Clinical Study Protocol

KCP-330-020

A PHASE 2-3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY OF SELINEXOR (KPT-330) VERSUS PLACEBO IN PATIENTS WITH ADVANCED UNRESECTABLE DEDIFFERENTIATED LIPOSARCOMA (DDLS)

SEAL Study: Selinexor in Advanced Liposarcoma

Drug Development Phase:	Phase 2-3
Investigational Product:	Selinexor (KPT-330)
Indication:	Liposarcoma
EudraCT Number:	2015-003594-14
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA USA 02459
Protocol Date and Version:	16 September 2015 Version 1.0 (Original) 11 March 2016 Version 2.0 (Amendment 1; not implemented) 01 November 2016 Version 3.0 (Amendment 2) 06 July 2017 Version 4.0 (Amendment 3) 29 September 2017 Version 5.0 (Amendment 4) 23 August 2018 Version 6.0 (Amendment 5; not implemented) 10 September 2018 Version 7.0 (Amendment 6) 30 January 2020 Version 8.0 (Amendment 7) 21 May 2020 Version 9.0 (Amendment 8)

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study No. KCP-330-020 dated 21 May 2020 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPD

May 22, 2020

PPD **, PhD, MBA**
PPD
Karyopharm Therapeutics Inc.

Date

PPD

PPD

PPD **, MD**
PPD
Karyopharm Therapeutics Inc.

Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. KCP-330-020 dated 21 May 2020 regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices (International Council for Harmonisation [ICH] E6) and applicable Food and Drug Administration (FDA) requirements:

Name of Principal Investigator:

Principal Investigator's Signature:	
Principal Investigator's Name:	
Institution:	
Date:	

PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics Inc.	**Investigational Product:** Selinexor (KPT-330)	**Developmental Phase:** Phase 2-3

Title of Study: A Phase 2-3 Multicenter, Randomized, Double-blind Study of Selinexor (KPT-330) versus Placebo in Patients with Advanced Unresectable Dedifferentiated Liposarcoma (DDLS)

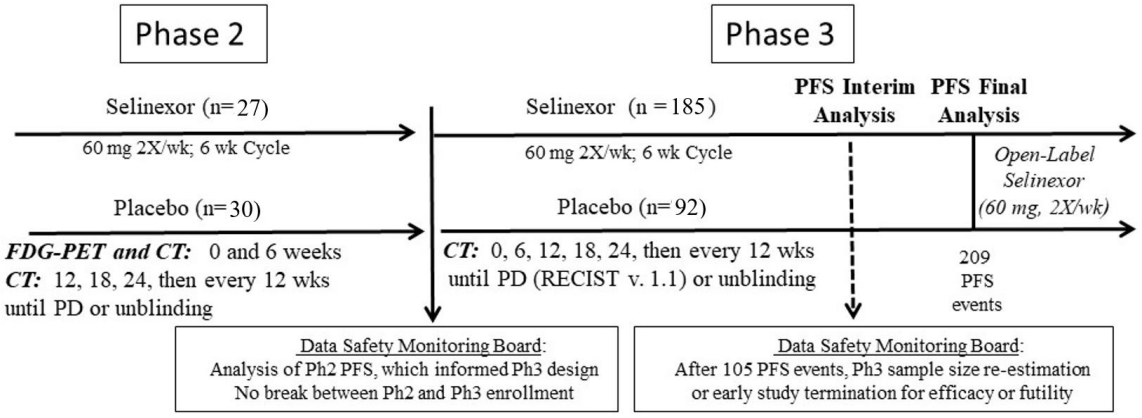
Study Name: SEAL: **Se**linexor in **A**dvanced **L**iposarcoma

Protocol Number: KCP-330-020

Indication: Dedifferentiated Liposarcoma (DDLS)

Study Design Overview:

This is a Phase 2-3, multicenter, randomized, double-blind, placebo-controlled study. Approximately 334 total patients will be randomized (57 patients in Phase 2 and approximately 277 patients in Phase 3). Enrollment in Phase 2 has been completed. There was no break between Phase 2 and Phase 3 enrollment. The study overview is presented in the figure below:



Patients in the placebo arm who have PD will have the option to cross over to open-label selinexor.

Phase 2:
Fifty-seven patients were randomized to selinexor or placebo in a 1:1 allocation. Randomization was stratified based on the following stratification factors for patients enrolled under protocol Versions ≤ 4: number of prior systemic therapies (1 versus ≥ 2) and prior eribulin use (prior eribulin versus no prior eribulin). The preplanned analysis of progression-free survival (PFS; after 40 PFS events were observed) was performed and served as a guideline to inform the final design of the Phase 3 portion of the study.

Phase 3:
The Phase 3 accrual period began immediately after enrollment of the Phase 2 portion was completed and will be approximately 30 months.
Approximately 277 patients will be randomized to selinexor (~185 patients) or placebo (~92 patients) in a 2:1 allocation.
Randomization will be stratified based on (a) prior eribulin use (prior eribulin versus no prior eribulin), (b) prior trabectedin (Yondelis®) use (prior trabectedin versus no prior trabectedin), and (c) the number of prior systemic therapies excluding eribulin and trabectedin (2 versus ≥ 3).
All radiographic responses will be determined by the central reader (see the *Imaging Manual* for

Sponsor:	Investigational Product:	Developmental Phase:
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more details).
Patients who have progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 (Eisenhauer 2009), will discontinue blinded study treatment and their treatment assignment will be unblinded.

- Patients in the placebo arm who have PD will have the option to cross over to open-label selinexor.
- Patients in the selinexor arm who have PD will only be allowed to continue on selinexor (as open-label treatment) if the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor.

