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

Mrinal Gounder[1], Albiruni Abdul Razak[2], Neeta Somaiah[3], Sant Chawla[4], Javier Martin-Broto[5], Giovanni Grignani[6], Scott Schuetze[7], Bruno Vincenzi[8], Andrew J. Wagner[9], Bartosz Chmielowski[10], Robin L. Jones[11], Richard F. Riedel[12], Silvia Stacchiotti[13], Elizabeth T. Loggers[14], Kristen N. Ganjoo[15], Axel Le Cesne[16], Antoine Italiano[17], Xavier Garcia del Muro[18], Melissa Amber Burgess[19], Sophie Piperno-Neumann[20], Christopher Ryan[21], Didier Cupissol[22], Antonio Lopez-Pousa[23], Mary Mulcahy[24], Charles Forscher[25], Nicolas Penel[26], Tracey Duncan[27], Osnat Ben-Shahar[27], Yosef Landesman[27], Dayana Michel[27], Hongwei Wang[27], Jatin J. Shah[27], Sharon Shacham[27], Michael G Kauffman[27], Steven Attia[28]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Princess Margaret Cancer Centre, Toronto, ON; [3]Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Sarcoma Oncology Center, Santa Monica, CA; [5]Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/Universidad de Sevilla, Seville, Spain; [6]Division of Medical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Candiolo (TO), Italy; [7]University of Michigan, Ann Arbor, MI; [8]Policlinico Universitario Campus, Bio-Medico, Rome, Italy; [9]Dana-Farber Cancer Institute, Boston, MA; [10]Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; [11]The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; [12]Duke Cancer Institute, Duke University Medical Center, Durham, NC; [13]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [14]Fred Hutchinson Cancer Research Center, Seattle, WA; [15]Stanford Cancer Institute, Stanford, CA; [16]Institut Gustave Roussy, Villejuif, France; [17]Institut Bergonié, Bordeaux, France; [18]Catalan Institute of Oncology, IDIBELL, University of Barcelona, Barcelona, Spain; [19]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA; [20]Institut Curie, Paris, France; [21]Oregon Health & Science University, Portland, Oregon; [22]Department of Medical Oncology, Centre Val d'Aurelle, Montpellier, France; [23]Department of Cancer Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [24]The Robert H Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [25]Cedars-Sinai Medical Center, Los Angeles, CA; [26]Centre Oscar Lambret and Lille University, Lille, France; [27]Karyopharm Therapeutics Inc., Newton, MA; [28]Mayo Clinic, Jacksonville, FL

