

# Selinexor in Advanced, Metastatic Dedifferentiated Liposarcoma: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial

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**PURPOSE** Antitumor activity in preclinical models and a phase I study of patients with dedifferentiated liposarcoma (DD-LPS) was observed with selinexor. We evaluated the clinical benefit of selinexor in patients with previously treated DD-LPS whose sarcoma progressed on approved agents.

**METHODS** SEAL was a phase II-III, multicenter, randomized, double-blind, placebo-controlled study. Patients age 12 years or older with advanced DD-LPS who had received two-five lines of therapy were randomly assigned (2:1) to selinexor (60 mg) or placebo twice weekly in 6-week cycles (crossover permitted). The primary end point was progression-free survival (PFS). Patients who received at least one dose of study treatment were included for safety analysis (ClinicalTrials.gov identifier: [NCT02606461](https://clinicaltrials.gov/ct2/show/study/NCT02606461)).

**RESULTS** Two hundred eighty-five patients were enrolled (selinexor, n = 188; placebo, n = 97). PFS was significantly longer with selinexor versus placebo: hazard ratio (HR) 0.70 (95% CI, 0.52 to 0.95; one-sided  $P = .011$ ; medians 2.8 v 2.1 months), as was time to next treatment: HR 0.50 (95% CI, 0.37 to 0.66; one-sided  $P < .0001$ ; medians 5.8 v 3.2 months). With crossover, no difference was observed in overall survival. The most common treatment-emergent adverse events of any grade versus grade 3 or 4 with selinexor were nausea (151 [80.7%] v 11 [5.9%]), decreased appetite (113 [60.4%] v 14 [7.5%]), and fatigue (96 [51.3%] v 12 [6.4%]). Four (2.1%) and three (3.1%) patients died in the selinexor and placebo arms, respectively. Exploratory RNA sequencing analysis identified that the absence of *CALB1* expression was associated with longer PFS with selinexor compared with placebo (median 6.9 v 2.2 months; HR, 0.19;  $P = .001$ ).

**CONCLUSION** Patients with advanced, refractory DD-LPS showed improved PFS and time to next treatment with selinexor compared with placebo. Supportive care and dose reductions mitigated side effects of selinexor. Prospective validation of *CALB1* expression as a predictive biomarker for selinexor in DD-LPS is warranted.

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## INTRODUCTION

Liposarcoma is one of the most common soft tissue sarcoma type in adults, representing 24% and 45% of extremity and retroperitoneal soft tissue sarcomas, respectively.<sup>1</sup> Liposarcomas are classified into five distinct types with dedifferentiated liposarcoma (DD-LPS) being

the most common subtype.<sup>2</sup> While surgery is the primary therapy for localized liposarcomas, approximately 40% of patients eventually die from advanced unresectable or metastatic disease, emphasizing the need for effective new drugs.<sup>2</sup> Standard palliative chemotherapy for advanced disease includes single agent or combinations of

## ASSOCIATED CONTENT

### Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Current treatment options of advanced dedifferentiated liposarcoma (DD-LPS) are limited in number and efficacy. The SEAL trial evaluated monotherapy with selinexor, a selective inhibitor of nuclear export, and, to our knowledge, is the first and largest study conducted exclusively on patients with DD-LPS whose sarcoma progressed on approved agents with no further approved therapeutic options.

### Knowledge Generated

Single-agent oral selinexor provided prolonged progression-free survival, time to next treatment, and reduced pain in patients with previously treated DD-LPS. Exploratory molecular biomarker data revealed *CALB1* expression to be associated with selinexor resistance resulting in a potential application for future patient stratification.

### Relevance

Our results provide the rationale to further investigate selinexor in patients with advanced or metastatic DD-LPS and as a basis to further assess selinexor treatment in patients with DD-LPS with *CALB1* expression.

parenteral chemotherapies including doxorubicin and ifosfamide, or eribulin or trabectedin, which are indicated for treatment of liposarcoma. Gemcitabine and docetaxel may be used but have mainly been evaluated in earlier lines of primarily well-differentiated LPS.<sup>3</sup> First-line treatment of DD-LPS with doxorubicin monotherapy has shown an overall response rate (ORR) between 0% and 8% with a median progression-free survival (PFS) ranging from 1.5 to 4 months.<sup>3,6</sup> Anthracycline-containing regimens as a front-line treatment for retroperitoneal well-differentiated/DD-LPS have resulted in an ORR of 26% with a median PFS and overall survival (OS) of 4 and 25 months, respectively.<sup>3</sup> Second or subsequent lines of therapy with US Food and Drug Administration–approved agents eribulin and trabectedin result in a median PFS of approximately 2 months.<sup>7,8</sup>

*MDM2* and *CDK4* amplifications are hallmarks of DD-LPS.<sup>9,10</sup> *MDM2* is an E3-ligase which tags the tumor suppressor protein p53 (and other proteins) with ubiquitin for proteasome-mediated degradation, primarily in the cytoplasm of the cell. A majority of DD-LPS tumor cells that overexpress *MDM2* carry wild-type p53, consistent with the notion that p53 is inactivated in these tumors through *MDM2*-facilitated degradation.<sup>11</sup> Nuclear export of p53 is mediated by exportin-1 (XPO1) alone, but it is greatly facilitated by *MDM2*-mediated ubiquitination of p53.<sup>12</sup> *CDK4* expression is associated with poor survival in patients with DD-LPS. The tumor suppressor protein p21 (CIP1/WAF1) is a negative regulator of *CDK4*, and nuclear p21 attenuates *CDK4* activity. XPO1 facilitates the nuclear export and consequent functional inactivation of p21, thus potentiating the effect of *CDK4*. Overexpression of XPO1 has been reported in sarcomas,<sup>13</sup> while *MDM2* and *CDK4* amplifications and expression are associated with poor survival in patients with DD-LPS.<sup>9,10</sup>

Selinexor is a potent, oral, selective inhibitor of nuclear export compound that specifically blocks XPO1 by covalently and reversibly binding to cysteine-528, an essential

residue for XPO1 cargo binding.<sup>14-16</sup> Blockade of XPO1 leads to nuclear retention and functional activation of multiple tumor suppressor proteins. Treatment with selinexor has demonstrated increased p53 nuclear accumulation and retention followed by reactivation of its tumor suppressor activity, even in the presence of *MDM2* overexpression.<sup>13,17</sup> When selinexor was administered both in vitro and in vivo, there were increased levels of nuclear p21 and downregulation of *CDK4*-mediated oncogenic pathways.<sup>13,17,18</sup> Furthermore, in cancer, nuclear factor kappa B (NF- $\kappa$ B) activates pro-oncogenic, chemotherapy resistance and inflammatory gene transcription activity. This activity is inhibited endogenously by several proteins, the most potent of which is I $\kappa$ B (inhibitor of NF- $\kappa$ B). I $\kappa$ B is exported from the nucleus—and its NF- $\kappa$ B inhibiting activity blocked, solely by XPO1. Therefore, inhibition of XPO1 by selinexor prevents I $\kappa$ B transport to the cytoplasm and, instead, leads to its accumulation in the nucleus and potent inhibition of NF- $\kappa$ B pro-oncogenic activity.<sup>19</sup>

Currently approved for use in patients with multiple myeloma<sup>20,21</sup> and diffuse large B-cell lymphoma,<sup>14</sup> selinexor has demonstrated antitumor activity in in vitro and in vivo models of DD-LPS, inducing apoptosis in multiple liposarcoma cell lines, including those with *MDM2* and *CDK4* amplification<sup>17</sup> and downregulating *CDK4*-mediated oncogenic pathways through increased nuclear retention of p21, a negative regulator of *CDK4* in vitro.<sup>17</sup> In murine xenograft models of human liposarcoma, selinexor inhibited tumor growth and reduced levels of XPO1,<sup>22</sup> increased nuclear retention of p53,<sup>23</sup> and inhibited NF- $\kappa$ B.<sup>19</sup>

In a phase I clinical trial of selinexor in advanced sarcomas, patients with DD-LPS had prolonged stable disease.<sup>18</sup> We therefore conducted a phase II-III randomized trial to evaluate the activity of selinexor in patients with advanced or metastatic DD-LPS who had two-five prior lines of systemic therapy and report here the phase III results.