Patients who discontinue blinded study treatment at the discretion of the Investigator for reasons other than PD are not allowed to receive open-label selinexor.
An interim analysis was conducted after 108 PFS events had occurred. Based on the safety and efficacy data, the DSMB recommendation was continuation of the study with no change to safety monitoring and no sample size adjustment. Approximately 34 months will be required to complete the primary Phase 3 PFS analysis. The primary endpoint analysis will be performed approximately 4 months after enrollment of the last patient, once 209 PFS events are observed. Treatment assignment for all patients will be unblinded at the time of the primary PFS analysis and all Phase 3 patients will be evaluable for assessment of the primary endpoint.
Patients who are on blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 may proceed as follows:

- Patients in the placebo arm may cross over to open-label selinexor (60 mg twice weekly).
- Patients in the selinexor arm will continue selinexor but as open-label treatment.

All patients who have PD while receiving open-label selinexor will discontinue selinexor and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor.

Objectives:

Phase 2

Phase 2 Primary Objective

- Assess and compare progression-free survival (PFS) of patients with advanced unresectable DDLS treated with selinexor (60 milligrams [mg]) or placebo twice weekly. PFS is defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause.

Phase 2 Secondary Objectives

- Compare time to progression (TTP) on study treatment, per RECIST v. 1.1, with TTP on the patient's last prior systemic therapy.
- Determine the overall response rate (ORR: Complete Response [CR] + Partial Response [PR]), supported by duration of response (DOR). Responses will be defined by RECIST v. 1.1.
- Assess changes at 6 weeks in tumor glucose metabolism, density, and size using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) (diagnostic).
- Assess safety of each treatment arm.

Phase 3

Phase 3 Primary Objective

Assess and compare PFS of patients with advanced unresectable DDLS treated with selinexor (60 mg) or placebo twice weekly. PFS is defined as the time from date of randomization until

Sponsor: Karyopharm Therapeutics Inc.	**Investigational Product:** Selinexor (KPT-330)	**Developmental Phase:** Phase 2-3

the first date of PD, per RECIST v. 1.1, or death due to any cause. Evaluation of the radiographic data for the PFS primary endpoint will be based on data from a scan review by the independent central reader.

Phase 3 Secondary Objectives

- Assess Overall Survival (OS), measured from date of randomization until death due to any cause.
- Compare TTP on study treatment, per RECIST v. 1.1, with TTP on the patient's last prior systemic therapy.
- Assess Quality of Life (QoL) and patient-reported outcomes as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and the EuroQoL- Group Health Questionnaire (EQ-5D-5L).
- Determine the ORR, supported by DOR. Responses will be defined by RECIST v. 1.1.
- Assess PFS according to the Investigator based on clinical and/or radiologic criteria.
- Assess safety of each treatment arm.

Study Population:
This study will enroll patients ≥ 12 years of age with DDLS per World Health Organization (WHO) Response Criteria (Miller 1981) for Phase 2 and per RECIST v. 1.1 (Eisenhauer 2009) for Phase 3 who have received at least 2 but no more than 5 prior systemic therapies for the treatment of liposarcoma who meet all of the inclusion criteria and none of the exclusion criteria.

Study Treatment, Dose, and Mode of Administration:
Blinded Study Treatment (Phases 2 and 3): Selinexor at a fixed oral dose of 60 mg or matching placebo will be given twice weekly during Weeks 1-6 of each 6-week (42-day) cycle until PD per RECIST v. 1.1, intolerability, consent withdrawal, or unblinding.
Open-label Selinexor:
Patients on open-label selinexor will receive selinexor 60 mg twice-weekly during Weeks 1-6 of each six-week (42-day) cycle until PD, intolerability, or consent withdrawal.

Duration of Treatment and Follow-up:
Following a 21-day screening period, patients may receive study treatment until they meet the criteria for discontinuation of study treatment or withdraw from the study.
Patients will be followed for survival until the end of the study, withdrawal criteria are met, or death.

Statistical Methods:
Based on the planned analysis of PFS by WHO and RECIST v. 1.1 Criteria in the Phase 2 portion of the study, the response criteria for the primary analysis (PFS) were changed from WHO to RECIST v. 1.1 in Version 4.0 of the protocol. Consequently, data from the Phase 2 portion of the study will be excluded from the final efficacy analysis in order to maintain statistical integrity and preserve overall Type I error rate. (Phase 2 safety data will be integrated with the Phase 3 safety data in the final safety analysis.)

Phase 2:
All Phase 2 analyses will be conducted among Phase 2 patients only.
Phase 2 Primary Endpoint Analysis:
The primary endpoint PFS for Phase 2 is defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause.
A preplanned preliminary analysis of PFS after 40 PFS events was conducted with an 11 August 2017 data cut with 49 eligible patients whose treatment assignments were available. Patients were analyzed in the treatment arm to which they were randomized. The preliminary PFS

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analysis was conducted by both WHO and RECIST v. 1.1 Criteria and served as a guideline to inform the final design of the Phase 3 portion of the study.
At the time of the preliminary PFS analysis, there were 48 events by WHO (22 selinexor, 26 placebo) and 28 events by RECIST v.1.1. (10 selinexor, 18 placebo). Both analyses showed trends favoring selinexor over placebo, while RECIST v. 1.1 results show a more significant effect size (hazard ratio [HR] of 0.84, 95% CI [0.47, 1.49] by WHO as compared with HR of 0.60, 95% CI [0.28, 1.31] by RECIST v. 1.1). A Landmark analysis based on RECIST v. 1.1 for patients continuing on study after 45 days showed a more significant HR of 0.24 (95% CI [0.05, 1.15]) in favor of selinexor.
Of the 57 patients in Phase 2, 56 met the eligibility criteria for the study. The formal primary Phase 2 PFS analysis will be performed on all 56 eligible patients randomized to study treatment in Phase 2 when their treatment assignments are unblinded. Phase 2 patients will be analyzed in the treatment arm to which they are randomized.

Phase 3:

The final efficacy analysis will be conducted among Phase 3 patients only.