Background: De-Differentiated Liposarcoma

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

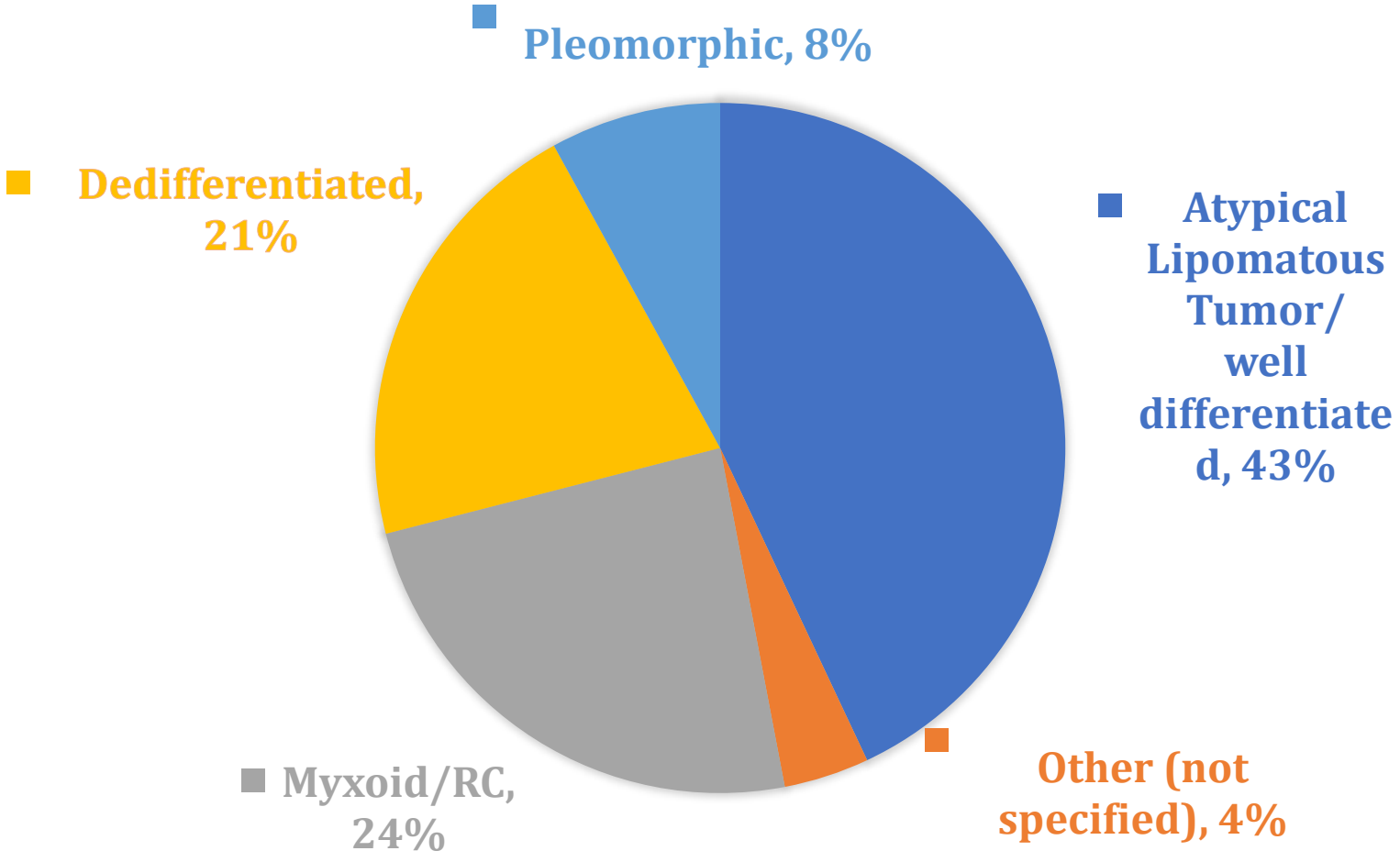


Figure adapted from Brennan M, et. al, Management of Soft Tissue Sarcoma, 2016

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) 115 (AIM)	4	25
Stacchiotti, Gelderblom (EORTC/STBSG, ESMO 2020)	109	6% (Dox) 21% (AIM)	3.7	17.3

Jones RL, et. al., European Journal of Cancer, 2005; Italiano A, Annals of Oncology, 2011; Stacchiotti_ Chemo in liposarcoma EORTC_ESMO2020; Livingstonet al., Scientific Reports, 2017

Systemic Treatments De-Differentiated Liposarcoma:

Second line – Eribulin and Trabectedin

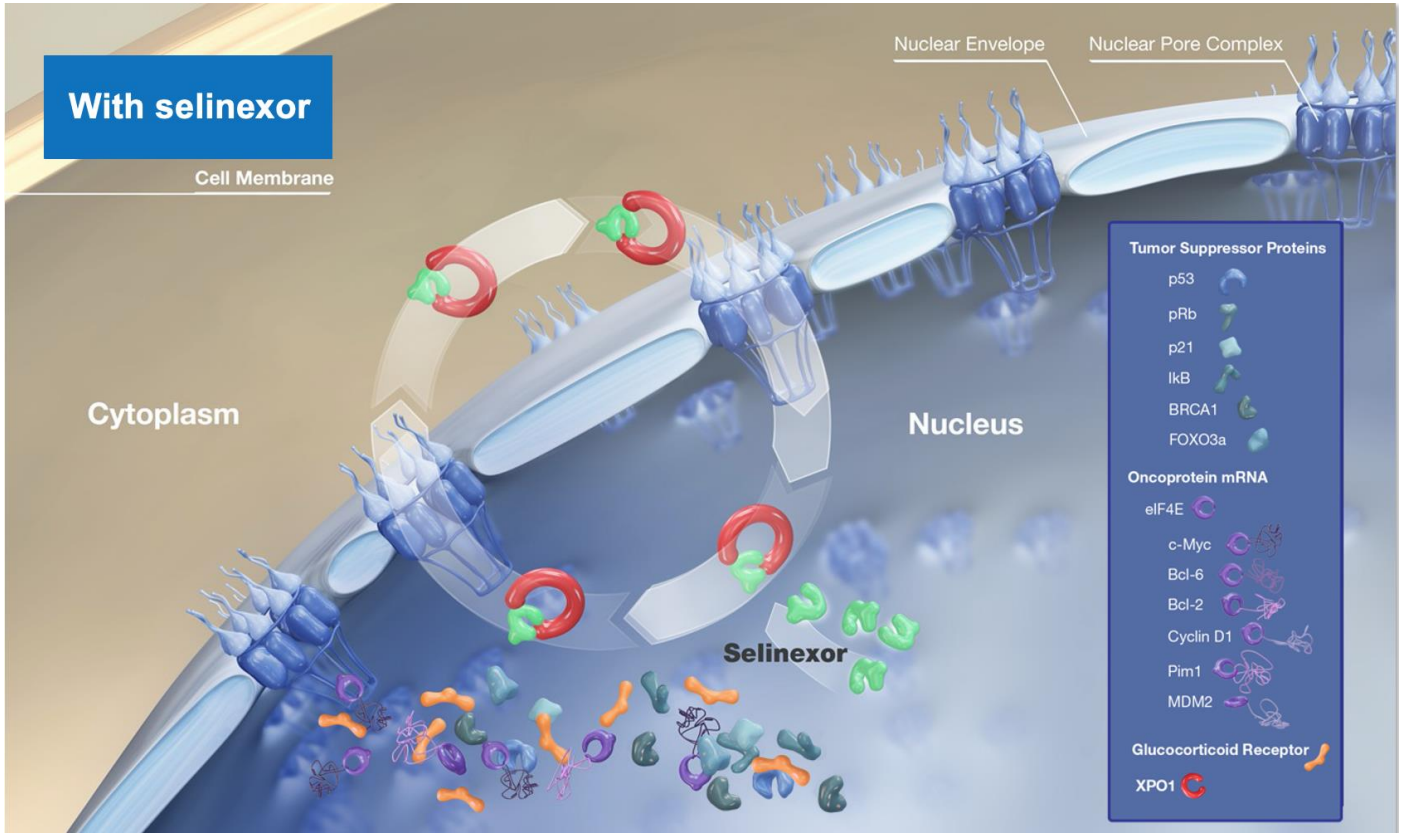
- Palliative

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

Novel therapies are needed in DDLPS

Demetri G et. al. JCO 2016;
Demetri G, Schoffski P, and Chawla S, JCO 2017

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



Exportin 1 (XPO1, CRM1) is the major nuclear export protein for[1,2,3]:

- **Tumor suppressor proteins** (e.g., p53, pRb, IkB, 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[1]
- Inhibits the growth of sarcoma tumors[4]
- Induces expression of genes that promote adipogenesis[1]

