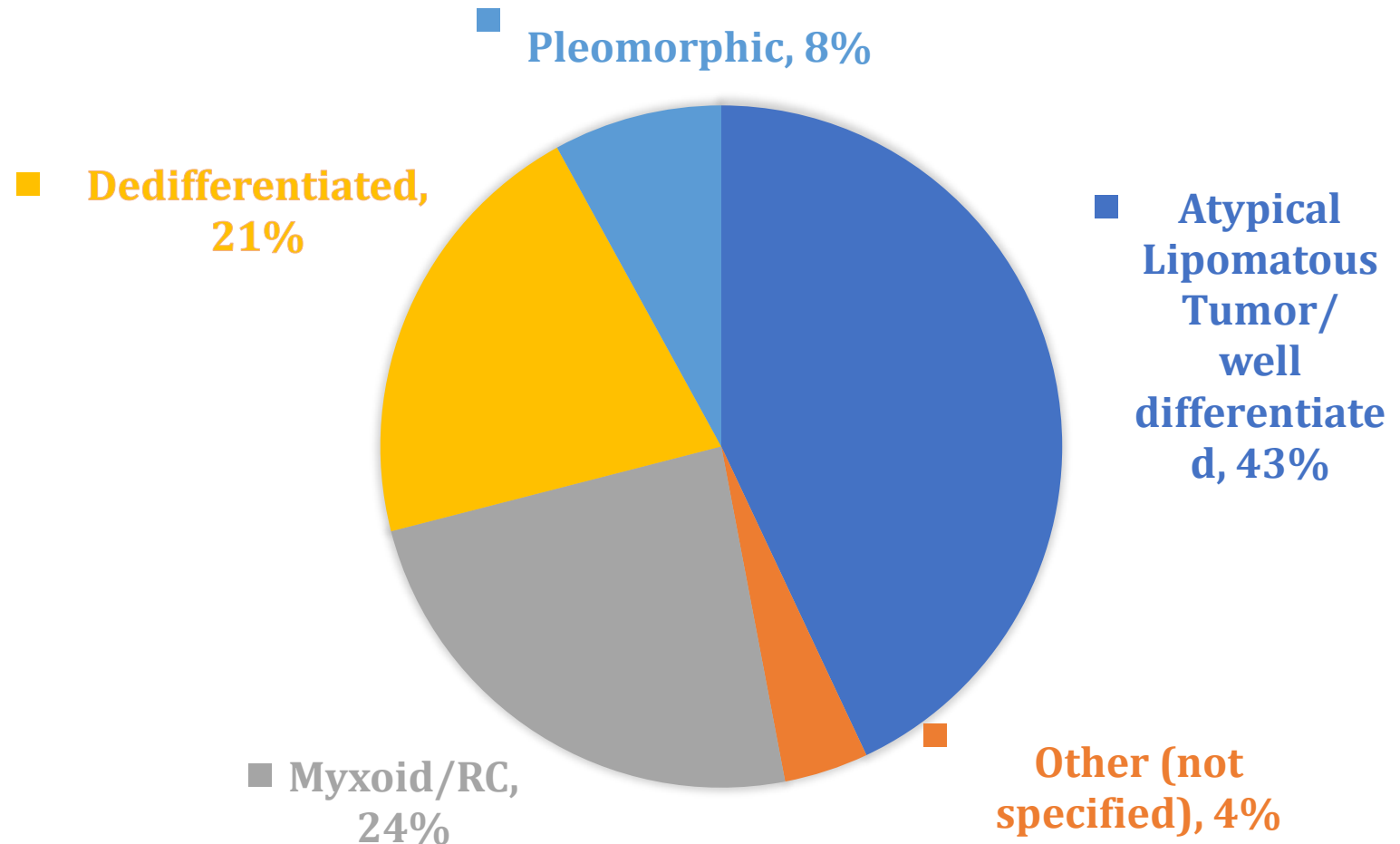
# SEAL: Phase 3, Randomized, Double Blind, Cross-Over, Study of Selinexor versus Placebo in Advanced Unresectable DeDifferentiated Liposarcoma (DDLs)

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# Background: De-Differentiated Liposarcoma

- Liposarcoma represent ~ 15-20% of STS
- Localized disease – surgical approach



# Systemic Treatments De-Differentiated Liposarcoma:

First line – Doxorubicin +/- Ifosfamide Limited Activity

- Palliative

Retrospective Studies	Patients	ORR	Median PFS (months)	Median OS (months)
Jones, Judson (Marsden, UK)	16	8% (Dox) 17% (AIM)	2	NR
Italiano, Bui (EORTC and MSKCC)	171	7.5% (Dox) 11% (combi)	4	15
Livingston, Somaiah (MDACC)	84	0% (Dox) 11% (AIM)	4	25
Stacchiotti, Gelderblom (EORTC/STBSG, ESMO 2020)	109	6% (Dox) 21% (AIM)	3.7	17.3