Phase 3 Primary Endpoint Analysis

The primary PFS analysis will be performed on the intent-to-treat (ITT) population for Phase 3 patients and on the per-protocol (PP) population as a supportive analysis. The stratified log-rank test will be used to test the null hypothesis that the PFS distributions are the same for both treatment groups versus the alternative hypothesis that the duration of PFS for the selinexor arm is longer than the placebo arm using a 1-sided test and alpha=0.025 level of significance, adjusted using the Cui, Hung, and Wang (CHW) method (Cui 1999).

Phase 3 Sample Size and Statistical Power

Per protocol, the Phase 3 sample size was re-evaluated based on the Phase 2 results. Sample size calculations were conducted under the following assumptions:

CCI [redacted]

Based on these assumptions, approximately 277 eligible patients will be randomized to receive either selinexor (60 mg twice weekly) or placebo in a blinded manner to observe 209 PFS events.

CCI [redacted]

Table 1: Schedule of Assessments and Study Activities: Blinded Phase 2 and Phase 3

	Screening (visits may be combined at site discretion)		Randomized Blinded Treatment						End of Blinded Treatment (EoBT)	Only for patients NOT proceeding to open-label selinexor	
Visit/Call Name	**Visit 1**	**Visit 2**	**Cycle 1**		**Cycle 2**		**Cycle ≥ 3**		**EoBT Visit[19]**	**Safety Follow-up Call[20]**	**Survival Follow-up[21]**
Schedule of Visit	**≤ 21 days prior to C1 D1**	**≤ 14 days prior to C1 D1**	**Days 1, 8, 15, 22, 29, 36**	**Day 3 only[22]**	**Days 1, 15, 29**	**Days 10, 24, 38[22]**	**Days 1, 22**	**Days 10, 17, 31, 38[22]**	**≤ 14 days of last blinded dose**	**30 days after last dose**	**every 3 months**
Visit window [±days]			**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**	**+ 1 day**		**+7 days**	**±14 days**
Visit number (in clinic)	**1**	**2**	**3-8**	**Phone**	**9-11**	**Phone**	**≥ 12**	**Phone**	**In Office**	**Phone**	**Phone**
Informed consent for blinded study treatment[1]	X										
Informed consent for open-label selinexor treatment[1]									X (if applicable)		
Patient History											
Inclusion /exclusion criteria	X										
Demography	X										
Medical history	X										
Clinical Assessments											
Physical examination and vital signs (blood pressure, pulse, temperature)[2]	X		X		X		X		X		
Weight (indoor clothing without shoes)	X		X		X		X		X		
Height (without shoes)	X				X (D1 only)		X (D1 only)		X		
BSA[3]	X				X (D 1 only)		X (D1 only)		X		
ECOG	X		X (D1 only)		X (D1 only)		X (D1 only)		X		
12-lead ECG[4]	X		X[5] (D1 only)		X[5] (D1 only)				X		

	Screening (visits may be combined at site discretion)		Randomized Blinded Treatment						End of Blinded Treatment (EoBT)	Only for patients NOT proceeding to open-label selinexor	
Visit/Call Name	**Visit 1**	**Visit 2**	**Cycle 1**		**Cycle 2**		**Cycle ≥ 3**		**EoBT Visit[19]**	**Safety Follow-up Call[20]**	**Survival Follow-up[21]**
Schedule of Visit	**≤ 21 days prior to C1 D1**	**≤ 14 days prior to C1 D1**	**Days 1, 8, 15, 22, 29, 36**	**Day 3 only[22]**	**Days 1, 15, 29**	**Days 10, 24, 38[22]**	**Days 1, 22**	**Days 10, 17, 31, 38[22]**	**≤ 14 days of last blinded dose**	**30 days after last dose**	**every 3 months**
Visit window [±days]			**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**	**+ 1 day**		**+7 days**	**±14 days**
Visit number (in clinic)	**1**	**2**	**3-8**	**Phone**	**9-11**	**Phone**	**≥ 12**	**Phone**	**In Office**	**Phone**	**Phone**
Laboratory Assessments											
Urinalysis[4]	X		X (D1 only)		X (D1 only)		X (D1 only)		X		
Hematology[4]	X		X (D1 only)		X (D1 only)		X (D1 only)		X		
Complete serum chemistry[4]	X		X (D1 only)		X (D1 only)		X (D1 only)		X		
Limited serum chemistry[4]			X (D8, D15, D22, D29, D36)		X (D15, D29)		X (D22 only)				
Coagulation tests[4]	X		X (D1 only)		X (D1 only)		X (D1 only)		X		
Pregnancy test (if applicable)[4, 23]		X[6]			X (D1 only)		X (D1 only)		X		
Tumor biopsy[7]	X		X (C1 D22 only; or may be taken on C2 D1)		X (C2 D1 only; if not taken on C1 D22)				X[8]		

	Screening (visits may be combined at site discretion)		Randomized Blinded Treatment						End of Blinded Treatment (EoBT)	Only for patients NOT proceeding to open-label selinexor	
Visit/Call Name	**Visit 1**	**Visit 2**	**Cycle 1**		**Cycle 2**		**Cycle ≥ 3**		**EoBT Visit[19]**	**Safety Follow-up Call[20]**	**Survival Follow-up[21]**
Schedule of Visit	**≤ 21 days prior to C1 D1**	**≤ 14 days prior to C1 D1**	**Days 1, 8, 15, 22, 29, 36**	**Day 3 only[22]**	**Days 1, 15, 29**	**Days 10, 24, 38[22]**	**Days 1, 22**	**Days 10, 17, 31, 38[22]**	**≤ 14 days of last blinded dose**	**30 days after last dose**	**every 3 months**
Visit window [±days]			**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**	**+ 1 day**		**+7 days**	**±14 days**
Visit number (in clinic)	**1**	**2**	**3-8**	**Phone**	**9-11**	**Phone**	**≥ 12**	**Phone**	**In Office**	**Phone**	**Phone**
Imaging											
Phase 2 FDG- PET and CT[9]		X			X (D1 only; 6 weeks post-first dose)						
Phase 3 CT (preferred) or MRI scan for tumor measurement[10]	X				X (D1 only; 6 weeks post-first dose)						
Phase 2[9] and Phase 3[10] CT (preferred) or MRI scan for tumor measurement							X (D1 of Cycles 3, 4, 5, then of every odd # cycle)		X (if ≥ 4 weeks since last prior scan AND required to document disease or clinical progression)		
Diagnosis/ assessment of progression/ extent of liposarcoma following each tumor scan (RECIST v. 1.1)[11]		X			X (D1 only)		X (when tumor scans are performed)		X (If tumor scan is performed)		
Treatment assignment query of patient and Investigator (after determination of PD)[12]					(X)		(X)		(X)		