## METHODS

### Study Design and Participants

The SEAL trial was a phase II-III, multicenter, randomized, double-blind study of selinexor versus placebo in patients with advanced unresectable DD-LPS including 70 sites in 10 countries. Patients were randomly assigned in a 2:1 ratio. The Protocol (online only) was approved by institutional review boards at individual enrolling institutions and performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. Disease response was assessed by an Independent Review Committee.

Eligible patients age 12 years or older had histologically confirmed DD-LPS with measurable disease per RECIST v1.1 as assessed by an independent review committee, had shown radiologic evidence of disease progression, and had received two-five prior systemic therapies. An Eastern Cooperative Oncology Group performance status of  $\leq 1$ , creatinine clearance  $> 30$  mL/min, and adequate laboratory hematopoietic and hepatic function were required. Patients with other subtypes of liposarcoma or with known central nervous system metastases were excluded. A full list of inclusion or exclusion criteria is provided in the Data Supplement (online only). All patients provided written informed consent.

### Procedures

Selinexor (60 mg) or matching placebo was administered twice weekly in 6-week cycles. Random assignment was stratified on the basis of (1) prior eribulin use (prior eribulin *v* no prior eribulin), (2) prior trabectedin use (prior trabectedin *v* no prior trabectedin), and (3) the number of prior systemic therapies excluding eribulin and trabectedin ( $\leq 2$  *v*  $\geq 3$ ). Stratification by prior eribulin or trabectedin was implemented as these are the most recently approved agents for the treatment of LPS. With a 2:1 random assignment, a block size of six was used. Supportive care measures included a 5-hydroxytryptamine-3 antagonist (eg, ondansetron), olanzapine and, if needed, low-dose glucocorticoids. Treatment was administered until disease progression, discontinuation, or unacceptable side effects. If radiographic progression was confirmed by central independent radiology review in the placebo arm, eligible patients were allowed to cross over to selinexor. Patients on selinexor with confirmed progression were permitted to continue selinexor if their treating physician considered them to be benefiting from the therapy.

### Outcomes

The primary end point was PFS, defined as the time from date of random assignment until the first date of progression confirmed by central radiographic review, on the basis of RECIST v1.1, or death due to any cause. Secondary end points were OS (additional details in the Data

Supplement), OS among patients who did not cross over, time to progression on study treatment, ORR, duration of response, time to next treatment, and health-related quality of life (HR-QoL). Exploratory end points included tumor biomarker analysis in tumor tissue. Adverse events (AEs) were graded according to National Cancer Institute, Division of Cancer Treatment and Diagnosis Common Terminology Criteria for Adverse Events Grading Scale, version 4.03.<sup>24</sup>

### Exploratory Molecular Correlative Studies

Per preplanned analysis, RNA sequencing was performed on formalin-fixed paraffin-embedded resected tumors or tumor biopsies of patients who were treated on study for at least one complete cycle. Details of the patient samples analyzed are included in the Data Supplement.

### Statistical Analysis

The sample size was designed to have 90% power to detect a hazard ratio (HR) of 0.6 between selinexor and placebo for the primary efficacy end point of PFS, using a one-sided test with a nominal level of 0.025. The intent-to-treat population was used for efficacy analysis and consisted of all patients randomly assigned to study treatment. The safety population included patients who received at least one dose of blinded study treatment. For categorical variables, summary tabulations of the number and percentage of patients within each category were used (with a category for missing data) of the parameter, as well as two-sided 95% CIs. For continuous variables, summary statistics included the number of patients, mean, median, standard deviation, minimum, and maximum. For time-to-event variables, the Kaplan-Meier method was used for descriptive summaries. SAS version 9.4 was used for the analysis.

### Role of Funding Source

The funder of the trial was involved in trial design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

## RESULTS

### Patient Characteristics

A total of 285 patients were enrolled in the phase III component of the trial with 188 and 97 patients randomly assigned to selinexor or placebo, respectively (Fig 1). Both arms were balanced with a median age of 65 years (interquartile range, 56.0-71.0). The most common primary site of disease at study entry was retroperitoneal (73.4% selinexor; 68.0% placebo). The majority of patients had metastatic disease at study entry (71.3% selinexor; 80.4% placebo) and had prior treatment with doxorubicin, gemcitabine, eribulin, or trabectedin (Table 1).

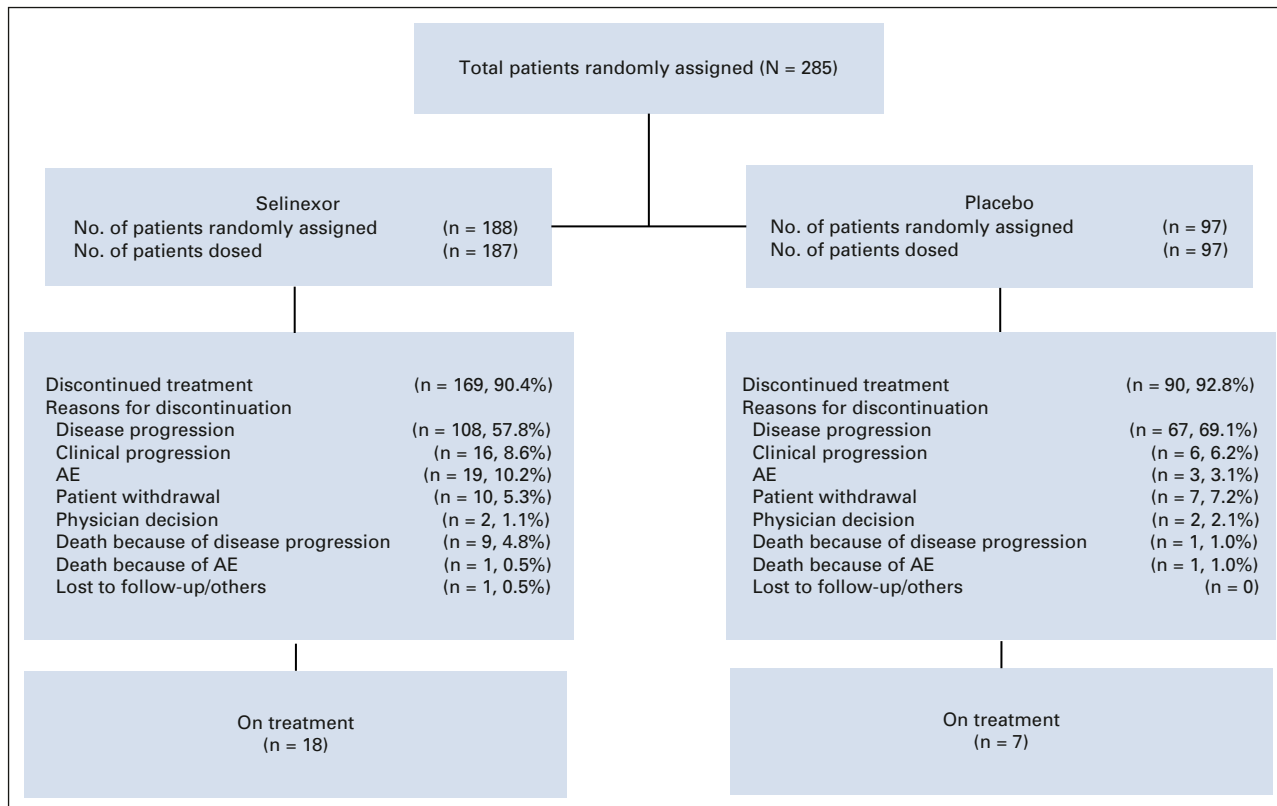


FIG 1. CONSORT diagram. AE, adverse event.