# Systemic Treatments De-Differentiated Liposarcoma:

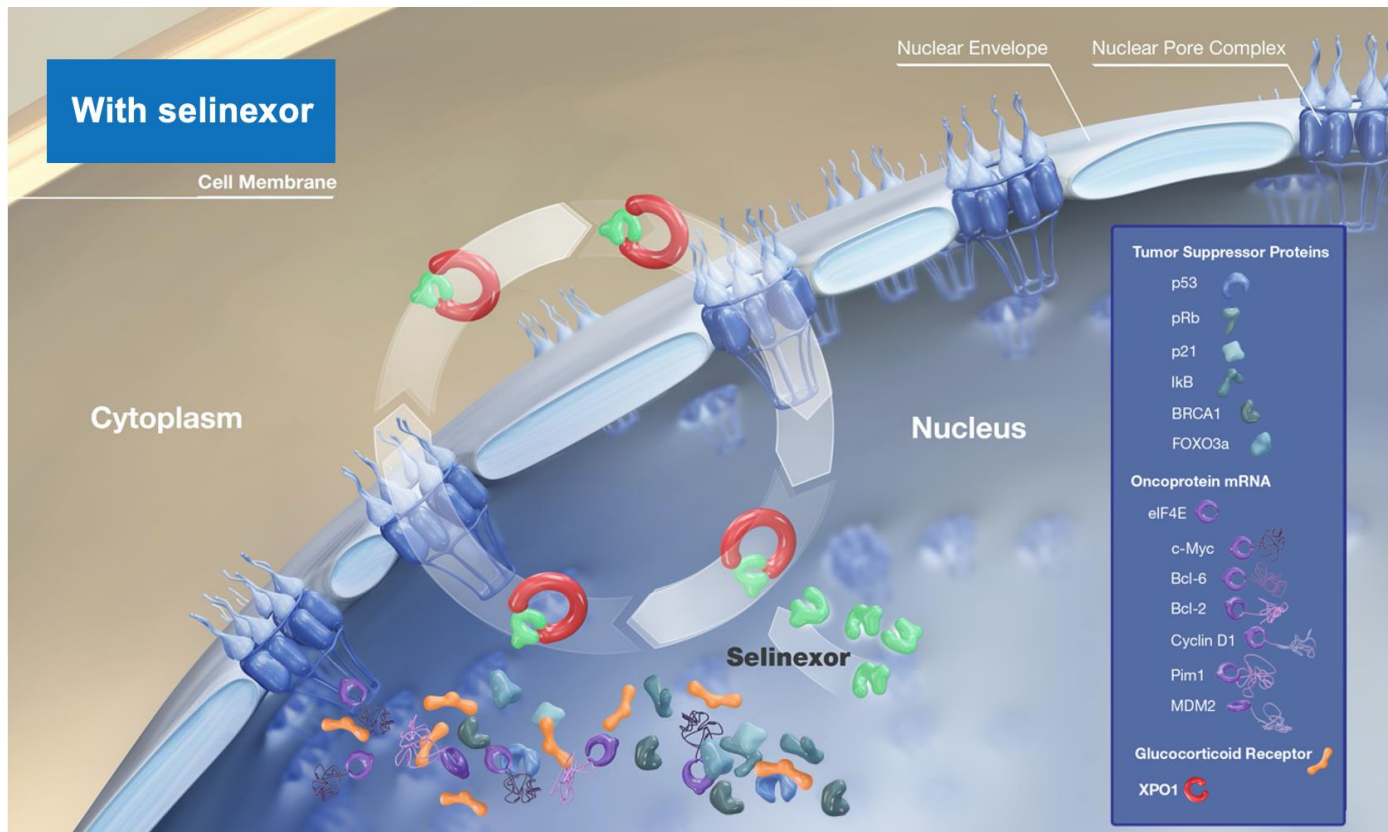
## Second line – Eribulin and Trabectedin

- Palliative

Prospective Studies	Patients	ORR	Median PFS (months)	Median OS (months)
<b>Trabectedin vs DTIC</b> Phase 3 (subgroup analysis including only DDLs)	45	NR	2.2 (HR 0.68)	No improvement
<b>Eribulin vs DTIC</b> Phase 3 (subgroup analysis including only DDLs)	31	NR	2.0 (HR 0.69)	18

**Novel therapies are needed in DDLPS**

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



**Exportin 1 (XPO1, CRM1) is the major nuclear export protein for<sup>1,2,3</sup>:**

- **Tumor suppressor proteins** (e.g., **p53**, pRb, IκB, FOXO3a)
- eIF4E-bound oncoprotein mRNAs (e.g., **MDM2**, c-Myc, Cyclin D1, Bcl-2, Bcl-xL)
- **Both MDM2 and p53** contain nuclear localization signal domains that use XPO1 for nuclear to cytoplasmic degradation.

**Selinexor is an oral selective XPO1 inhibitor that:**

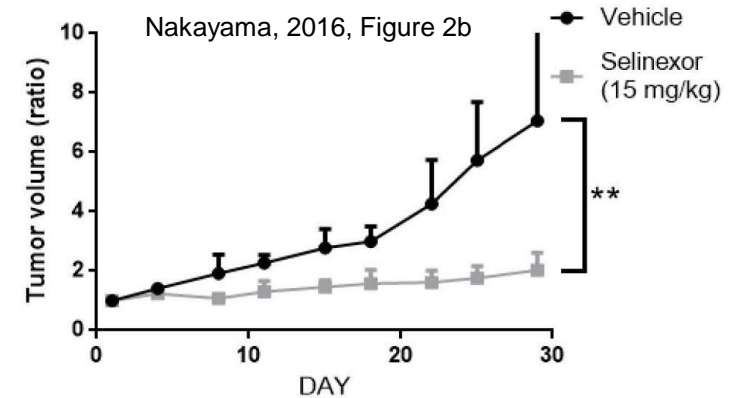
- Induces cell cycle arrest and apoptosis in sarcoma cell lines<sup>1</sup>
- Inhibits the growth of sarcoma tumors<sup>4</sup>
- Induces expression of genes that promote adipogenesis<sup>1</sup>

Selinexor is currently approved in multiple myeloma and diffuse large B cell lymphoma.

# Selinexor in Liposarcoma

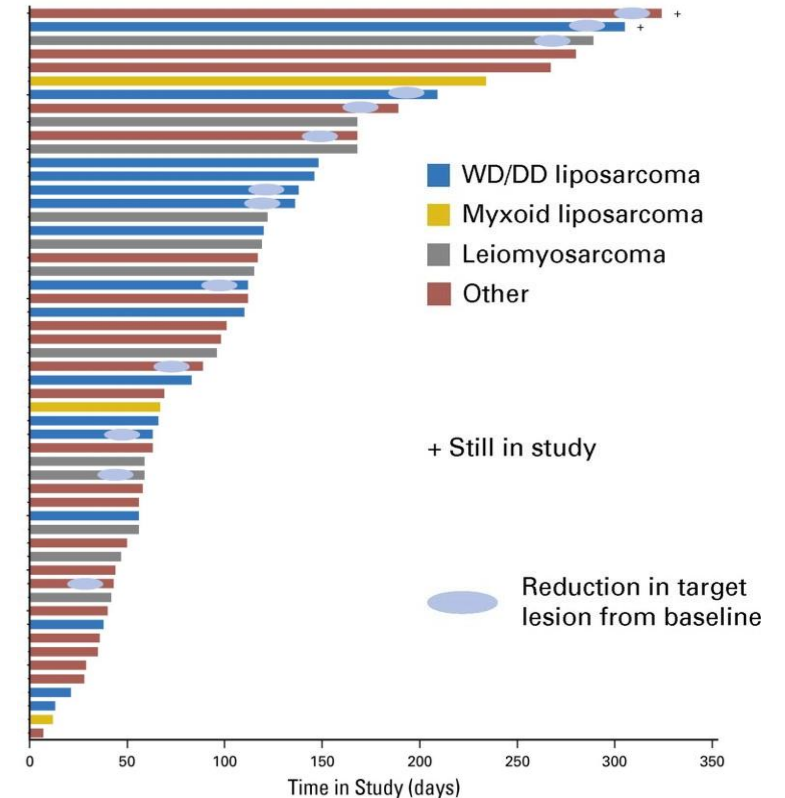
## Selinexor demonstrated anti-tumor activity against DDLS in preclinical studies