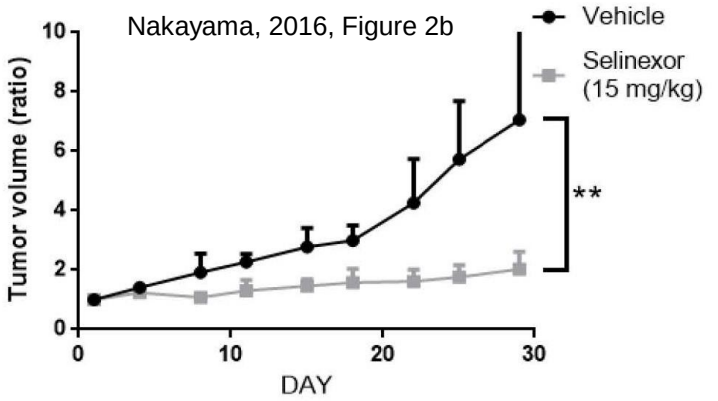
Selinexor is currently approved in multiple myeloma and diffuse large B cell lymphoma.

[1]Senapedis, 2014; [2]Culjkovic-Kraljacic 2012; [3]Garg 2017; [4] Nakayama 2016

Selinexor in Liposarcoma

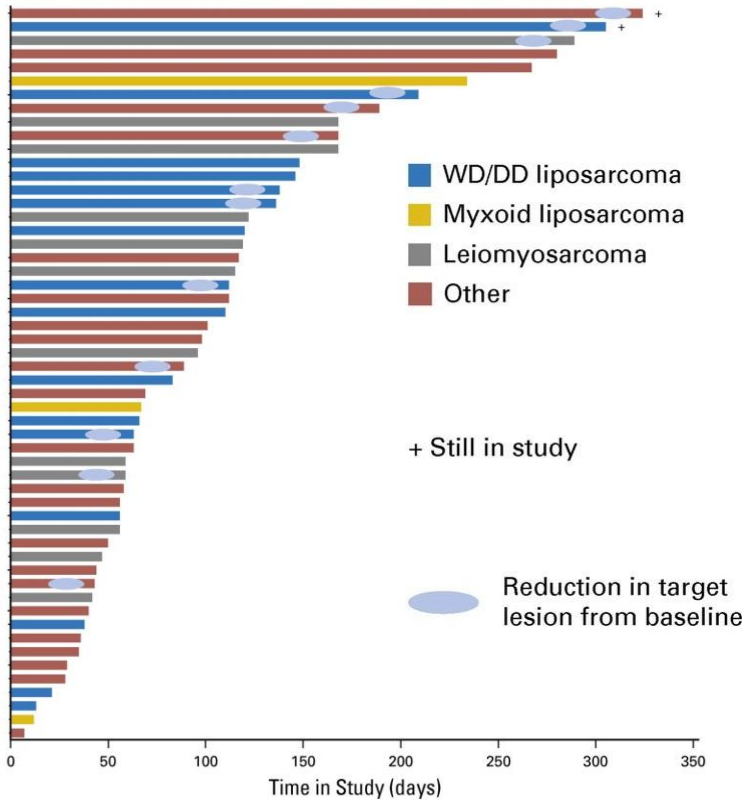
Selinexor demonstrated anti-tumor activity against DDLS in preclinical studies

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



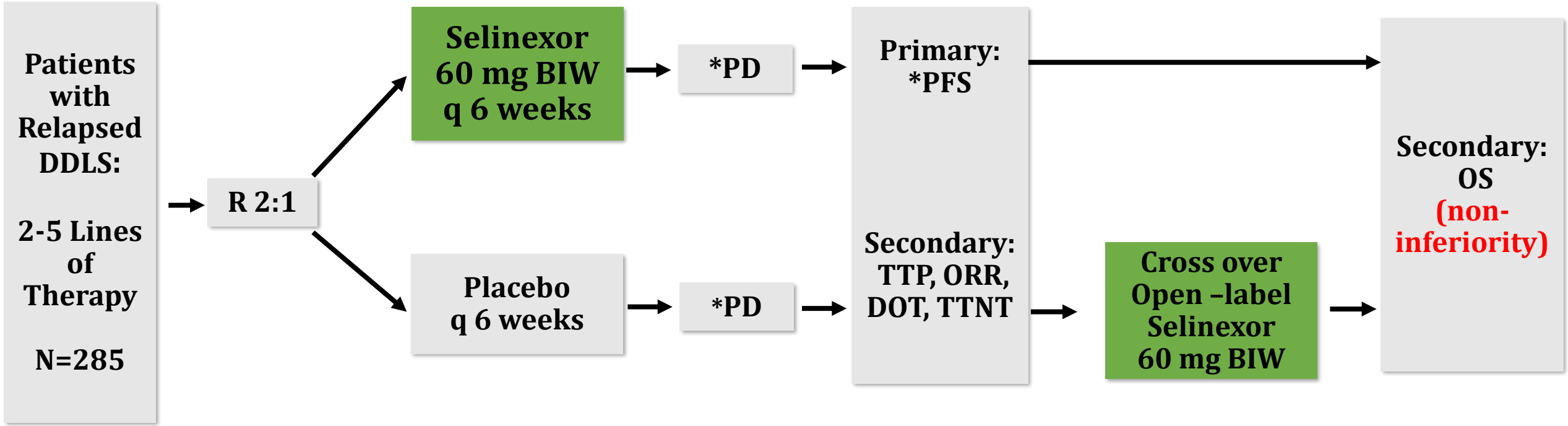
Selinexor demonstrated anti-tumor activity in DDLS in Phase 1 clinical study

- 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



Nakayama and Wagner, 2016; Garg, 2017; Gounder M, JCO 2016

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 ≥ 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