	Screening (visits may be combined at site discretion)		Randomized Blinded Treatment						End of Blinded Treatment (EoBT)	Only for patients NOT proceeding to open-label selinexor	
Visit/Call Name	**Visit 1**	**Visit 2**	**Cycle 1**		**Cycle 2**		**Cycle ≥ 3**		**EoBT Visit[19]**	**Safety Follow-up Call[20]**	**Survival Follow-up[21]**
Schedule of Visit	**≤ 21 days prior to C1 D1**	**≤ 14 days prior to C1 D1**	**Days 1, 8, 15, 22, 29, 36**	**Day 3 only[22]**	**Days 1, 15, 29**	**Days 10, 24, 38[22]**	**Days 1, 22**	**Days 10, 17, 31, 38[22]**	**≤ 14 days of last blinded dose**	**30 days after last dose**	**every 3 months**
Visit window [±days]			**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**	**+ 1 day**		**+7 days**	**±14 days**
Visit number (in clinic)	**1**	**2**	**3-8**	**Phone**	**9-11**	**Phone**	**≥ 12**	**Phone**	**In Office**	**Phone**	**Phone**
CCI											
Nutritional consultation[4, 15]			X (D1 only)								
Quality of Life questionnaires[16]		X			X (D1 only, predose)		X (D1 only, predose)		X		
Eligibility confirmation by Sponsor: after screening and before randomization		X									
Randomization		X									
Study treatment: in clinic dosing and dispensing of for home use[17]			X		X		X				
Adverse events	Throughout										
Serious adverse events	Throughout										
Concomitant medications	Throughout										

	Screening (visits may be combined at site discretion)		Randomized Blinded Treatment						End of Blinded Treatment (EoBT)	Only for patients NOT proceeding to open-label selinexor	
Visit/Call Name	**Visit 1**	**Visit 2**	**Cycle 1**		**Cycle 2**		**Cycle ≥ 3**		**EoBT Visit[19]**	**Safety Follow-up Call[20]**	**Survival Follow-up[21]**
Schedule of Visit	**≤ 21 days prior to C1 D1**	**≤ 14 days prior to C1 D1**	**Days 1, 8, 15, 22, 29, 36**	**Day 3 only[22]**	**Days 1, 15, 29**	**Days 10, 24, 38[22]**	**Days 1, 22**	**Days 10, 17, 31, 38[22]**	**≤ 14 days of last blinded dose**	**30 days after last dose**	**every 3 months**
Visit window [±days]			**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**	**+ 1 day**		**+7 days**	**±14 days**
Visit number (in clinic)	**1**	**2**	**3-8**	**Phone**	**9-11**	**Phone**	**≥ 12**	**Phone**	**In Office**	**Phone**	**Phone**
Inquiry about antineoplastic therapy after discontinuation of blinded study treatment[18]									X	X	X

AE: adverse event; BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoS; end of study; FDG = ^{18}F-fluorodeoxyglucose; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = progressive disease; CCI [redacted]; CCI [redacted]; QoL = Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; WHO = World Health Organization.

[1] Informed consent for blinded study treatment is required prior to the first study-specific measures; note age at time of consent. Informed consent for open-label selinexor is required before any study-specific measures for open-label selinexor are conducted at the Open-label C1D1 Visit. For adolescent patients (permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority), a separate Assent Form must be signed by the patient at the time of informed consent.

[2] Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. Blood pressure should be assessed on the same arm throughout the study. Physical examinations will be performed on the scheduled day, even if study treatment is being interrupted.

[3] BSA will be calculated to verify that BSA > 1.2 m^2 to ensure that an individual patient's selinexor dose would not exceed 70 mg/m^2 twice weekly. If the patient's weight fluctuates substantially, BSA should be re-calculated at each treatment visit. BSA should be re-calculated prior to any selinexor/placebo dose change.

[4] The following assessments may be performed if clinically indicated during the study: ECGs, urinalysis, hematology, complete or limited serum chemistry, coagulation tests, pregnancy testing, and nutritional consultation. Clinical laboratory tests will be collected and analyzed on the scheduled day, even if study treatment is being interrupted (see Section 10.6.2.1).

[5] ECGs on Day 1 of Cycles 1 and 2 during blinded study treatment are to be performed just prior to the blood sample taken 2 hours postdose (approximately at the expected t_{max} of plasma selinexor).

[6] For females of childbearing potential only; must have a negative serum hCG pregnancy test at Screening within 3 days before the first dose of blinded study treatment. Test sensitivity for hCG must be ≥ 25 mIU/mL.