## Efficacy

Selinexor was associated with a 30% improvement in PFS as compared with placebo (HR, 0.70; 95% CI, 0.52 to 0.95; one-sided  $P = .01$ ; two-sided  $P = .02$ ; median PFS 2.8 months and 2.1 months, respectively; Table 2). At 12 weeks or longer, the PFS was significantly longer with selinexor (46.8%,  $n = 88$ ; 95% CI, 39.6 to 55.1) when compared with placebo (34.0%,  $n = 33$ ; 95% CI, 29.1 to 50.7; one-sided  $P = .02$ ; two-sided  $P = .04$ ). The 6- and 12-month PFS rates for selinexor and placebo were 23.9% (95% CI, 17.7 to 32.4) v 13.9% (95% CI, 29.1 to 50.7) and 8.4% (95% CI, 4.3 to 16.2) v 2.0% (95% CI, 0.3 to 13.4), respectively (Fig 2A). Of the 135 (71.8%) and 74 (76.3%) PFS events in the selinexor and placebo arms, respectively, there were 10 (5.3%) deaths with selinexor and five (5.2%) with placebo. The ORR on the basis of RECIST v1.1 per independent central radiologic review was 2.7% (five patients) with selinexor, while no responses were observed with placebo. Three patients from the selinexor arm continued into selinexor open-label after radiographic progressive disease because of continued clinical benefit. The median duration of response was 7.4 months (95% CI, not reached to not reached) with selinexor. The time to next treatment was also significantly longer with selinexor versus placebo (HR, 0.49 [95% CI, 0.37 to 0.66], one-sided  $P < .0001$ ; two-sided  $P = .0002$ ; medians 5.8 months v 3.2 months). Of note, the number of patients receiving

subsequent therapies was similar in each arm (Data Supplement). Following independent radiographic confirmation of progression, 58.8% patients on placebo arm crossed over to receive open-label selinexor. At a median follow-up of 14.6 months (interquartile range, 8.2-23.5), there was no difference in OS for selinexor and placebo (HR, 1.02; 95% CI, 0.73 to 1.42, one-sided  $P = .54$ ; two-sided  $P = 1.08$ ; median 10.0 months v 12.9 months; Fig 2B). OS among patients who did not cross over showed a HR of 0.69 (95% CI, 0.43 to 1.11; one-sided  $P = .06$ ; two-sided  $P = .12$ ; median 10.0 months with selinexor v 9.1 months with placebo).

## Safety

Discontinuation of study treatment because of treatment-emergent adverse events (TEAEs) occurred in 10.2% of patients on selinexor and 3.1% of patients on placebo. Overall, the most frequently reported TEAEs were nausea (80.7% v 39.2%), decreased appetite (60.4% v 22.7%), fatigue (51.3% v 32.0%), and weight loss (42.2% v 9.3%), the majority of which were grade 1 or 2 and reversible. Most common grade 3/4 AEs were anemia (18.7% v 8.2%), hyponatremia (nearly all asymptomatic, 10.7% v 0%), asthenia (10.2% v 0%), and thrombocytopenia (10.2% v 0%) with selinexor and placebo, respectively (Table 3). Two of 71 (2.8%) patients in the selinexor arm with thrombocytopenia had grade 3 bleeding: duodenal invasion by the

**TABLE 1.** Baseline Demographic and Clinical Characteristics

Characteristic	Selinexor (n = 188)	Placebo (n = 97)
Age		
Median, years (range)	65.0 (33-84)	65.0 (31-85)
Distribution, No. (%)		
18-64	92 (48.9)	46 (47.5)
65-74	73 (38.8)	41 (42.3)
≥ 75	23 (12.2)	10 (10.3)
Male sex, No. (%)	114 (60.6)	64 (66.0)
Race, No. (%)		
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	35 (18.6)	13 (13.4)
Geographic region, No. (%)		
North America	90 (47.9)	55 (56.7)
Europe and Israel	98 (52.1)	42 (43.3)
ECOG performance status score, No. (%) <sup>a</sup>		
0	71 (37.8)	41 (42.3)
1	117 (62.2)	56 (57.7)
Median duration from most recent progression, months (range)	0.87 (0.1-6.7)	0.66 (0.1-15.5)
Median time since initial diagnosis, months (range)	52.1 (5-328)	51.1 (11-301)
Disease stage category at study entry, No. (%)		
Metastasis	134 (71.3)	78 (80.4)
Lung	28 (14.9)	16 (16.5)
Liver	12 (6.4)	9 (9.3)
Peritoneal cavity	47 (25.0)	26 (26.8)
Other	47 (25.0)	27 (27.8)
Primary/extension site of study entry liposarcoma lesion, No. (%)		
Extremity (lower plus upper)	9 (4.8)	3 (3.1)
Retroperitoneum	138 (73.4)	66 (68.0)
Other	33 (17.6)	22 (22.7)
Median prior antineoplastic regimen, No. (range)	2 (1-6)	2 (1-7)
Prior antineoplastic regimen, No. (%)		
1 <sup>b</sup>	7 (3.7)	6 (6.2)
2	97 (51.6)	47 (48.5)
≥ 3	84 (44.7)	44 (45.3)
Previous systemic therapy		
Eribulin	66 (35.1)	35 (36.1)
Anthracyclines	165 (87.8)	84 (86.6)
Anthracyclines plus alkylating agents	168 (89.4)	87 (89.7)
Gemcitabine plus taxanes	72 (38.3)	28 (28.9)
Trabectedin	69 (36.7)	36 (37.1)
Dacarbazine	25 (13.3)	7 (7.2)
MDM2 inhibitor	8 (4.3)	1 (1.0)

(continued on following page)

**TABLE 1.** Baseline Demographic and Clinical Characteristics (continued)

Characteristic	Selinexor (n = 188)	Placebo (n = 97)
CDK4 inhibitor	33 (17.6)	21 (21.6)
Immune checkpoint inhibitor	13 (6.9)	13 (13.4)
Tyrosine kinase inhibitor	61 (32.4)	30 (30.9)
Other	9 (4.8)	9 (9.3)
Prior radiotherapy, No. (%)		
Yes	86 (45.7)	45 (46.4)
Prior surgery, No. (%)		
Yes	168 (89.4)	82 (84.5)
No. of prior surgeries		
Median (range)	2 (1-10)	2 (1-7)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup>ECOG performance status scores range from 0 to 5, with higher scores reflecting greater disability.

<sup>b</sup>Represents patients enrolled before amendment requiring  $\geq 2$  prior antineoplastic regimens.

tumor in one patient and bleeding from an anastomotic ulcer in the other. Of note, there were no reports of febrile neutropenia. Unique grade 3/4 AEs with selinexor included increased creatinine (1.6%), blurred vision (0.5%), and dizziness (1.1%; Table 3).

Serious TEAEs were reported in 38.0% patients with selinexor and 18.6% patients with placebo, of which GI disorders were the most frequent in both arms: selinexor (11.8%) and placebo (6.2%; Data Supplement). The most common TEAEs leading to discontinuation with selinexor were fatigue (2.7%) and cardiac failure (1.1%). With placebo, the most frequent TEAEs leading to discontinuation were sepsis (2.1%), abdominal pain (1.0%), and decreased appetite (1.0%). Compared with placebo, patients treated with selinexor had a higher rate of AEs leading to

dose reduction (35.8% v 3.1%) and interruption (63.1% v 16.5%). TEAEs leading to death were similar for selinexor (2.1%) and placebo (3.1%).