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

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) ≥1500/
  - Platelets ≥100,000/mm3
  - Hemoglobin (Hb) ≥9 g/dL
- Adequate hepatic function and adequate renal function: **Serum creatinine clearance of ≥ 30 mL/min**

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

Characteristic	Selinexor (N = 188)	Placebo (N = 97)
Age[1], 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)

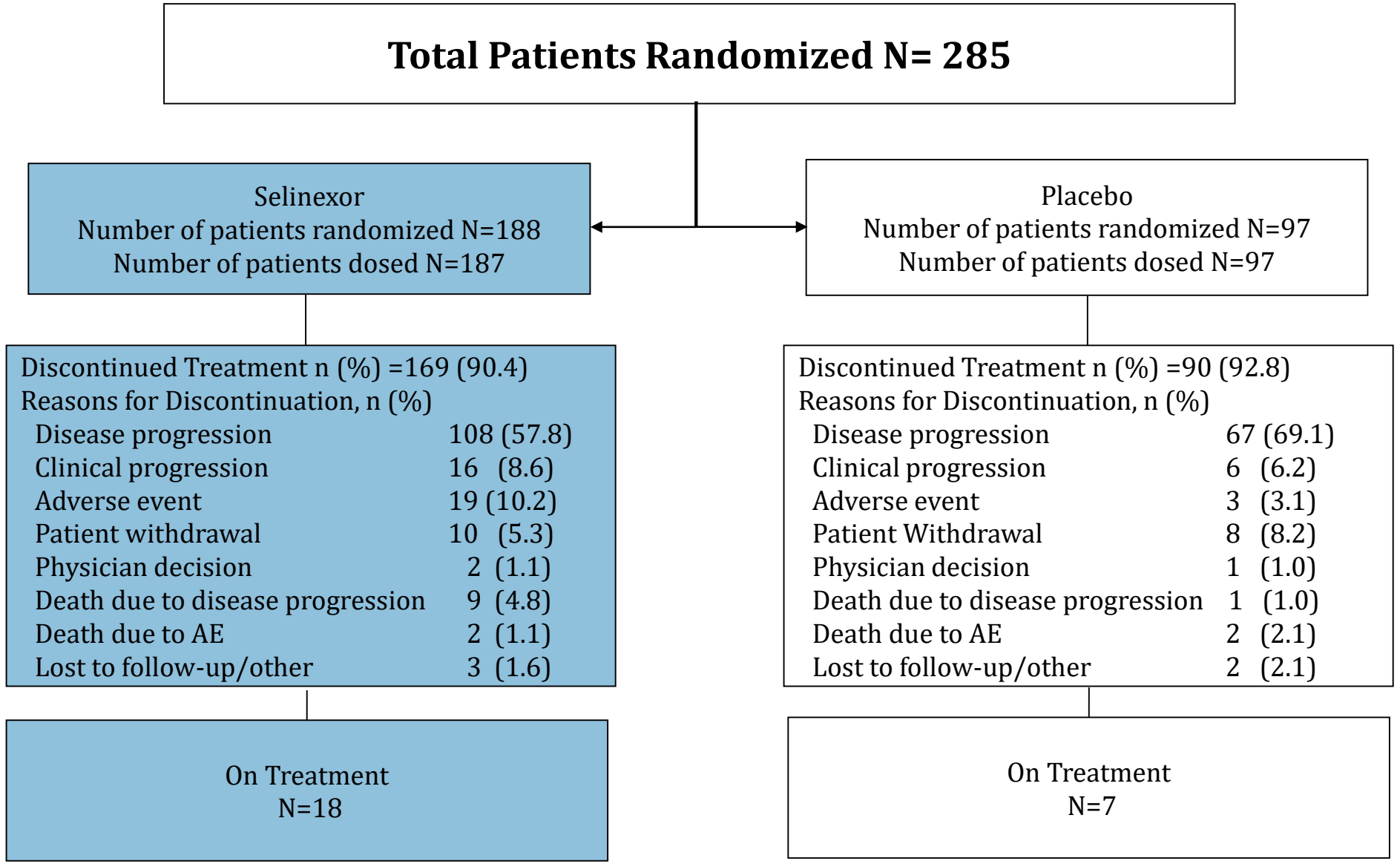
Characteristic	Selinexor (N = 188)	Placebo (N = 97)
ECOG[2] Performance Status, n (%)		
0	71 (37.8)	41 (42.3)
1	117 (62.2)	56 (57.7)
Median duration from most recent progression (range) — months	0.90 (0.1 - 6.97)	0.72 (0.1 – 16.5)
Median duration from initial diagnosis (range) — yr	4.3 (0 - 27)	4.3 (1 - 25)
Disease Stage Category at Study Entry, n (%)		
Localized/Locally advanced and unresectable	37 (19.7)	15 (15.5)
Distant Metastasis	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)
Retroperitoneum	**148 (78.7)**	**73 (75.3)**
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