[7] A tumor biopsy will be collected during Screening in order to perform confirmatory histology at a central laboratory (results not required for randomization and initiation of treatment) unless appropriate archival material (ie, of DDLS tissue) is available (see Section 10.4). If sufficient material is available from the pretreatment (screening) biopsy sample (archival or fresh), a portion of the sample will be used for CCI testing and one additional tumor biopsy will be collected at either Cycle 1 Day 22 or Cycle 2 Day 1 for CCI to assess treatment-related changes using immunohistochemical, genomic, and/or proteomic assays (see Section 10.11.3). Biopsies are required if feasible. The feasibility of the biopsy procedure, in terms of patient safety and tumor accessibility, will be determined by the Investigator. Note: This second biopsy (eg, either Cycle 1 Day 22 or Cycle 2 Day 1) should not be collected from adolescent/pediatric patients for exploratory studies if there appears to be a potential for serious risk for the patient.

[8] Tumor biopsy at the EoBT Visit for patients who were in the placebo arm and are crossing over to open-label selinexor only. If the patient has archival material (ie, of dedifferentiated liposarcoma tissue) collected at Screening, Cycle 1 Day 22, or Cycle 2 Day 1 within 12 months prior to the first dose of open-label selinexor, that sample may substitute for the biopsy at the EoBT Visit. Patients in the selinexor arm who continue on selinexor but as open-label treatment are not required to have an additional tumor biopsy at the EoBT Visit.

[9] ***Phase 2 patients***: FDG-PET and CT (diagnostic) scans will be performed during Screening (within 14 days of first dose of blinded study treatment) and approximately 6 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycle 2) to assess tumor size, density, and SUV. Note: If the FDG-PET scan is contraindicated, then CT (preferred) or MRI scan should be used instead, so that, for a given patient, the same imaging modality is maintained throughout the study. Copies of scan data will be provided to a central imaging lab for two-dimensional and three-dimensional measurements for correlation with tumor responses. Additional tumor assessments using CT (preferred) or MRI scans will be performed at approximately 12, 18, and 24 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycles 3, 4, and 5), then every 12 weeks (ie, Day 1 of odd-numbered Cycles $\geq$ 7) thereafter until PD or unblinding to assess tumor size (one, two, and three dimensions) and evaluate site of disease and distant sites (abdomen, pelvis, chest).

[10] ***Phase 3 patients***: CT (or MRI if CT is contraindicated) scans will be performed during Screening (within 21 days of first dose of blinded study treatment) and approximately 6, 12, 18, and 24 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycles 2, 3, 4, and 5), then every 12 weeks (ie, Day 1 of odd-numbered Cycles $\geq$ 7) thereafter until PD or unblinding to assess tumor size (one, two and three dimensions) and evaluate site of disease and distant sites (abdomen, pelvis, chest). For a given patient, the same imaging modality should be maintained throughout the study. Patients in the placebo arm who have clinical progression must have subsequent radiographic progression determined by the central reader in order to receive open-label selinexor. Copies of scan data will be provided to the central reader for two-dimensional and three-dimensional measurements for determination of tumor responses (see *Imaging Manual* for details).

[11] Assessment of liposarcoma per RECIST v. 1.1 (Eisenhauer 2009; Appendix 2).

[12] After PD determination but prior to unblinding, record independent responses from the patient and the Investigator regarding which study treatment (active [selinexor] or placebo) they believe the patient received during blinded study treatment. If treatment assignment is unblinded for reasons other than PD (eg, if unblinding is required for clinical management of a clinically important SAE leading to discontinuation of study treatment and knowledge of the received study treatment is required for clinical management and treatment of the SAE), query should be performed prior to unblinding.

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[15] The nutritional consultation should occur on C1 D1 before the first dose of blinded study treatment (or within the Screening Period). See Section 10.7.3.

[16] The QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) should be completed prior to study treatment administration if study treatment is administered on the same day that the questionnaires are completed. See Section 10.7.1.

[17] Study treatment dosing (selinexor or placebo) is twice weekly (eg, Days 1, 3, 8, 10, etc.) during Weeks 1-6 of each 6-week (42-day) cycle. For doses on non-clinic days, the patient will be provided with doses to take home.

[18] Information on any antineoplastic therapies used after discontinuation of blinded study treatment will be collected at the EoBT Visit (Section 9.1.6), Safety Follow-up Calls (Section 9.1.7), and during Survival Follow-up (Section 9.2.6).

[19] Phase 3 patients in the selinexor arm who continue on selinexor but as open-label treatment must complete the EoBT Visit before their next scheduled dose.

[20] The Safety Follow-up Call must be performed for all patients (ie, with or without EoBT Visit) who are not proceeding to open-label selinexor. The purpose of this call is to assess patient status, follow-up on any AEs that were not resolved at the EoBT Visit, and collect information on any antineoplastic therapies used since discontinuation of blinded study treatment.

[21] After discontinuation of blinded study treatment, a call will be made to the patient (or the patient's family) every 3 months until the EoS (Section 11.4) to inquire about the patient's liposarcoma status and to obtain available information (including treatment type, response, and time of response for assessment of CCI) on any antineoplastic therapies used since discontinuation of blinded study treatment. For patients who progress on post-study treatment antineoplastic therapy, the Investigator should enter the date of progression from the medical record in the eCRF if that information is available to the Investigator. See Section 10.7.4.

[22] Phone call to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

- Cycle 1: the telephone contact with the patient must take place on Day 3 (+ 1 day).
- Cycle 2: the telephone contact with the patient will be made on Day 10 (+ 1 day), Day 24 (+ 1 day) and Day 38 (+ 1 day), corresponding to Day 3 (+ 1 day) of every week in Cycle 2 in which a clinic visit does not occur.
- Cycle ≥ 3: the telephone contact with the patient will be made on Day 10 (+ 1 day), Day 17 (+ 1 day), Day 31 (+ 1 day) and Day 38 (+1 day), corresponding to Day 3 (+ 1 day) of every week in Cycles ≥ 3 in which a clinic visit does not occur.