- XPO1 was overexpressed in liposarcoma cell lines and selinexor induced cell cycle arrest and apoptosis in these cell lines and xenografts

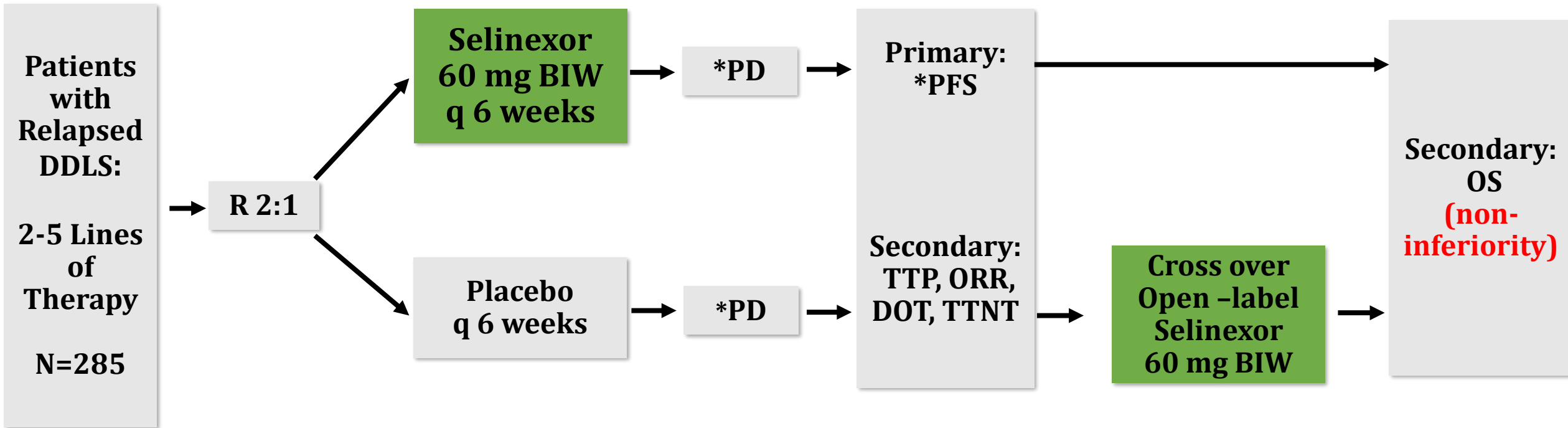


## Selinexor demonstrated anti-tumor activity in DDLS in Phase 1 clinical study

- Selinexor induced a reduction in target lesion size in 6/15 (40%) and stable disease for 4 months or longer in 7/15 (47%); GMI >1.33



# SEAL: Phase 3, Randomized, Double Blind, Cross-Over, Study of Selinexor versus Placebo in Advanced Unresectable Dedifferentiated Liposarcoma (DDLs) Study Design



## Stratification Factors:

- 1) prior eribulin use
- 2) prior trabectedin and
- 3) # prior therapies (2 versus  $\geq 3$ )

\* PD based on Independent Radiology Review using RECIST 1.1 Imaging done q 6 weeks C1 through C5, C6 on q 12 weeks

# SEAL: Study Endpoint and Design

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## **Primary Endpoint – Progression Free Survival**

- Primary objective was met with a two-sided p-value from stratified log-rank test of 0.0228, which is below the allocated alpha of 0.0488

## **Secondary Endpoint(s) – Overall Survival (non-inferiority), ORR**

### **Sample size**

- median PFS of 1.6 months (placebo) and 2.7 months (selinexor); a hazard ratio (HR) of 0.6
- 1-sided alpha of 0.025 (superiority), stratified log-rank test, 90% power
- 2:1 randomization favoring selinexor
- 209 PFS events required for the final efficacy analysis;



# SEAL: Study Design

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## Inclusion Criteria

- Pathology confirmation of De-differentiated Liposarcoma
- Investigator assessed radiologic evidence of disease progression within 6 months prior to randomization and requiring systemic treatment
- Must have received at least 2 but no more than 5 prior systemic therapies for the treatment of liposarcoma.
- Adequate laboratory functional values:
  - Absolute neutrophil count (ANC)  $\geq 1500$ /
  - Platelets  $\geq 100,000$ /mm<sup>3</sup>
  - Hemoglobin (Hb)  $\geq 9$  g/dL
- Adequate hepatic function and adequate renal function: **Serum creatinine clearance of  $\geq 30$  mL/min**

# SEAL: Baseline Demographics and Clinical Characteristics are Comparable for the Two Study Arms

Characteristic	Selinexor (N = 188)	Placebo (N = 97)
Age <sup>1</sup> , years		
Median (Range)	65.0 (33 - 84)	65.0 (31 - 85)
Distribution — no. (%)		
18–64 yr	92 (48.9)	46 (47.4)
65–74 yr	73 (38.8)	41 (42.3)
≥75 yr	23 (12.2)	10 (10.3)
Sex n (%)		
Females	114 ( 60.6)	64 ( 66.0)
Males	74 ( 39.4)	33 ( 34.0)
Race n (%)		
Asian	9 (4.8)	3 (3.1)
Black or African American	3 (1.6)	1 (1.0)
White	139 (73.9)	80 (82.5)
Other/Missing	37 (19.7)	13 (13.4)
Geographic Region n (%)		
North America	90 (47.9)	55 (56.7)
Europe and Israel	98 (52.1)	42 (43.3)