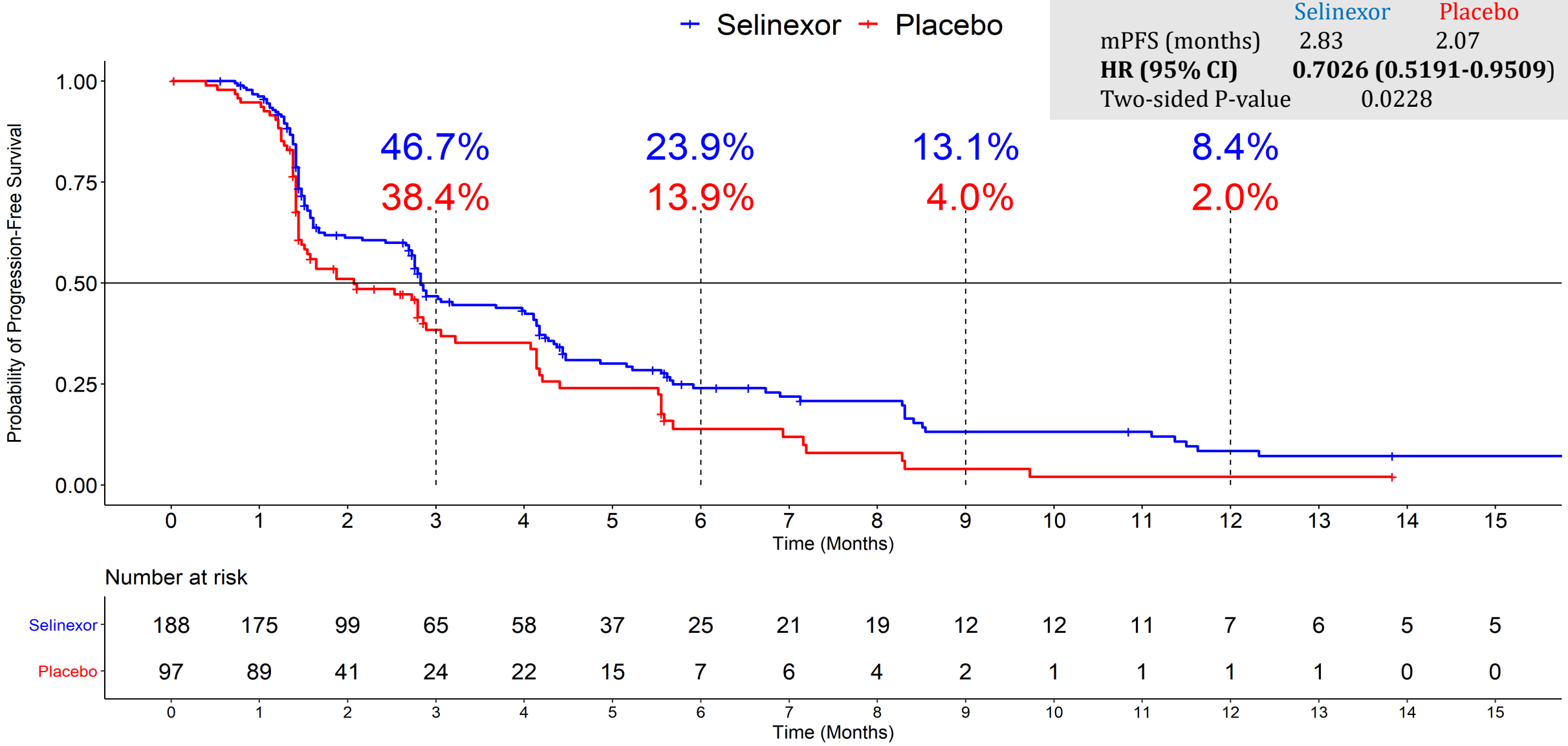
Prior Therapies	Selinexor (N = 188)	Placebo (N = 97)
Number of Prior Antineoplastic Regimen		
Median (range)	2 (1 - 6)*	2 (1 - 7)*
Mean (STD)	2.7 (1.08)	2.8 (1.19)
Distribution – Number of Prior Regimen, n (%)		
≤2*	104 (55.3)	54 (55.7)
≥3	84 (44.7)	43 (44.3)
Previous Systemic Therapy		
Eribulin	66 (35.1)	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



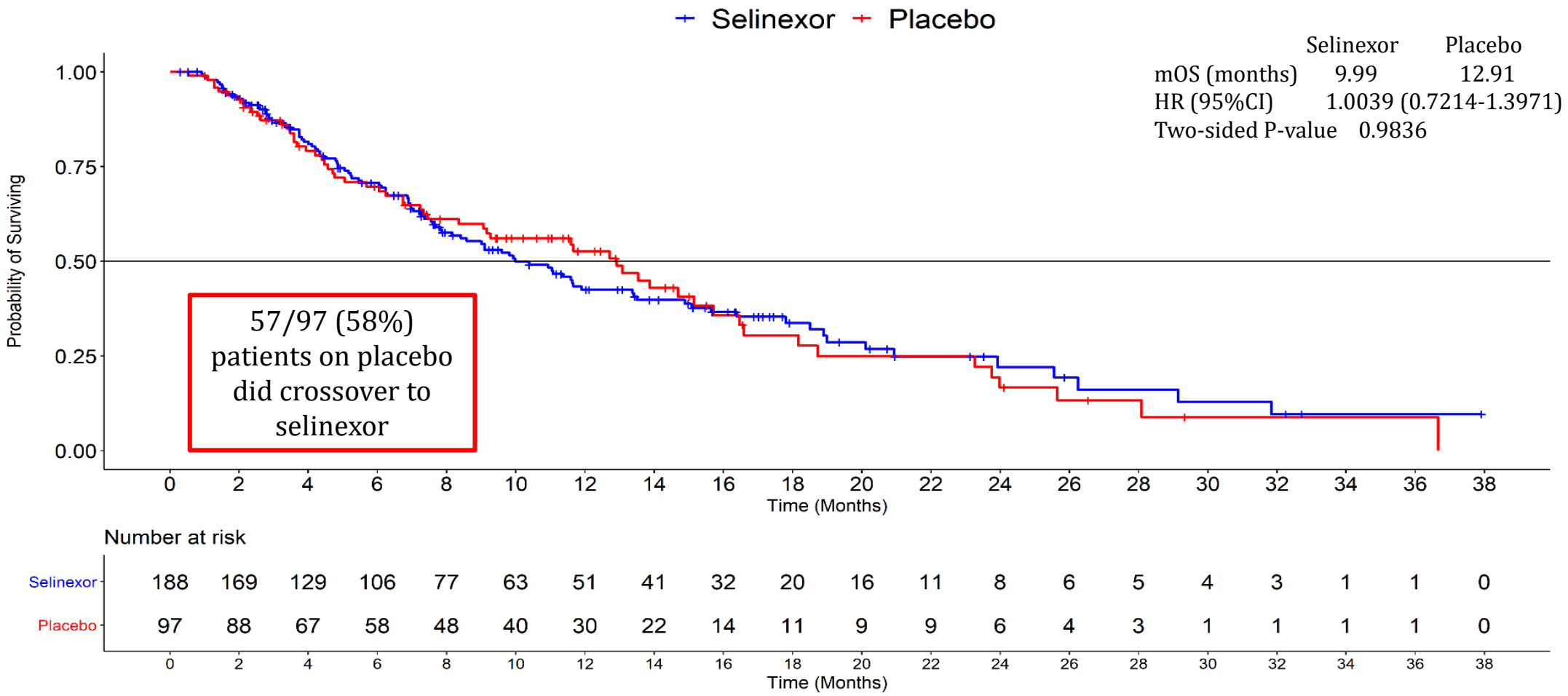
PFS Based on Independent Radiology Review – ITT