[23] For female patients of childbearing potential only; pregnancy testing (serum hCG or high sensitivity urine) is required prior to dosing on Day 1 of Cycles ≥ 2 and at the EoBT Visit or within 3 days before the first dose of open-label selinexor (serum hCG). A positive urine pregnancy test will be confirmed by a serum pregnancy test. Test sensitivity for hCG must be ≥25 mIU/mL.

Table 2: Schedule of Assessments and Study Activities: Open-Label Selinexor

- EoBT Visit serves as baseline of Open-Label Selinexor; The EoBT Visit may occur at open-label (OL)-C1 D1 visit but must be ≤ 14 days of last blinded dose. OL C1 D1 must occur within 14 days of the EoBT Visit.
- Patients in the selinexor arm who continue selinexor but as open-label treatment must complete the EoBT Visit before their next scheduled selinexor dose to maintain continuity of selinexor dosing from blinded to open-label treatment.
- Physical examination assessments and laboratory assessments done at the EoBT Visit do not need to be repeated at OL-C1 D1.

	Open-Label Cycle 1 (42 days/6 wks) per cycle)		**Open-Label Cycle 2**		**Open-Label Cycle ≥ 3**	**End of Treatment (EoT) Visit**	**Safety Follow-up Call[15]**	**Survival Follow-up[16]**
Schedule of Visit	**Days 1, 8*, 15*, 22, 29* and 36***	**Day 3 only[17]**	**Days 1, 15 and 29***	**Days 10, 24 and 38[17]**	**Days 1 and 22**	**≤ 14 days Post-Last Dose**	**30 days after last dose**	**Every 3 months**
Visit window [±days]	**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**		**+7 days**	**±14 days**
Visit number	**OL1-6**	**Phone**	**OL7-9**	**Phone**	**OL ≥ 10**	**In Office**	**Phone**	**Phone**
Open-label informed consent[1]	X (if not obtained at EoBT Visit)							
Clinical Assessments (if performed at EoBT, do not repeat at C1 D1)								
Physical examination and vital signs (blood pressure, pulse, temperature)[2]	X		X		X	X		
Weight (indoor clothing without shoes)	X		X		X	X		
Height (without shoes)			X (D1 only)		X (D1 only)	X		
BSA[3]			X (D1 only)		X (D1 only)	X		
ECOG	X (D1 only)		X (D1 only)		X (D1 only)	X		
12-lead ECG[4]	X (D1 only)					X		

	Open-Label Cycle 1 (42 days/6 wks) per cycle)		Open-Label Cycle 2		Open-Label Cycle ≥ 3	End of Treatment (EoT) Visit	Safety Follow-up Call[15]	Survival Follow-up[16]
Schedule of Visit	**Days 1, 8*, 15*, 22, 29* and 36***	**Day 3 only[17]**	**Days 1, 15 and 29***	**Days 10, 24 and 38[17]**	**Days 1 and 22**	**≤ 14 days Post-Last Dose**	**30 days after last dose**	**Every 3 months**
Visit window [±days]	**±1 day**	**+ 1 day**	**± 2 days**	**+ 1 day**	**± 2 days**		**+7 days**	**±14 days**
Visit number	**OL1-6**	**Phone**	**OL7-9**	**Phone**	**OL ≥ 10**	**In Office**	**Phone**	**Phone**
Laboratory Assessments (if performed at EoBT, do not repeat at C1 D1)								
Urinalysis[4]	X (D1 only)		X (D1 only)		X (D1 only)	X		
Hematology[4]	X (D1 only)		X (D1 only)		X (D1 only)	X		
Complete serum chemistry[4]	X (D1 only)		X (D1 only)		X (D1 only)	X		
Limited serum chemistry[4]	X (D8, D15, D22, D29, D36)		X (D15, D29)		X (D22 only)			
Coagulation tests[4]	X (D1 only)		X (D1 only)		X (D1 only)	X		
Pregnancy test[4, 5, 18]			X (D1 only)		X (D1 only)	X		
Tumor biopsy[6] (Only patients who cross over from placebo)	X (C1 D22 only; or may be taken on C2 D1)		X (C2 D1 only; if not taken on C1 D22)					
Imaging								
CT (preferred) or MRI scan for tumor measurement[7]			X (D1 only)		X (D1 of every odd # cycle)	X (if ≥ 4 weeks since last prior scan AND required to document disease or clinical progression)		
Assessment of progression/ extent of liposarcoma following each tumor scan (RECIST v. 1.1)[8]			X (D1 only)		X (when tumor scans are performed)	X (If tumor scan is performed)		

	Open-Label Cycle 1 (42 days/6 wks) per cycle)		Open-Label Cycle 2		Open-Label Cycle ≥ 3	End of Treatment (EoT) Visit	Safety Follow-up Call[15]	Survival Follow-up[16]
Schedule of Visit	Days 1, 8*, 15*, 22, 29* and 36*	Day 3 only[17]	Days 1, 15 and 29*	Days 10, 24 and 38[17]	Days 1 and 22	≤ 14 days Post-Last Dose	30 days after last dose	Every 3 months
Visit window [±days]	±1 day	+ 1 day	± 2 days	+ 1 day	± 2 days		+7 days	±14 days
Visit number	OL1-6	Phone	OL7-9	Phone	OL ≥ 10	In Office	Phone	Phone
CCI [redacted]								
Nutritional consultation[4, 11]	X (D1 only							
Quality of Life questionnaires[12]	X (D1 only, predose)		X (D1 only, predose		X (D1 only, predose)	X		
Selinexor: in clinic dosing and dispensing of for home use[13]	X		X		X			
AEs and SAEs	Throughout							
Concomitant medications	Throughout							
Inquiry about antineoplastic therapy after discontinuation of open-label selinexor[14]						X	X	X

*Visits are not required for patients who continue selinexor but as open-label treatment.

BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PD= progressive disease; CCI [redacted]; QoL = Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.

[1] Informed consent for open-label selinexor is required before any study-specific measures for open-label selinexor are conducted at the Open-label C1D1 Visit. For adolescent patients (permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority), a separate Assent Form must be signed by the patient at the time of informed consent.