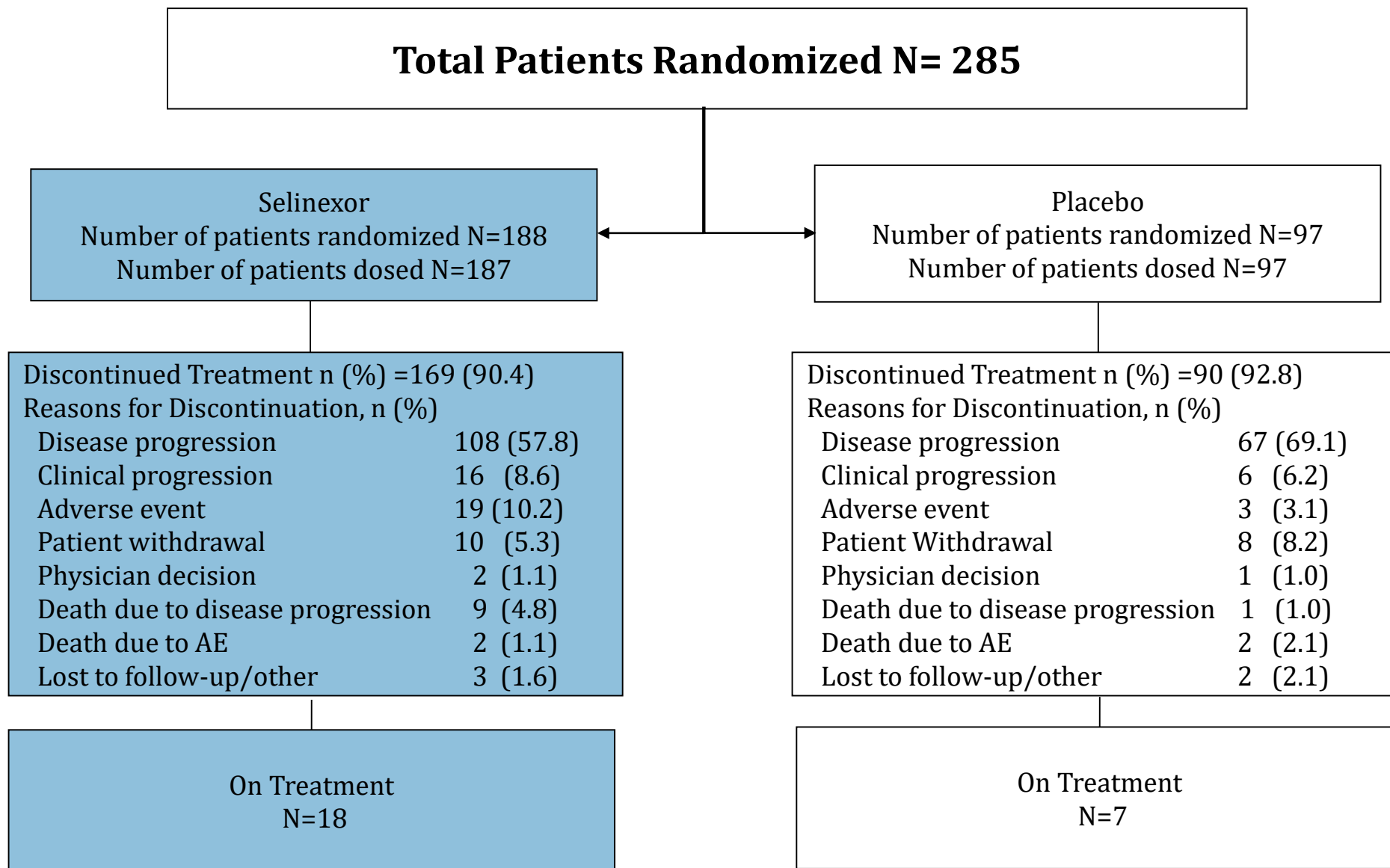
Characteristic	Selinexor (N = 188)	Placebo (N = 97)
ECOG <sup>2</sup> Performance Status, n (%)		
0	71 (37.8)	41 (42.3)
1	117 (62.2)	56 (57.7)
Median duration from <b>most recent progression</b> (range) — months	0.90 (0.1 - 6.97)	0.72 (0.1 - 16.5)
Median duration from initial diagnosis (range) — yr	4.3 (0 - 27)	4.3 (1 - 25)
Disease Stage Category at Study Entry, n (%)		
Localized/Locally advanced and unresectable	37 ( 19.7)	15 ( 15.5)
<b>Distant Metastasis</b>	129 ( 68.6)	70 ( 72.2)
Unknown/Missing	22 ( 11.7)	12 ( 12.4)
Primary Site of Initial Liposarcoma Lesion, n (%)	188 ( 100.0)	95 ( 97.5)
Extremity (Lower + Upper)	11 ( 5.9)	3 ( 3.1)
<b>Retroperitoneum</b>	<b>148 ( 78.7)</b>	<b>73 ( 75.3)</b>
Other	29 ( 15.4)	19 ( 19.6)

[1] Age is the age at date of randomization. [2] ECOG=Eastern Cooperative Oncology Group.