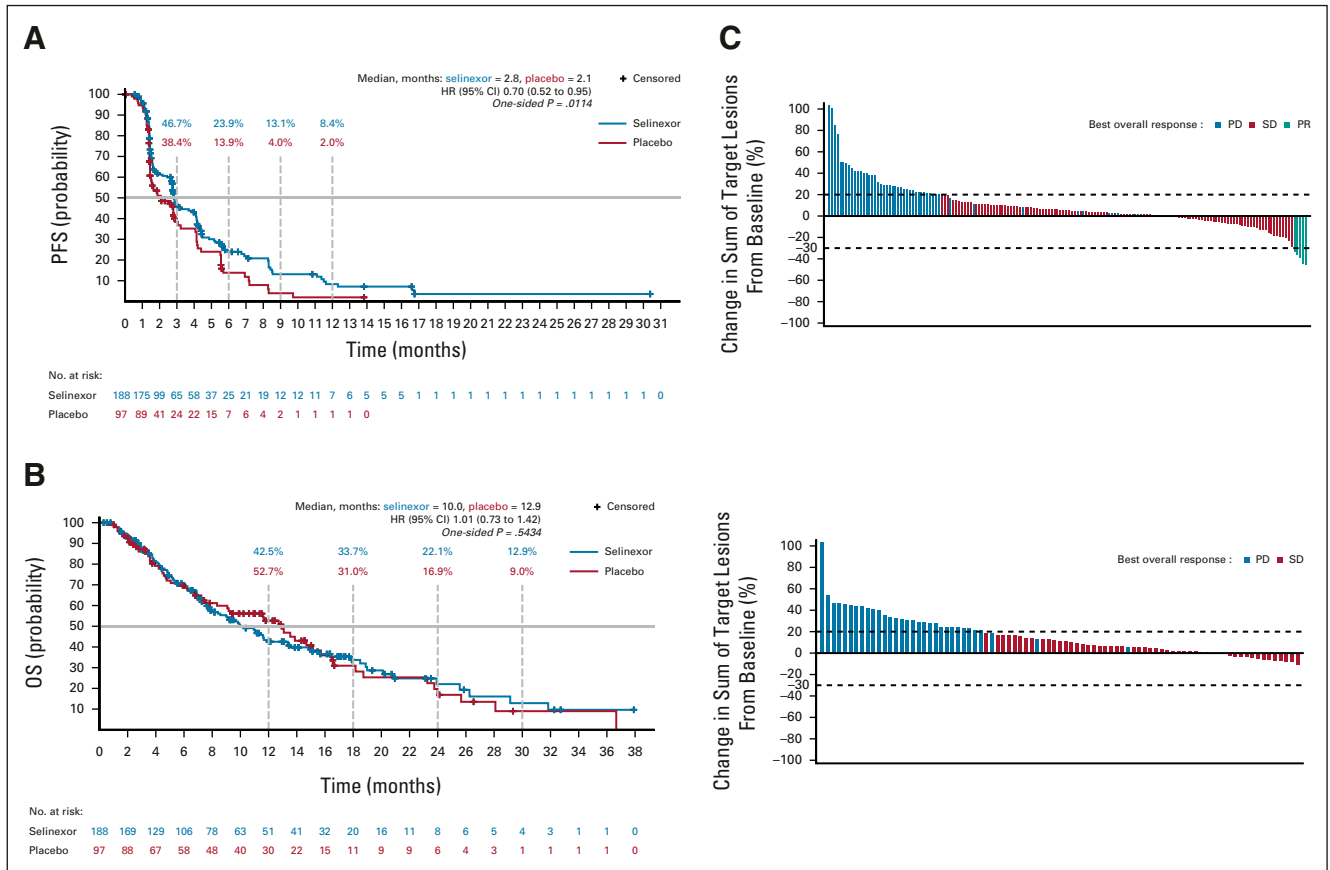
#### Exploratory Molecular Correlative Studies

To identify potential genetic markers of response to selinexor, we performed RNA sequencing of pretreatment tumor samples from two nonoverlapping sets of 55 patients treated with at least one full cycle of selinexor. Set 1 included patients for whom a radiographically measured target lesion was recently biopsied and available for sequencing. Biopsies from lesions that decreased in size were defined as selinexor sensitive ( $-6\%$  to  $-73\%$ ,  $n = 8$ ), and those from lesions that increased in size were defined as resistant ( $+10\%$

**TABLE 2.** Efficacy

Response Category	Selinexor (n = 188)	Placebo (n = 97)	One-Sided P	Two-Sided P
PFS, median (months)	2.8	2.1	.01	.02
OS, median (months)	10.0	12.9	.54	1.08
Objective response rate				
No. with response	5	0		
Rate, % (95% CI)	2.7 (0.9 to 6.1)	0 (0)		
Best overall response, No. (%)				
CR	0	0		
PR	5 (2.7)	0		
SD	111 (59.0)	53 (54.6)		
PD	50 (26.6)	32 (33.0)		
Response could not be evaluated	22 (11.7)	10 (10.3)		
Time to progression, median (months)	2.8	2.1	.01	.02
Time to next treatment, median (months)	5.8	3.2	< .0001	.0002

Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.



**FIG 2.** Efficacy by treatment arm. (A) Median progression-free survival. Kaplan-Meier curves by treatment arm. (B) Median OS. Kaplan-Meier curves by treatment arm. (C) Best overall response waterfall plots during blinded treatment: selinexor (upper panel) and placebo (lower panel). HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

to +93%,  $n = 9$ ; Data Supplement). Set 2 included patients who were stratified on the basis of PFS and RECIST response criteria. Patients who experienced progressive disease within 3 months of starting selinexor were defined as poor benefit ( $n = 22$ ), and patients who were progression-free for at least 6 months or achieved a partial response were defined as favorable benefit ( $n = 16$ ; Fig 3A; Data Supplement). Differential expression analysis of sensitive and resistant tumors in set 1 (target size change comparison) revealed that expression of *CALB1* (calbindin 1) was strongly associated with resistance to selinexor (multiple test correction adjusted  $P$  value [ $P_{adj}$ ] =  $7.5 \times 10^{-20}$ ), and sensitive tumors lacked expression of *CALB1* (Figs 3B and 3C; Data Supplement). In set 2 (short v long PFS), *CALB1* was among the top differentially expressed genes and its expression was significantly higher in tumors from patients with short ( $< 3$  months) PFS ( $P = 2.54 \times 10^{-05}$ ;  $P_{adj} = .0091$ ; Figs 3D and 3E; Data Supplement). Finally, paired post-treatment tumor tissues from a patient who initially responded to selinexor and then developed a resistant metastasis were available, and RNA sequencing showed that the selinexor-resistant tumor had 52-fold higher

expression of *CALB1* compared with the sensitive tumor (Fig 3F).

In an exploratory analysis of patients whose tumors had no detectable *CALB1* expression ( $n = 30$ ), those randomly assigned to selinexor ( $n = 16$ ) had significantly improved PFS compared with placebo (6.9 v 2.2 months; HR = 0.19 [0.07 to 0.56],  $P = .001$ ; Fig 3G; Data Supplement). In addition, among patients on the selinexor arm, those with no tumor *CALB1* expression ( $n = 16/45$ ) had improved PFS compared with those whose tumors expressed *CALB1* ( $n = 29/45$ ; 6.9 v 1.7 months; HR = 0.45 [0.21 to 0.95],  $P = .03$ ; Fig 3H). There was no association between PFS and *CALB1* expression among patients on the placebo arm ( $P = .44$ ; Fig 3I; Data Supplement) or in an analysis of the DD-LPS cohort of The Cancer Genome Research Atlas (TCGA) database (Data Supplement).<sup>25</sup>

## DISCUSSION

To our knowledge, SEAL is the first and largest global phase II-III trial focused exclusively on patients with relapsed and refractory DD-LPS who had received all agents of known clinical benefit. Despite the rarity of this tumor type (approximately 2,200 in the United States annually<sup>26</sup>), feasibility