[2] Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. Blood pressure should be assessed on the same arm throughout the study. Physical examinations will be performed on the scheduled day, even if study treatment is being interrupted.

[3] BSA will be calculated to verify that BSA > 1.2 m^2 to ensure that an individual patient's selinexor dose would not exceed 70 mg/m^2 twice weekly. If the patient's weight fluctuates substantially, BSA should be re-calculated at each treatment visit. BSA should be re-calculated prior to any selinexor/placebo dose change.

[4] The following assessments may be performed if clinically indicated during the study: ECGs, urinalysis, hematology, complete or limited serum chemistry, coagulation tests, pregnancy testing, and nutritional consultation. Clinical laboratory tests will be collected and analyzed on the scheduled day, even if study treatment is being interrupted (see Section 10.6.2.1).

[5] Females of childbearing potential who are proceeding to open-label selinexor must have a negative serum hCG pregnancy test at the EoBT Visit (or within 3 days before the first dose of open-label selinexor). Test sensitivity for hCG must be ≥ 25 mIU/mL.

[6] Tumor biopsy to be taken only from patients who cross over from blinded placebo to open-label selinexor. If a biopsy sample was obtained during blinded treatment (pre- or post-dosing) within 12 months prior to the first dose of open-label selinexor, one additional biopsy will be taken at either Cycle 1 Day 22 OR Cycle 2 Day 1 for CCI. Portions of this biopsy will be formalin-fixed and frozen-unfixed as described in the *Laboratory Manual*. Biopsies are required if feasible. The feasibility of the biopsy procedure, in terms of patient safety and tumor accessibility, will be determined by the Investigator. This second biopsy (eg, either Cycle 1 Day 22 or Cycle 2 Day 1) should not be collected from adolescent/pediatric patients for exploratory studies if there appear to be a potential for serious risks for the patient. Patients in the selinexor arm who continue on selinexor but as open-label treatment are not required to have an additional tumor biopsy on Cycle 1 Day 22 or Cycle 2 Day 1 of open-label treatment.

[7] CT (or MRI if CT contraindicated) scans will be performed approximately 6 and 12 weeks after the first dose of open-label selinexor (ie, Day 1 of Cycles 2 and 3), then every 12 weeks (ie, Day 1 of odd-numbered Cycles ≥ 5) thereafter until PD to assess tumor size (one, two and three dimensions) and evaluate site of disease and distant sites (abdomen, pelvis, chest). For a given patient, the same imaging modality should be maintained throughout the study. Copies of scan data will be provided to the central reader for two-dimensional and three-dimensional measurements for determination of tumor responses (see *Imaging Manual* for details).

[8] Assessment of liposarcoma per RECIST v. 1.1 (Eisenhauer 2009; Appendix 2) by the central reader.

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[redacted]

[11] For patients in the placebo arm who cross over to open-label selinexor, the nutritional consultation should occur on C1 D1 before the first dose of open-label selinexor. The nutritional consultation is not required at C1 D1 of open-label selinexor treatment for patients in the selinexor arm who continue on selinexor but as open-label treatment. See Section 10.7.3.

[12] The QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) should be completed prior to study treatment administration if study treatment is administered on the same day that the questionnaires are completed. See Section 10.7.1.

[13] Selinexor dosing is on Day 1 and 3 of Weeks 1-6 of each 6-week (42 day) cycle. For doses on non-clinic days, the patient will be provided doses to take home.

[14] Information on any antineoplastic therapies used after discontinuation of study treatment will be collected at the EoT Visit (Section 9.2.4), Safety Follow-up Calls (Section 9.2.5), and during Survival Follow-up (Section 9.2.6).

[15] The Safety Follow-up Call must be performed for all patients (ie, with or without an EoT Visit). The purpose of this call is to assess patient status, follow-up on any AEs that were not resolved at the EoT Visit, and information on any antineoplastic therapies used since discontinuation of open-label selinexor study treatment.

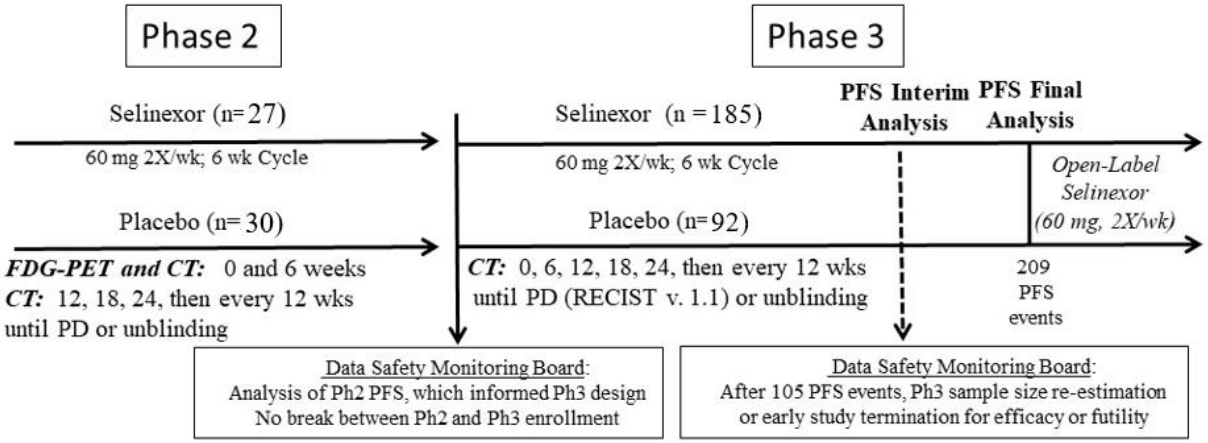
[16] After study discontinuation of open-label selinexor, a call will be made to the patient (or the patient's family) every 3 months until the EoS (Section 11.4) to inquire about the patient's liposarcoma status and to obtain available information (including treatment type, response, and time of response for assessment of CCI) on any antineoplastic therapies used since discontinuation of open-label selinexor. For patients who progress on post-study treatment antineoplastic therapy, the Investigator should enter the date of progression from the medical record in the eCRF if that information is available to the Investigator.