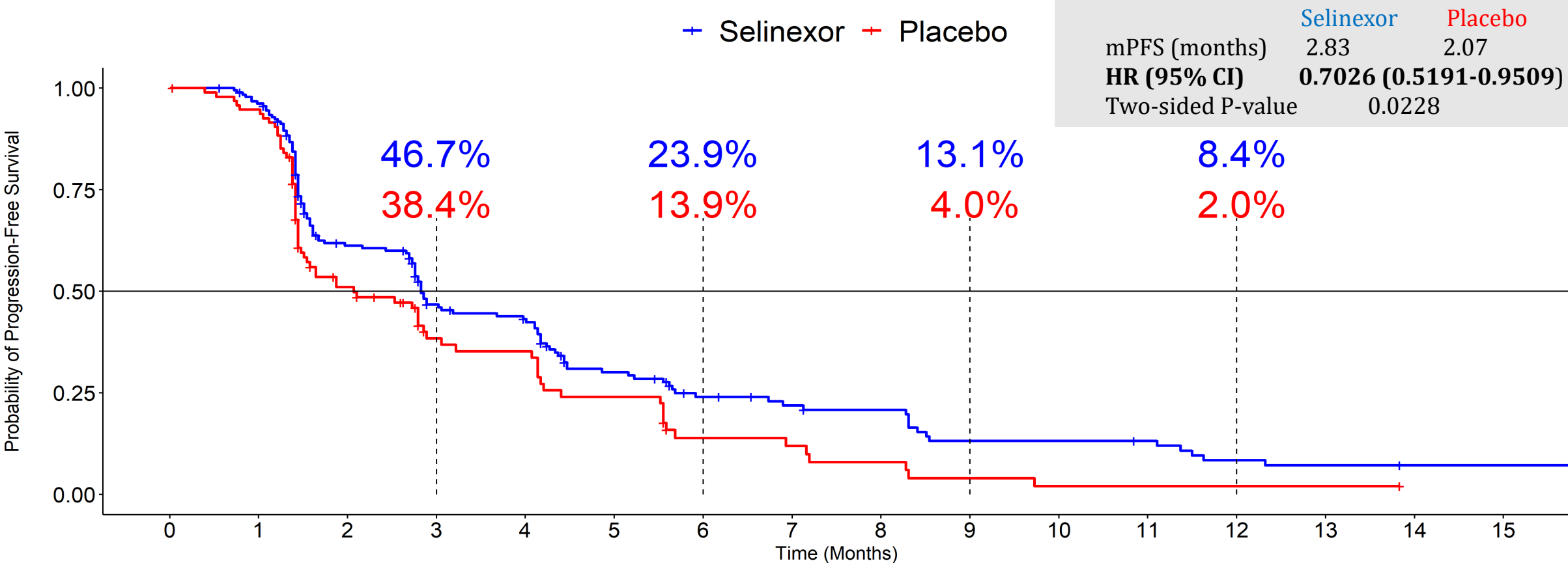
# Patients in SEAL were not Amenable to Surgery, were Heavily Pretreated, and had Exhausted All Available Treatment Options

Prior Therapies	Selinexor (N = 188)	Placebo (N = 97)
Number of Prior Antineoplastic Regimen		
Median (range)	2 (1 - 6)*	2 (1 - 7)*
Mean (STD)	2.7 (1.08)	2.8 (1.19)
Distribution – Number of Prior Regimen, n (%)		
≤2*	104 (55.3)	54 (55.7)
≥3	84 (44.7)	43 (44.3)
Previous Systemic Therapy		
Eribulin	66 (35.1)	35 (36.1)
Anthracyclines	168 (89.4)	86 (88.7)
Trabectedin	69 (36.7)	36 (37.1)
Others	61 (32.4)	30 (30.9)
Prior radiotherapy, n(%)		
Yes	86 (45.7)	45 (46.4)
Prior surgery, n(%)		
Yes	168 (89.4)	82 (84.5)
Number of Prior Surgeries		
Median (range)	2 (1 - 10)	2 (1 - 7)
Mean (STD)	2.3 (1.53)	2.1 (1.15)

# SEAL: Patient Disposition



# PFS Based on Independent Radiology Review - ITT

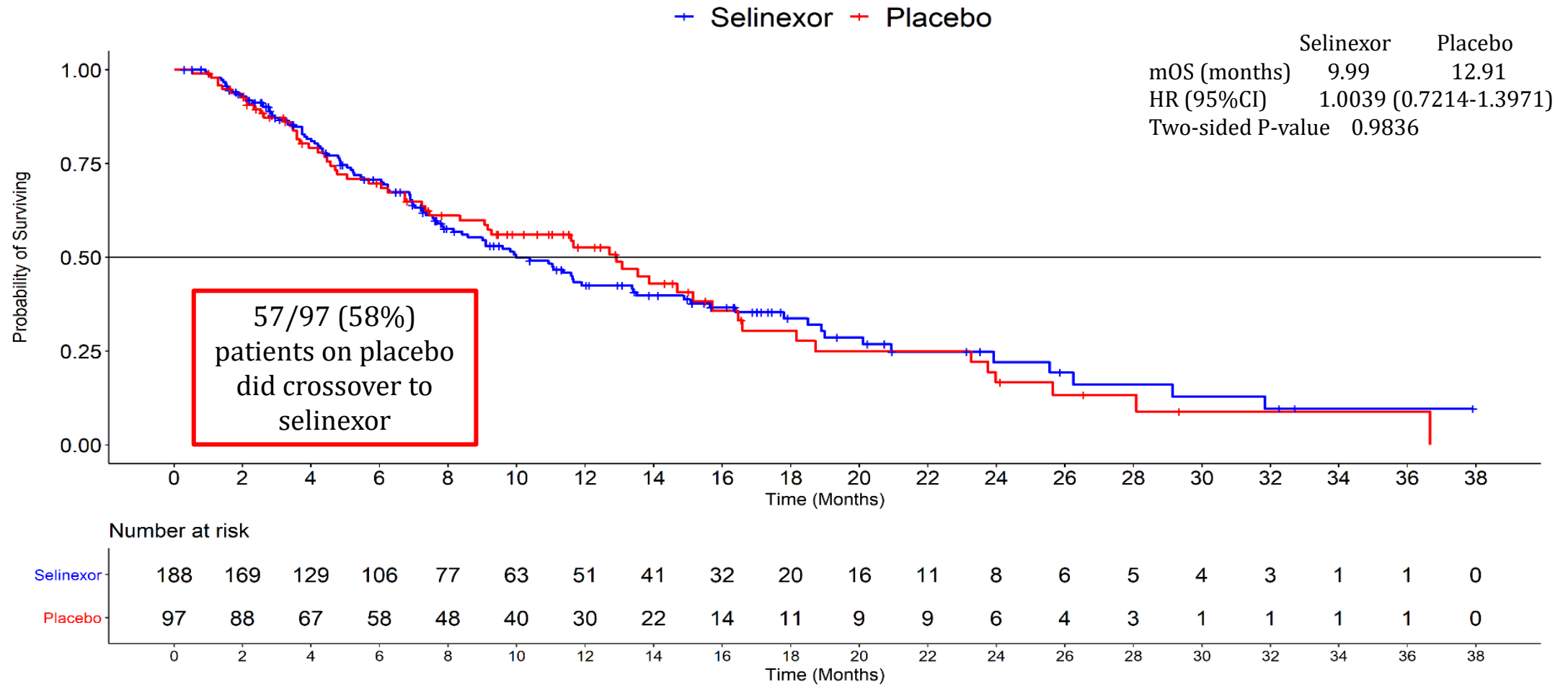


Number at risk

Selinexor	188	175	99	65	58	37	25	21	19	12	12	11	7	6	5	5
Placebo	97	89	41	24	22	15	7	6	4	2	1	1	1	1	0	0
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