	Selinexor	Placebo
mPFS (months)	2.83	2.07
HR (95% CI)	**0.7026 (0.5191-0.9509)**	
Two-sided P-value	0.0228	



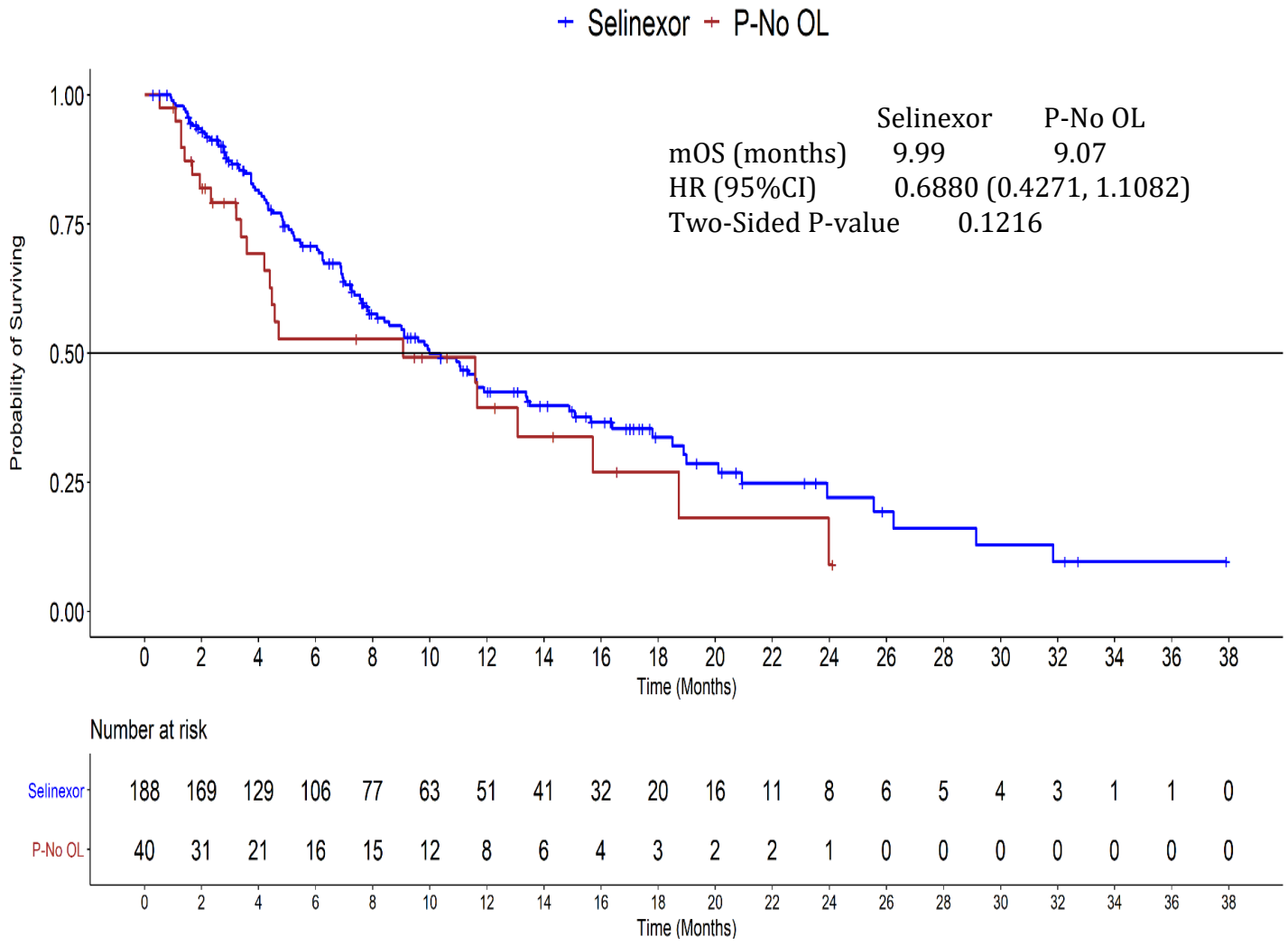
Final analysis based on 209 PFS events

SEAL: Overall Survival by Treatment Arm – ITT Phase 3



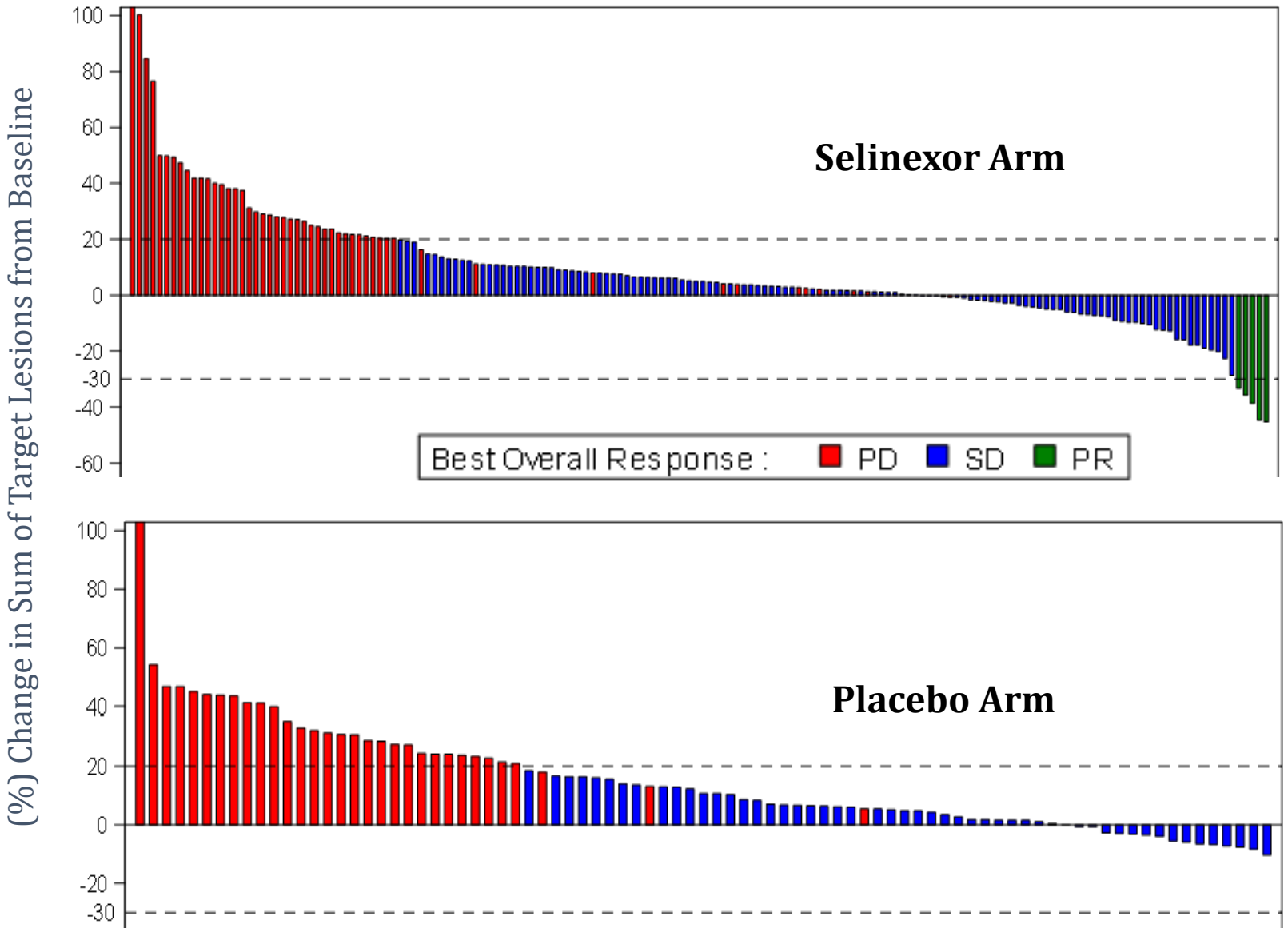
	Selinexor	Placebo
mOS (months)	9.99	12.91