TABLE 3. TEAEs

Event	Selinexor (n = 187)		Placebo (n = 97)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic AEs, No. (%)				
Anemia	88 (47.1)	35 (18.7)	22 (22.7)	8 (8.2)
Thrombocytopenia	71 (38.0)	19 (10.2)	5 (5.2)	0
Neutropenia	37 (19.8)	17 (9.1)	1 (1.0)	0
Nonhematologic AEs, No. (%)				
GI				
Nausea	151 (80.7)	11 (5.9)	38 (39.2)	0
Decreased appetite	113 (60.4)	14 (7.5)	22 (22.7)	1 (1.0)
Vomiting	92 (49.2)	6 (3.2)	12 (12.4)	3 (3.1)
Constipation	71 (38.0)	1 (0.5)	23 (23.7)	0
Diarrhea	75 (40.1)	5 (2.7)	17 (17.5)	2 (2.1)
Abdominal pain	45 (24.1)	10 (5.3)	31 (32.0)	2 (2.1)
Dysgeusia	51 (27.3)	0	4 (4.1)	0
Constitutional				
Fatigue	96 (51.3)	12 (6.4)	31 (32.0)	3 (3.1)
Weight decreased	79 (42.2)	1 (0.5)	9 (9.3)	0
Asthenia	58 (31.0)	19 (10.2)	10 (10.3)	0
Others				
Dyspnea	35 (18.7)	3 (1.6)	12 (12.4)	2 (2.1)
Hyponatremia	51 (27.3)	20 (10.7)	8 (8.2)	0
Increased creatinine	40 (21.4)	3 (1.6)	13 (13.4)	0
Dizziness	42 (22.5)	2 (1.1)	6 (6.2)	0
Blurred vision	41 (21.9)	1 (0.5)	3 (3.1)	0
Serious adverse event, No. (%)		71 (38.0)		18 (18.6)
TEAE leading to discontinuation, No. (%)	17 (9.1)		4 (4.1)	
Fatigue	5 (2.7)		0	
Cardiac failure	2 (1.1)		0	

NOTE. No reported febrile neutropenia. Events that have occurred in  $\geq 15\%$  of patients and had  $> 5\%$  difference between the arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

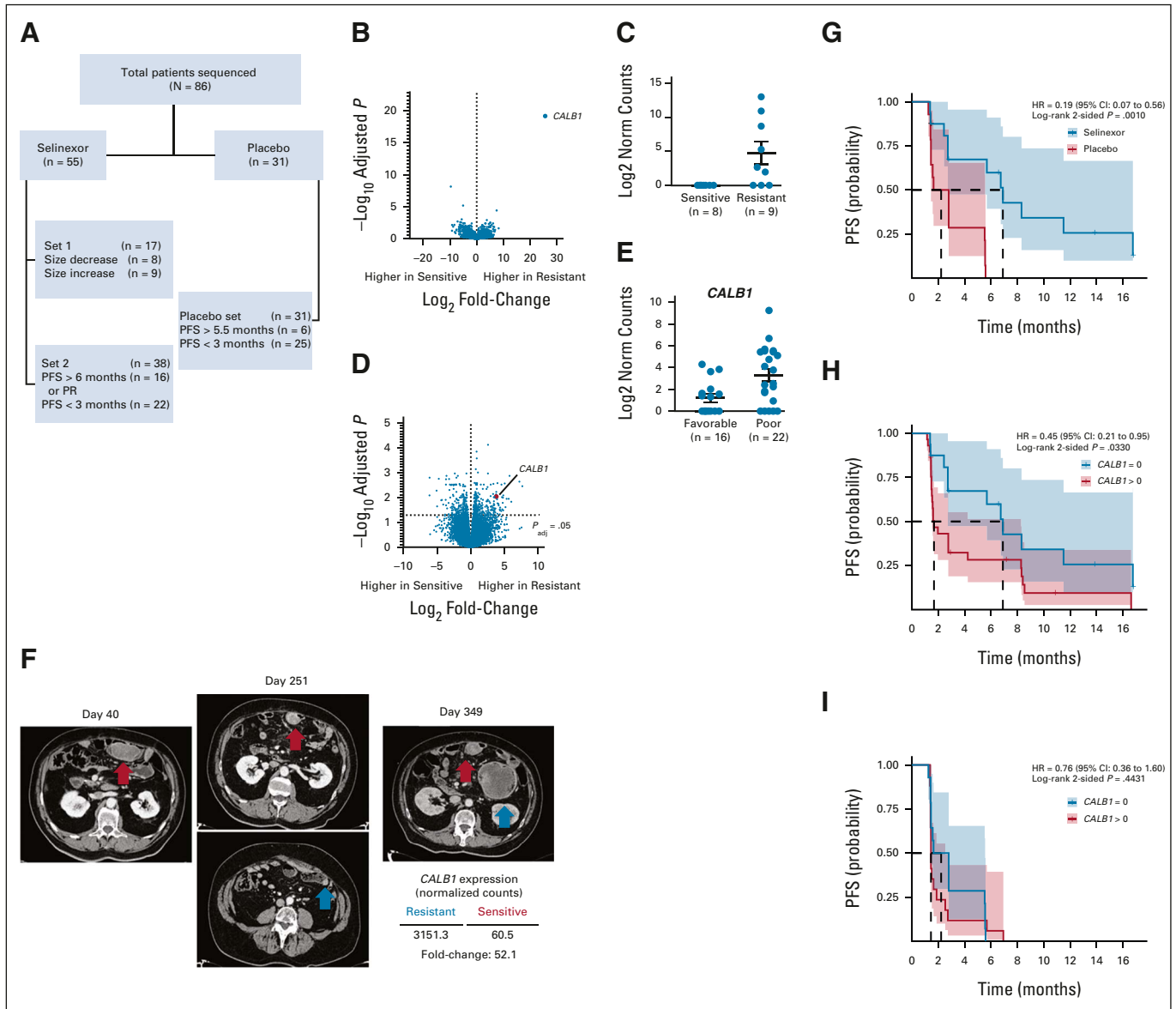
Abbreviation: TEAE, treatment-emergent adverse event.

of randomized studies in rare cancers was enabled by international cooperation.

In patients with advanced, refractory DD-LPS, oral, twice-weekly selinexor showed a 30% improvement in PFS. In the context of the HR of 0.7, the modest improvement (2.8 months) in the median PFS over placebo (2.1 months) is consistent with a benefit in a subset of the population. Along these lines, at 12 weeks or longer, the PFS was significantly longer with selinexor compared with placebo: 46.8%  $\nu$  34.0% (one-sided  $P = .02$ ). In this context, in the *first-line* setting, the median PFS for single-agent doxorubicin was 1.5 months while combinations with ifosfamide ranged from 2 to 4 months.<sup>3-6</sup> In the *third-line setting*, patients with DD-LPS randomly assigned to trabectedin also showed modest improvement in the

median PFS of 2.2 months ( $\nu$  1.9 months for dacarbazine) and did not show an improvement in OS (12.4 months  $\nu$  12.9 months for dacarbazine; HR 0.87).<sup>7</sup> Eribulin showed no improvement in median PFS (2.0  $\nu$  2.1 months for dacarbazine); however, in a small subset analysis of patients with DD-LPS, eribulin ( $n = 31$ ) demonstrated a significant improvement in OS (HR, 0.42, 18.0  $\nu$  8.1 months) over dacarbazine ( $n = 34$ ).<sup>8</sup> Single-arm, phase II studies of CDK4/6 inhibitors palbociclib and abemaciclib have demonstrated median PFS ranging from 18 to 30 weeks with most patients treated in the first-line (37%-50%) or second-line setting.<sup>27-29</sup> In contrast, 51.6% and 44.7% of patients in the SEAL study had failed two and three prior lines of therapies, respectively.