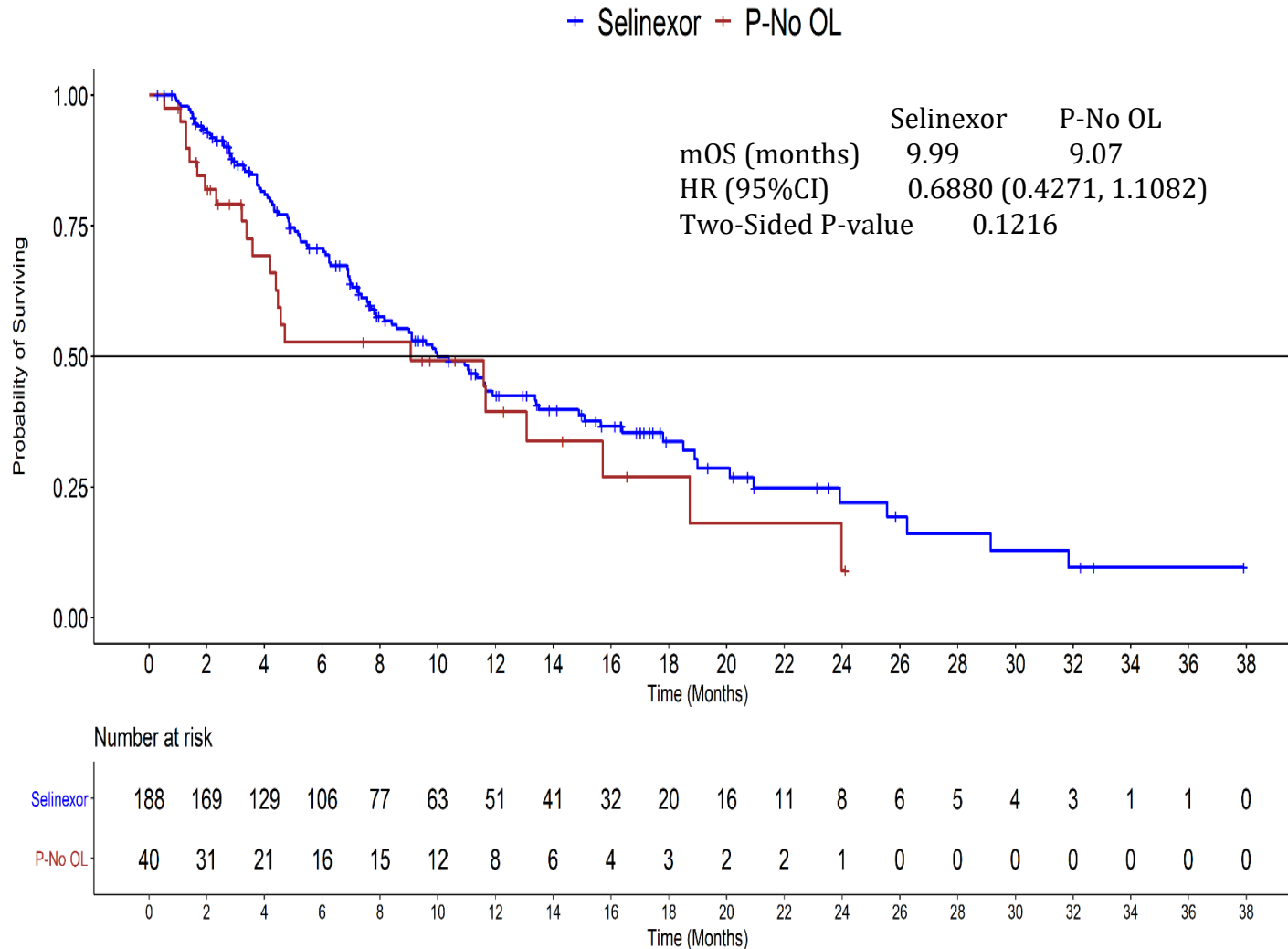
Final analysis based on 209 PFS events

# SEAL: Overall Survival by Treatment Arm - ITT Phase 3



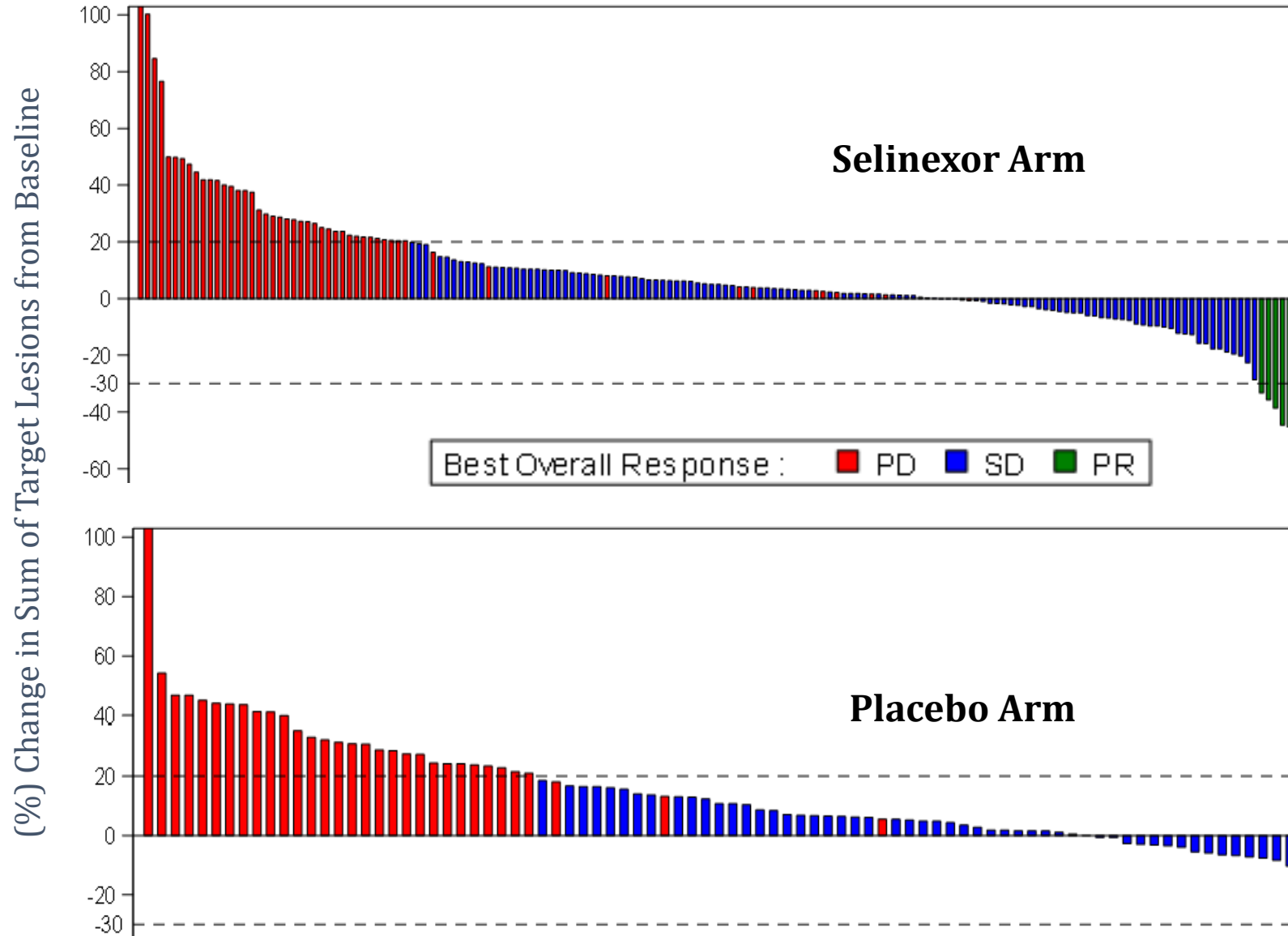
# SEAL: Overall Survival - Selinexor vs Placebo