HR (95%CI)	1.0039 (0.7214-1.3971)	
Two-sided P-value	0.9836	

SEAL: Overall Survival - Selinexor vs Patients on 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)

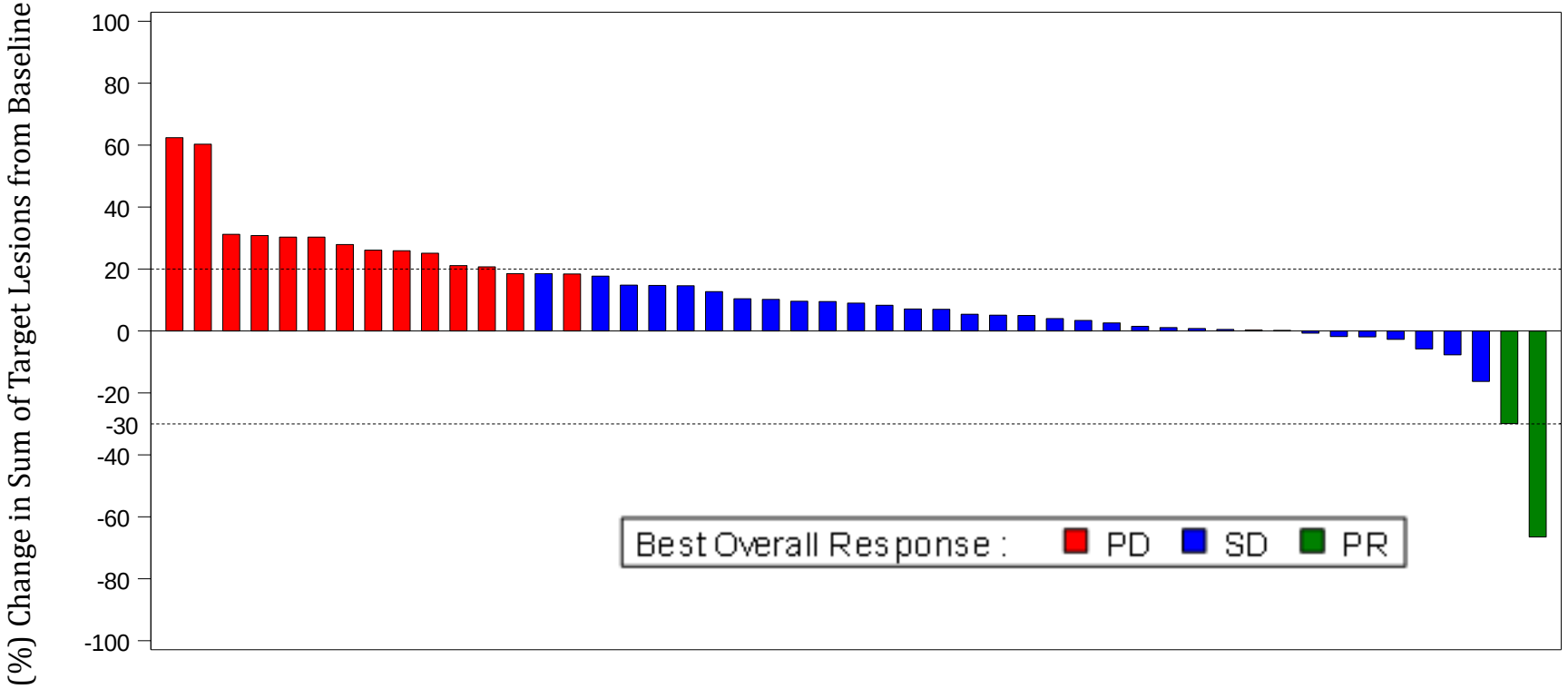
SEAL: Best Overall Response During Blinded Treatment – ITT (7.5% had reduction in disease burden > 15%)