**FIG 3.** *CALB1* expression is associated with selinexor resistance. (A) Flow diagram of patient samples that were sequenced. (B) Volcano plot showing the significance (y-axis) and fold-change (x-axis) of all genes compared between sensitive and resistant tumors in the set 1 comparison using RECIST tumor size change. (C) Expression of *CALB1* in the set 1 tumor samples. (D) Significance and fold-change of all genes in the set 2 comparison of patients with favorable and poor PFS. (E) Expression of *CALB1* in set 2. (F) CT scans from a patient who had a mesenteric lesion that steadily reduced in size over 4 months after starting selinexor treatment on SEAL and then remained stable. A scan on day 251 revealed a small nodule that rapidly grew while the patient continued selinexor treatment, until both tumors were resected on day 349. (G) PFS of phase III selinexor and placebo arm patients restricted to those patients without detectable *CALB1*. (H and I) PFS of phase III (H) selinexor or (I) placebo arm patients stratified by *CALB1* expression. Shaded areas represent 95% CIs. HR, hazard ratio; PFS, progression-free survival; PR, partial response.

With crossover to selinexor allowed on confirmation of progression for patients on placebo, the SEAL trial was designed to assess noninferiority for OS as key secondary end point; overall, there was no OS difference between the groups (HR of 1.0). In addition, as compared with the patients on placebo who did not cross over, those randomly assigned to selinexor showed a trend toward improved OS ( $P = .06$ ). Additionally, a significant improvement of time to next treatment was observed with

selinexor (HR, 0.50). In patients with refractory DD-LPS whose disease has progressed on two to five prior lines of therapy, a median PFS of 2.8 months with single-agent oral selinexor, while modest, is in line with currently used cytotoxic chemotherapies.<sup>7,8</sup> The ORR for selinexor in DD-LPS was low at 2.7%, which is similar to monotherapy with doxorubicin monotherapy, eribulin or trabectedin,<sup>4,6-8</sup> and CDK4/6<sup>27,29</sup> or investigational MDM2 inhibitors<sup>30</sup> that range from 0% to 8%.

Regarding HR-QoL, as recently published, a total of 255 patients completed baseline assessments, including 168 and 88 in the selinexor and placebo arms, respectively.<sup>31</sup> At baseline, pain scores were significantly higher in the selinexor group. By day 169, patients treated with selinexor had significant reductions in pain compared with placebo.

AEs with selinexor were mostly grade 1 and grade 2, GI and/or constitutional and required prophylactic antiemetics, supportive care, and dose modifications and/or reductions; the vast majority were reversible and tolerable. Nausea, dysgeusia, decreased appetite, vomiting, fatigue, and weight loss were notable (all grades). These symptoms were also reported, albeit at lower frequencies, in the placebo arm and reflect, at least in part, the natural history of DD-LPS. Grade 3/4 anemia, thrombocytopenia, and neutropenia occurred in 18.7%, 10.2%, and 9.1%, respectively. Notably, no febrile neutropenia, mucositis, transaminitis, or alopecia was observed.

Twice-weekly oral selinexor provides the convenience of oral (including at home) administration and absence of neuropathy and transaminase elevations, which occurred in 19% and 45% with eribulin and trabectedin, respectively. However, there is a need to counsel and actively manage GI and constitutional AEs with supportive care, and dose modifications are important. Antiemetic regimens used with selinexor include 5-hydroxytryptamine-3 inhibitors, olanzapine and, if needed, low-dose steroids. This was reflected in patients on selinexor who reported worse HR-QoL (except for pain levels) primarily during the first 43 days. With time, the differences between selinexor and placebo dissipated, and this presumably reflects the investigators' increased experience at addressing TEAEs. Finally, patients on the selinexor arm had significant improvements in pain symptoms, a critical issue for patients with advanced DD-LPS.<sup>32</sup>

The study demonstrated an overall improvement in PFS of 30%, while *median* PFS improvement was modest. Thus, a subset of patients had a significant and durable benefit with selinexor. To better delineate which patients

were more likely to benefit from selinexor, we conducted exploratory molecular biomarker studies using a representative subset of patients (Data Supplement). These analyses revealed that expression of *CALB1*, a calcium binding protein, was strongly associated with resistance to selinexor. We confirmed that *CALB1* is not a prognostic marker in DD-LPS, as there was no association between *CALB1* expression and outcomes in the placebo arm or the TCGA data. *CALB1* was an unexpected discovery as it is highly expressed in the central nervous system and kidneys, where it acts as a buffer and calcium sensor.<sup>33</sup> Although most human adult tissues do not express *CALB1*, its ectopic expression has been observed in several cancer types.<sup>34,35</sup> Recent functional studies have demonstrated a novel oncogenic activity of *CALB1* where it binds MDM2 to enhance MDM2-mediated suppression of p53 signaling.<sup>34</sup> This is especially important in the context of DD-LPS, as MDM2 overexpression, leading to p53 degradation, is a hallmark of this disease. Treatment with selinexor forces nuclear retention and functional activation of p53, even in the presence of high MDM2 levels. Thus, we speculate that *CALB1* expression could prevent selinexor from overcoming MDM2-mediated suppression of p53; laboratory work investigating this is ongoing.

In conclusion, to our knowledge, the SEAL trial was the first and largest study conducted exclusively on patients with heavily pretreated DD-LPS. The results of the SEAL study showed that the novel mechanism of action provided by single-agent oral selinexor conferred a 30% improvement in PFS with an important minority of patients deriving longer-term benefits as demonstrated by clinical improvements in 3-, 6-, and 12-month PFS. The most common AEs were typically low grade and reversible and could be mitigated with proactive supportive care. Further investigation is warranted for selinexor as a treatment for patients with DD-LPS with low or high *CALB1* expression. Oral selinexor may represent a therapeutic option for patients with DD-LPS who have exhausted treatments of known clinical benefit.

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Karyopharm Therapeutics agrees to share individual participant data that underlie the results reported in this article (after deidentification), including the study protocol and statistical analysis plan. Data availability will begin 9 months after publication and will be available 36 months after publication. To gain access, data requestors should submit a proposal to [medicalinformation@karyopharm.com](mailto:medicalinformation@karyopharm.com). Proposals will be reviewed by an independent review committee identified for this purpose.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Selinexor in Advanced, Metastatic Dedifferentiated Liposarcoma: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial**

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**Research Funding:** Amgen, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, Janssen, Karyopharm Therapeutics, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, TRACON Pharma

**Other Relationship:** Amgen, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, Janssen, Karyopharm Therapeutics, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, TRACON Pharma

**Javier Martin-Broto**

**Leadership:** Chairman of Spanish Sarcoma Group (GEIS) 2010–October 2018, GEIS Leadership Role. Vice-chair 2018-ongoing, CTOS Leadership Role. Board of directors 2015-2017, ESMO Leadership Role. Chair sarcoma faculty member 2018-2020, SELNET Leadership Role. Sarcoma European & Latin American Network

**Consulting or Advisory Role:** PharmaMar, Eli-Lilly, Bayer, Eisai, Roche, Daichii, Eli-Lilly, PharmaMar, Roche

**Speakers' Bureau:** PharmaMar, Eli-Lilly, Bayer, Eisai, Roche, Daichii

**Research Funding:** Lilly, PharmaMar, GSK, Eisai, Novartis, IMMIX Biopharma, Eisai, Daiichi Sankyo, Karyopharm, Celgene, Pfizer, BMS, Blueprint, Deciphera, Nektar, Forma, Amgen, Lixte

**Giovanni Grignani**

**Honoraria:** Bayer, Novartis, Lilly, Pfizer, Merck Serono, EISAI, PharmaMar, GlaxoSmithKline

**Consulting or Advisory Role:** EISAI, PharmaMar, Bayer, Merck, GlaxoSmithKline

**Speakers' Bureau:** GlaxoSmithKline

**Research Funding:** PharmaMar (Inst)

**Travel, Accommodations, Expenses:** PharmaMar, Tesaro

**Scott M. Schuetze**

**Research Funding:** Adaptimmune, Amgen, Blueprint Medicines, GlaxoSmithKline, Karyopharm Therapeutics

**Other Relationship:** Blueprint Medicines

**Bruno Vincenzi**

**Consulting or Advisory Role:** Lilly, GlaxoSmithKline, Abbott

**Speakers' Bureau:** PharmaMar

**Research Funding:** BD Bard

**Andrew J. Wagner**

**Honoraria:** Deciphera

**Consulting or Advisory Role:** Lilly, Daiichi Sankyo, Deciphera, Mundipharma, Cogent Biosciences, Epizyme, Boehringer Ingelheim, AADI