## Who Did NOT Crossover Post Progression (i.e. never received selinexor)



- Pre-specified sensitivity analysis to examine the effect of selinexor on overall survival among patients randomized to selinexor versus patients randomized to placebo and did not crossover to open-label selinexor (i.e., never received selinexor)
- Results suggest a trend towards an improvement in overall survival due to selinexor (not statistically significant)

# SEAL: Best Overall Response During Blinded Treatment – ITT (7.5% had reduction in disease burden > 15%)

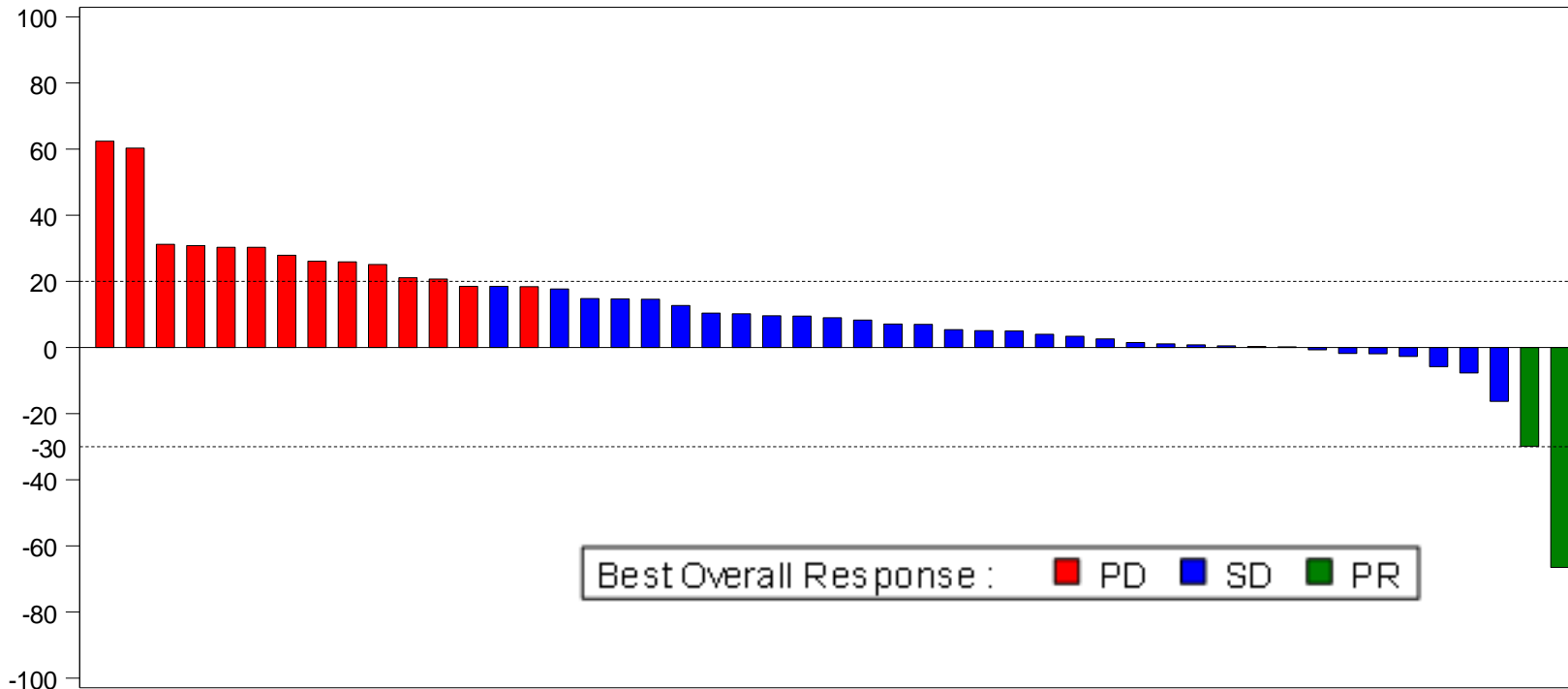


Patients with Target Lesion Reduction		
	Selinexor (N = 188)	Placebo (N = 97)
<b>&gt;=15% Reduction: N (%)</b>	<b>14 (7.5 %)</b>	<b>0</b>
<b>&gt;=30% Reduction: N (%)</b>	<b>5 (2.7 %)</b>	<b>0</b>



# SEAL: Best Overall Response to Selinexor who did Crossover During Open Label – (5.3% had reduction in disease burden > 15%)

(%) Change in Sum of Target Lesions from Baseline



Patients with Target Lesion Reduction	
	Selinexor (N = 57)
<b>&gt;=15% Reduction: N (%)</b>	<b>3 (5.3%)</b>
<b>&gt;=30% Reduction: N (%)</b>	<b>2 (3.5%)</b>