Patients with Target Lesion Reduction

	Selinexor (N = 188)	Placebo (N = 97)
>=15% Reduction: N (%)	14 (7.5 %)	0
>=30% Reduction: N (%)	5 (2.7 %)	0

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



Patients with Target Lesion Reduction	
	Selinexor (N = 57)
>=15% Reduction: N (%)	**3 (5.3%)**
>=30% Reduction: N (%)	**2 (3.5%)**

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
Constitutional				
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
Other				
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

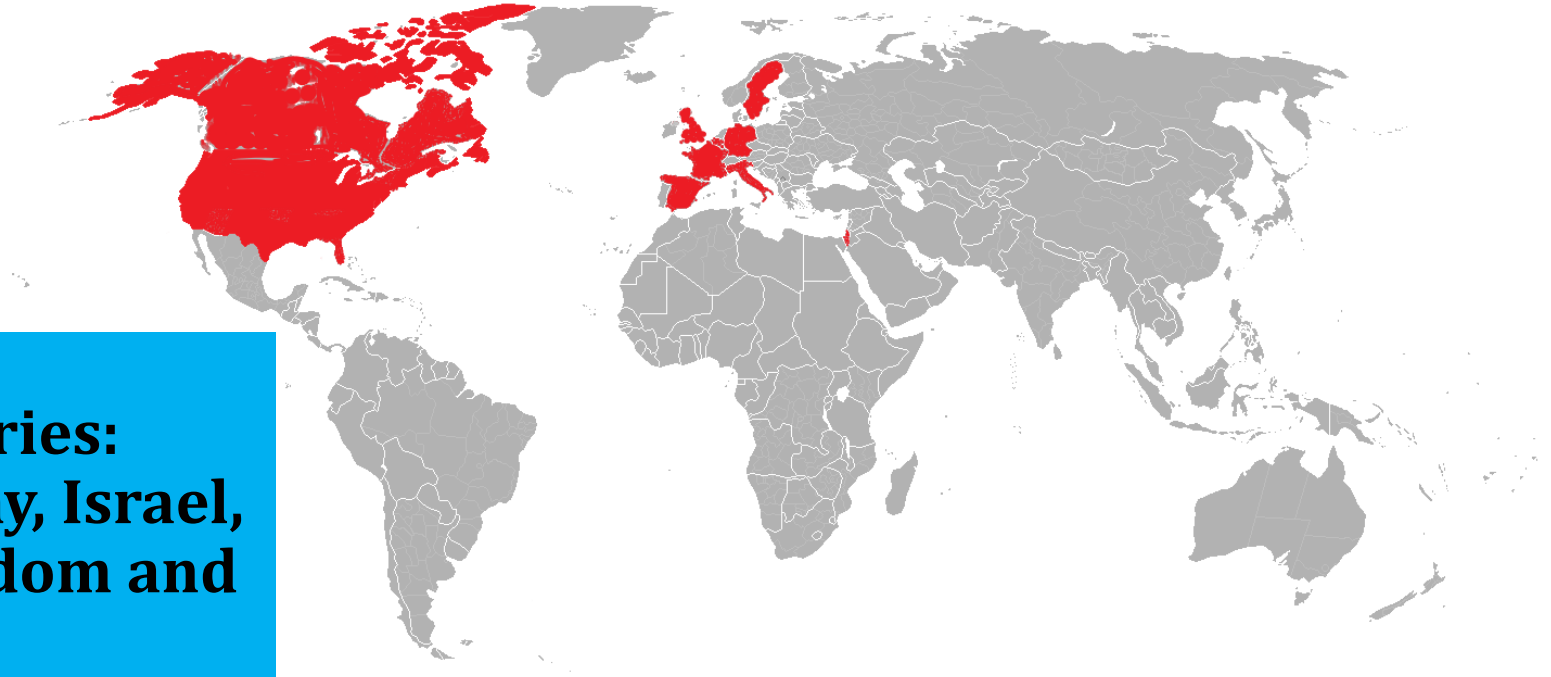
*Events that have occurred in ≥15% of patients

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 DDLPS 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!!!!!