**Research Funding:** Lilly (Inst), Plexikon (Inst), Daiichi Sankyo (Inst), Karyopharm Therapeutics (Inst), Deciphera (Inst), Foghorn Therapeutics (Inst), AADI (Inst), Rain Therapeutics (Inst)

**Bartosz Chmielowski**

**Consulting or Advisory Role:** Iovance Biotherapeutics, IDEAYA Biosciences, Sanofi, OncoSec, Genentech, Nektar, Novartis

**Research Funding:** Bristol Myers Squibb (Inst), MacroGenics (Inst), Array BioPharma (Inst), Daiichi Sankyo (Inst), Merck (Inst), Karyopharm Therapeutics (Inst), Infinity Pharmaceuticals (Inst), Rgenix (Inst), Biothera (Inst), Advenchen Laboratories (Inst), Idera (Inst), Neon Therapeutics (Inst), Xencor (Inst), Compugen (Inst), Iovance Biotherapeutics (Inst), PACT Pharma (Inst), RAPT Therapeutics (Inst), Immunocore (Inst), Lilly (Inst), IDEAYA Biosciences (Inst), Tolero Pharmaceuticals (Inst), Ascentage Pharma (Inst), Novartis (Inst), Atreca (Inst), Replimune (Inst), InstilBio (Inst), InstilBio (Inst)

**Robin L. Jones**

**Consulting Fees:** Adaptimmune, Athenex, Bayer, Boehringer Ingelheim, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunodesign, Lilly, Merck, Pharmamar, Springworks, Tracon, UptoDate

**Richard F. Riedel**

**Employment:** Limbguard

**Stock and Other Ownership Interests:** Limbguard

**Consulting or Advisory Role:** Bayer, Blueprint, Daiichi Sankyo, Deciphera, Ignyta, Lilly, Loxo, NanoCarrier, Springworks

**Research Funding:** AADI, Arog, Bayer, Blueprint, Daiichi Sankyo, Deciphera, GSK, Ignyta, Immune Design, Karyopharm Therapeutics, Lilly, NanoCarrier, Oncernal, Plexikon, Roche/Genentech, Springworks, TRACON Pharma

**Patents, Royalties, Other Intellectual Property:** PandoNet—Limbguard

**Other Relationship:** Daiichi Sankyo, Ignyta, NanoCarrier

**Silvia Stacchiotti**

**Consulting or Advisory Role:** Bavarian Nordic, Bayer, Daiichi Sankyo, Deciphera, Epizyme, Immune Design, Lilly, MaxiVax, PharmaMar

**Research Funding:** Advenchen Laboratories, Amgen, Bayer, Blueprint Medicines, Daiichi Sankyo, Epizyme, Karyopharm, Lilly, Novartis, Pfizer, PharmaMar

**Other Relationship:** Lilly, Takeda, PharmaMar

**Elizabeth T. Loggers**

**Research Funding:** Epizyme (Inst), Karyopharm Therapeutics (Inst), SpringWorks Therapeutics (Inst)

**Kristen Ganjoo**

**Consulting or Advisory Role:** Daiichi Sankyo, Foundation Medicine

**Axel Le Cesne**

**Honoraria:** Bayer, PharmaMar, Deciphera

**Antoine Italiano**

**Honoraria:** Bayer, Daiichi Sankyo, Lilly, Epizyme, Novartis, Roche, IPSEN

**Consulting or Advisory Role:** Roche, Daiichi Sankyo, Immune Design, Epizyme, Bayer, Lilly

**Research Funding:** Roche, Bayer, AstraZeneca/MedImmune, PharmaMar, MSD Oncology, Merck Serono

**Patents, Royalties, Other Intellectual Property:** BMS

**Xavier Garcia del Muro**

**Consulting or Advisory Role:** Bristol-Myers Squibb, EusaPharma, Ipsen, Lilly, Pfizer, PharmaMar, Roche

**Speakers' Bureau:** Astellas Pharma, Bristol-Myers Squibb, Ipsen, Pfizer, PharmaMar

**Research Funding:** AstraZeneca

**Other Relationship:** Bristol-Myers Squibb, Pfizer, Roche

**Melissa Burgess**

**Consulting or Advisory Role:** EMD Serono  
**Research Funding:** Merck & Co  
**Other Relationship:** SpringWorks Therapeutics  
**Uncompensated Relationships:** TRACON Pharmaceuticals

**Sophie Piperno-Neumann**

**Consulting or Advisory Role:** Immunocore, Atlanthera

**Christopher Ryan**

**Consulting or Advisory Role:** AstraZeneca, AVEO, Bristol Myers Squibb, Daiichi Sankyo, Exelixis, Partner Therapeutics, Synox  
**Research Funding:** Bristol Myers Squibb (Inst), Daiichi Sankyo (Inst), Exelixis (Inst), Genentech (Inst), GlaxoSmithKline/Novartis (Inst), Karyopharm Therapeutics (Inst), Merck (Inst), Pfizer (Inst), Xynomic Pharma (Inst), Nektar (Inst), Leducq (Inst)

**Charles Forscher**

**Speakers' Bureau:** Deciphera

**Anthony Elias**

**Stock and Other Ownership Interests:** AbbVie, Merck, Gilead Sciences, Allergan, Pfizer, Abbott Laboratories, Amgen, Bristol Myers Squibb, United Health Group, Align Oncology, Illumina, Exact Sciences, Lilly, Agilent, Cigna, Alexion Pharmaceuticals, Biogenex  
**Research Funding:** Astellas Pharma (Inst), Genentech (Inst), Deciphera (Inst), Xencor (Inst), Infinity Pharmaceuticals (Inst), Karyopharm Therapeutics (Inst), TopAlliance BioSciences Inc (Inst), Orinove (Inst), BioAtla (Inst)  
**Uncompensated Relationships:** Seiyax

**Tony Philip**

**Consulting or Advisory Role:** Daiichi Sankyo, Deciphera

**Thierry Alcindor**

**Consulting or Advisory Role:** Amgen, Bayer, Bristol-Myers Squibb, Eisai, Lilly, Merck, Novartis, Canada Pharmaceuticals, Pfizer/EMD Serono, Roche Canada, Taiho Pharmaceutical

**Bernd Kasper**

**Honoraria:** Bayer, GlaxoSmithKline, Pharmamar-zeltia  
**Consulting or Advisory Role:** Ayala Pharmaceuticals, Bayer, Blueprint Medicines, GlaxoSmithKline, SpringWorks Therapeutics

**Peter Reichardt**

**Consulting or Advisory Role:** Bayer, Clinigen, BMS, Roche, MSD, Deciphera, Novartis, Pfizer, PharmaMar, Lilly, Amgen

**Jean-Yves Blay**

**Honoraria:** Novartis, GSK, Bayer, Roche, Deciphera, Ignyta, BMS, MSD, Pharmamar, Karyopharm  
**Research Support:** Novartis, GSK, Bayer, Roche, Deciphera, Ignyta, BMS, MSD, Pharmamar, Karyopharm

**Christine Chevreau**

**Consulting or Advisory Role:** Bristol Myers Squibb, Ipsen, Pfizer, Eisai, GlaxoSmithKline  
**Travel, Accommodations, Expenses:** Ipsen

**Claudia Maria Valverde Morales**

**Consulting or Advisory Role:** Lilly, PharmaMar, Pfizer, Eisai, Bayer, Mundipharma, GlaxoSmithKline  
**Research Funding:** Lilly (Inst), Novartis (Inst), Pfizer (Inst), PharmaMar (Inst), Karyopharm Therapeutics (Inst), Incyte (Inst), Adaptimmune (Inst), GlaxoSmithKline (Inst)  
**Travel, Accommodations, Expenses:** PharmaMar, Lilly, Novartis, Pfizer, Bayer, Rovi