# SEAL: Selected Non-Haematological TEAEs\* – Phase 3

	Selinexor Arm (N = 187)		Placebo Arm (N = 97)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
GI				
Nausea	80.7	5.3	39.2	0
Decreased appetite	60.4	7.5	22.7	1.0
Vomiting	49.2	2.7	12.4	3.1
Constipation	37.4	0.5	23.7	0
Diarrhoea	40.1	2.7	17.5	2.1
Abdominal pain	23.5	5.3	32.0	2.1
Dysgeusia	26.7	0	4.1	0
<b>Constitutional</b>				
Fatigue	51.3	6.4	32.0	3.1
Weight decreased	41.7	0.5	9.3	0
Asthenia	31.0	10.2	10.3	0
<b>Other</b>				
Dyspnoea	19.3	2.1	12.4	2.1
Hyponatraemia	27.3	10.7	9.3	0
Increased creatinine	21.4	1.6	13.4	0
Dizziness	22.5	1.1	6.2	0
Blurred vision	22.5	1.1	3.1	0

\*Events that have occurred in ≥15% of patients and had > 5% difference between the arms.

## SEAL: Selected Haematological TEAEs\* – Phase 3

	Selinexor Arm (N = 187)		Placebo Arm (N = 97)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anaemia	46.5	18.7	22.7	8.2
Thrombocytopenia	38.0	10.2	5.2	0
Neutropenia	19.3	9.1	1.0	0

- No reported febrile neutropenia

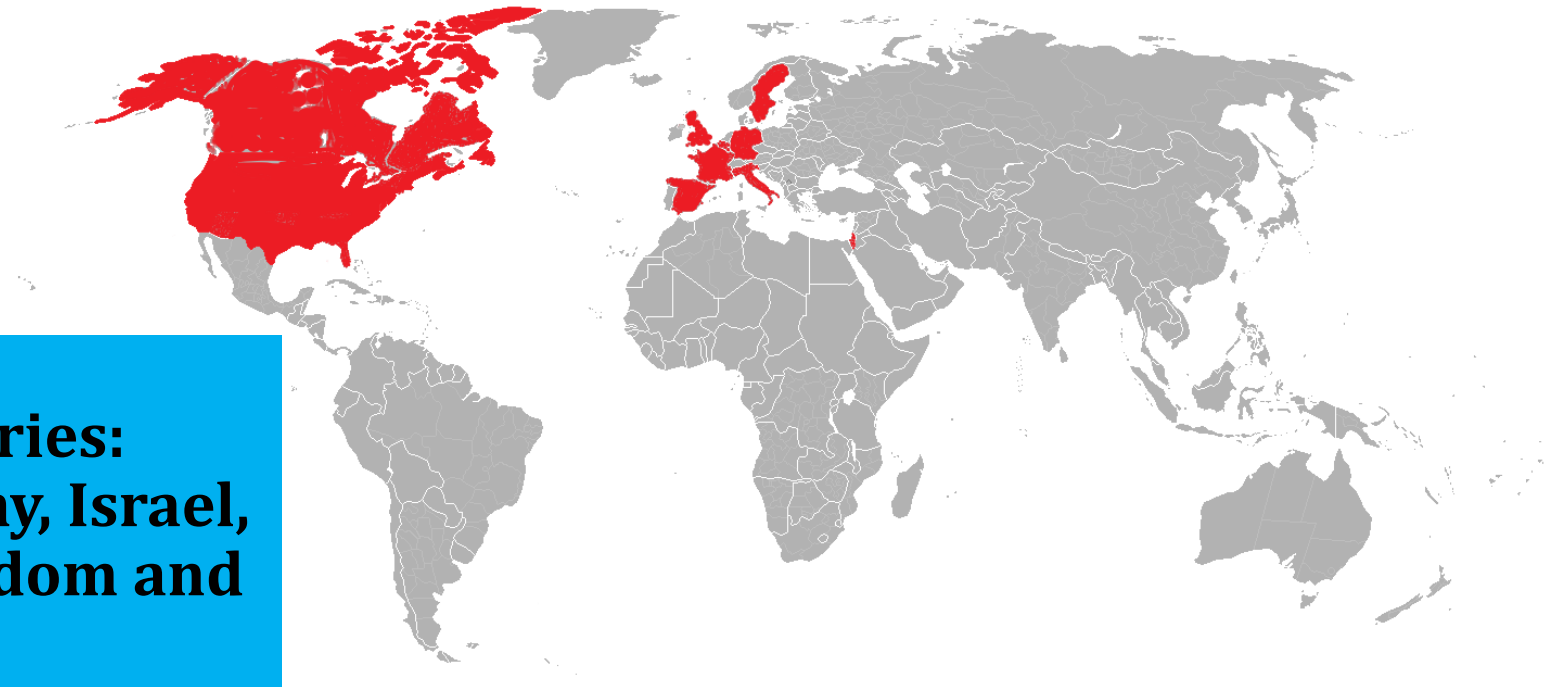
\*Events that have occurred in ≥15% of patients

# SEAL Trial Conclusions

- **Selinexor is novel first in class therapy that inhibits XPO1, activates Tumor Suppressor Proteins(TSP) and reduces onco-proteins, leveraging patients own innate TSP function and is foundational to cancer biology**
- **SEAL is the first and largest global phase 3 trial in patients with relapsed DDLS (n=285)**
- **SEAL met the primary endpoint**
  - **Selinexor significantly prolonged the PFS of heavily pretreated DDLS patients (HR 0.70, p = .0228)**
- **Side effects of oral selinexor in DDLS patients are well characterized, predictable and reversible**
  - The most common TEAEs (nausea, fatigue, decreased appetite, anemia, vomiting, and thrombocytopenia) were generally low grade
  - Oral selinexor was well tolerated in DDLS patients with supportive care and dose modifications

**In Patients with DDLS who have received at least 2 prior therapies, twice-weekly oral selinexor offers an effective, convenient, novel oral therapy**

# Acknowledgements SEAL Trial



**Global studies with 10 Countries:  
Belgium, Canada, France, Germany, Israel,  
Italy, Spain, Sweden, United Kingdom and  
USA**

**Sarcoma Community, PI, Patients, their  
Families and Caregivers**

**Thank you!!!!**