**Gary K. Schwartz**

**Stock and Other Ownership Interests:** Pfizer  
**Consulting or Advisory Role:** Bionaut Labs, Ellipses Pharma, Gencirq, Epizyme, Array BioPharma, Apexigen, Oncogenity, OnCusp, Concarlo, Shanghai Pharma, Astex Pharmaceuticals, January Therapeutics, Sellas Life Sciences, Purtech  
**Research Funding:** Astex Pharmaceuticals, Incyte (Inst), Calithera Biosciences (Inst), Lilly (Inst), Daiichi Sankyo (Inst), Fortress Biotech (Inst), Karyopharm Therapeutics (Inst), Oxford BioTherapeutics (Inst), Astex Pharmaceuticals (Inst), TopAlliance BioSciences Inc (Inst), Adaptimmune (Inst), Clovis Oncology (Inst), SpringWorks Therapeutics (Inst), TRACON Pharma (Inst)  
**Patents, Royalties, Other Intellectual Property:** Companion diagnostics for CD4 inhibitors (Inst), patent granted to develop a new technology called PNAs for cancer therapy  
**Travel, Accommodations, Expenses:** Array BioPharma, Epizyme

**James L. Chen**

**Consulting or Advisory Role:** Syapse, Tempus  
**Speakers' Bureau:** Foundation Medicine  
**Research Funding:** Eisai  
**Patents, Royalties, Other Intellectual Property:** MatchTX

**Hari Deshpande**

**Honoraria:** Daiichi Sankyo, Deciphera, Blueprint Medicines, Exelixis  
**Consulting or Advisory Role:** Daiichi Sankyo, Deciphera, Blueprint Medicines, Exelixis  
**Research Funding:** Deciphera, SpringWorks Therapeutics, Eisai  
**Travel, Accommodations, Expenses:** Deciphera, Daiichi Sankyo  
**Open Payments Link:** <https://openpaymentsdata.cms.gov/physician/156300>

**Elizabeth J. Davis**

**Honoraria:** MJH Life Sciences  
**Consulting or Advisory Role:** Deciphera  
**Speakers' Bureau:** Physicians' Education Resource  
**Research Funding:** Incyte (Inst), Five Prime Therapeutics (Inst), Genentech (Inst), Karyopharm Therapeutics (Inst), Bristol Myers Squibb (Inst), Actuate Therapeutics (Inst), TopAlliance BioSciences Inc (Inst)

**Florence Duffaud**

**Consulting or Advisory Role:** Bayer Health, BluPrint Oncology, GlaxoSmithKline  
**Travel, Accommodations, Expenses:** PharmaMar, Leo Pharma

**Antonio Casado Herráez**

**Consulting or Advisory Role:** Roche, PharmaMar, Eisai, Merck Sharp & Dohme  
**Research Funding:** Pharmamar (Inst)  
**Travel, Accommodations, Expenses:** Pharmamar, Roche, Lilly Spain  
**Other Relationship:** Lilly (Inst)

**Mikael Eriksson**

**Consultant or Advisory Role:** Blueprint Medicines, Clinigen, Bayer  
**Other Relationship:** Trial physician in the Scandinavian Sarcoma Group that receives trial support from Novartis

**Christian Meyer**

**Consulting or Advisory Role:** Deciphera, Intellisphere, AADI  
**Speakers' Bureau:** Novartis  
**Other Relationship:** UpToDate

**Margaret von Mehren**

**Honoraria:** Deciphera, NCCN, Blueprint  
**Consulting or Advisory Role:** Deciphera, NCCN, Blueprint  
**Research Funding:** Novartis  
**Travel, Accommodations, Expenses:** Deciphera, NCCN, Blueprint  
**Other Relationship:** Arog, GenMab, ASCO, Gradalis

**Brian A. Van Tine**

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**Leadership:** Polaris

**Honoraria:** Bionest Partner, Horizon CME, Research to Practice  
**Consulting or Advisory Role:** EMD Serono, Novartis, Epizyme, Daiichi Sankyo, Pfizer, Adaptimmune, Bayer, GlaxoSmithKline, Lilly, Cytokinetics, Apexigen, Deciphera Pharmaceuticals, Immune Design, ADRx, Ayala Pharmaceuticals, Intellisphere

**Speakers' Bureau:** Novartis, Lilly, Adaptimmune, GlaxoSmithKline  
**Research Funding:** Pfizer, Merck, TRACON Pharma, GlaxoSmithKline  
**Patents, Royalties, Other Intellectual Property:** Patent on the use of ME1 as a biomarker, patent on ALEXT3102, Accuronix Therapeutics-Licensing agreement, Sigma-2 Receptor Ligands and Therapeutic uses therefor (006766), Modular Platform for Targeted Therapeutic Delivery (006755), Sigma-2 Receptor Ligand Drug Conjugates as Antitumor Compounds, Methods of synthesis and Uses Thereof (014229)  
**Expert Testimony:** Health Advances  
**Travel, Accommodations, Expenses:** Adaptimmune, Advenchen Laboratories, GlaxoSmithKline, Lilly

**Aviad Zick**

**Research Funding:** Merck (Inst), Roche Molecular Diagnostics (Inst), Karyopharm Therapeutics (Inst)

**Alexander Lee**

**Consulting or Advisory Role:** Astex Pharmaceuticals, AstraZeneca/MedImmune  
**Patents, Royalties, Other Intellectual Property:** Material and methods for stratifying and treating cancers

**Anna Estival Gonzalez**

**Honoraria:** Roche, MSD Oncology, AstraZeneca Spain, Bayer, PharmaMar, Takeda

**Travel, Accommodations, Expenses:** Lilly, Roche, Roche, PharmaMar, Bristol Myers Squibb, Bayer, MSD, Pfizer, AstraZeneca Spain, Takeda

**Mark A. Dickson**

**Employment:** Memorial Sloan Kettering Cancer Center

**Research Funding:** Karyopharm Inc, AADI, Eli-Lilly, National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30CA008748)

**Dayana Michel**

**Employment:** Karyopharm Therapeutics

**Travel, Accommodations, Expenses:** Karyopharm Therapeutics

**Changting Meng**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Travel, Accommodations, Expenses:** Karyopharm Therapeutics

**Jianjun Liu**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Osnat Ben-Shahar**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Dane R. Van Domelen**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Christopher J. Walker**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Patents, Royalties, Other Intellectual Property:** Pending patents for biomarkers related to selinexor efficacy

**Travel, Accommodations, Expenses:** Karyopharm Therapeutics

**Hua Chang**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Travel, Accommodations, Expenses:** Karyopharm Therapeutics

**Yosef Landesman**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Jatin J. Shah**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Sharon Shacham**

**Employment:** Karyopharm Therapeutics

**Stock and Other Ownership Interests:** Karyopharm Therapeutics

**Patents, Royalties, Other Intellectual Property:** 8999996, 9079865, 9714226, PCT/US12/048319, and I574957 on hydrazide-containing nuclear transport modulators and uses. Pending patents: PCT/US12/048319, 499/2012, PI20102724, and 2012000928 on hydrazide-containing nuclear transport modulators and uses

**Michael G. Kauffman**

**Employment:** Karyopharm Therapeutics

**Stock:** Karyopharm Therapeutics

**Steven Attia**

**Research Funding:** AB Science, Adaptimmune, Advenchen Laboratories, Bavarian Nordic, Bayer, Blueprint Medicines, BTG, CBA Pharma, CytRx Corporation, Daiichi Sankyo, Deciphera, Desmoid Tumor Research Foundation, Epizyme, FORMA Therapeutics, Genmab, GlaxoSmithKline, Gradalis, Immune Design, Incyte, Karyopharm Therapeutics, Lilly, Merck, Novartis, Philogen, PTC Therapeutics, Takeda, TRACON Pharma

**Other Relationship:** Immune Design

No other potential conflicts of interest were reported.