[17] Phone call to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

- Cycle 1: the telephone contact with the patient must take place on Day 3 (+ 1 day).
- Cycle 2: the telephone contact with the patient will be made on Day 10 (+ 1 day), Day 24 (+ 1 day) and Day 38 (+ 1 day), corresponding to Day 3 (+ 1 day) of every week in Cycle 2 in which a clinic visit does not occur.

[18] For female patients of childbearing potential only; pregnancy testing (serum hCG or high sensitivity urine) is required prior to dosing on Day 1 of Cycles ≥ 2 and at the EoT Visit (serum hCG). A positive urine pregnancy test will be confirmed by a serum pregnancy test. Test sensitivity for hCG must be ≥ 25 mIU/mL.

Figure 1: Study Flow Chart



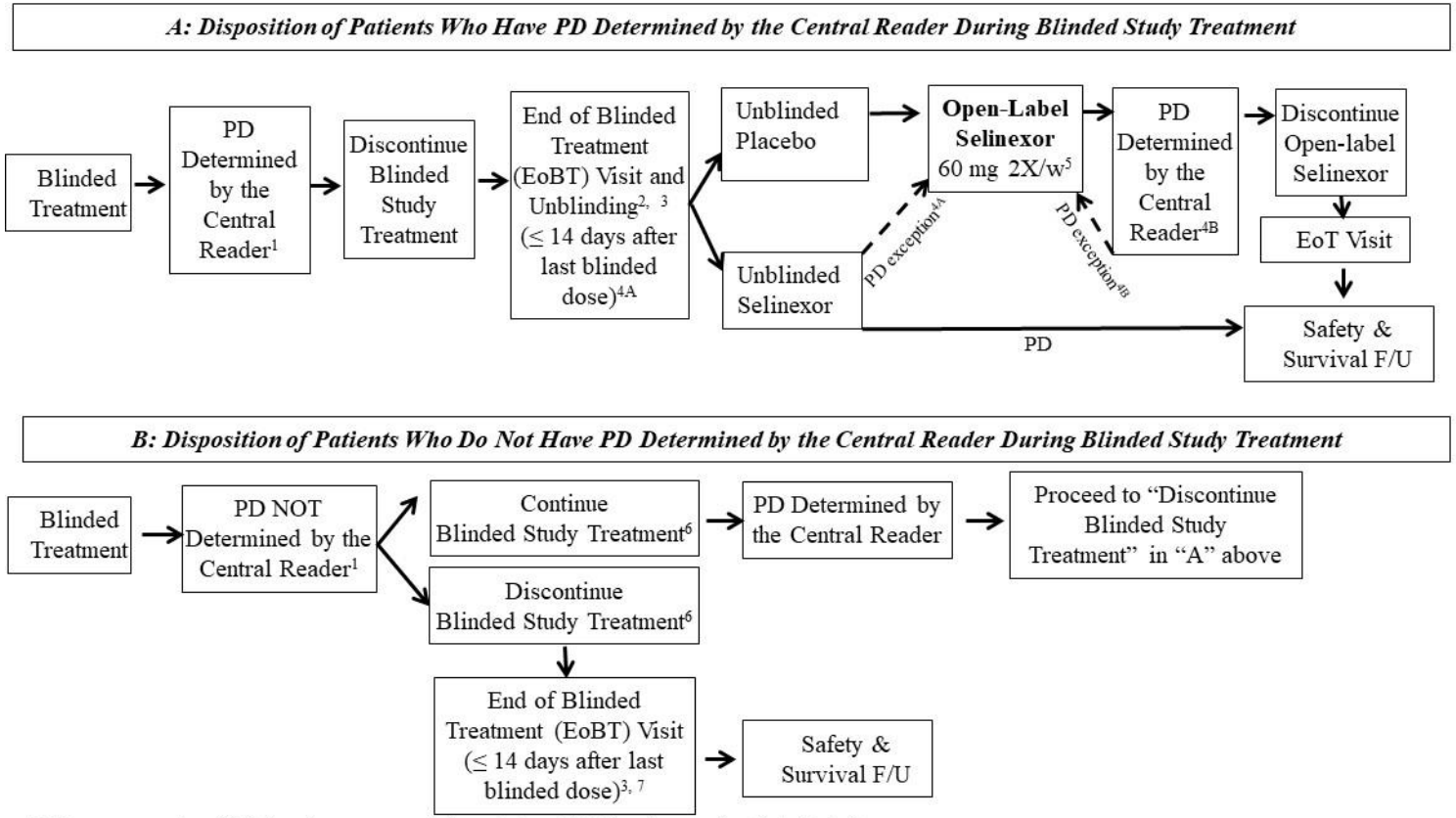
Phase 2

- 1:1 randomization/blinded (planned: n=50: 25 pbo, 25 selinexor/ actual: n=57).
  - Stratified by prior eribulin vs no prior eribulin and number of prior systemic therapies (1 vs ≥ 2)
- Primary efficacy endpoint: PFS by RECIST v. 1.1
- Key secondary efficacy endpoints
  - TTP
  - ORR/DOR
  - Tumor glucose metabolism, density and size
- Patients who have PD (per Who Response Criteria under protocol versions ≤ 3 or per RECIST v. 1.1 under protocol versions ≥ 4) determined by the central reader will be unblinded: 1) if in the placebo arm may cross over to open-label selinexor; 2) if in the selinexor arm and the patient may derive benefit from continued treatment, the patient may elect to continue selinexor but as open-label treatment

Phase 3

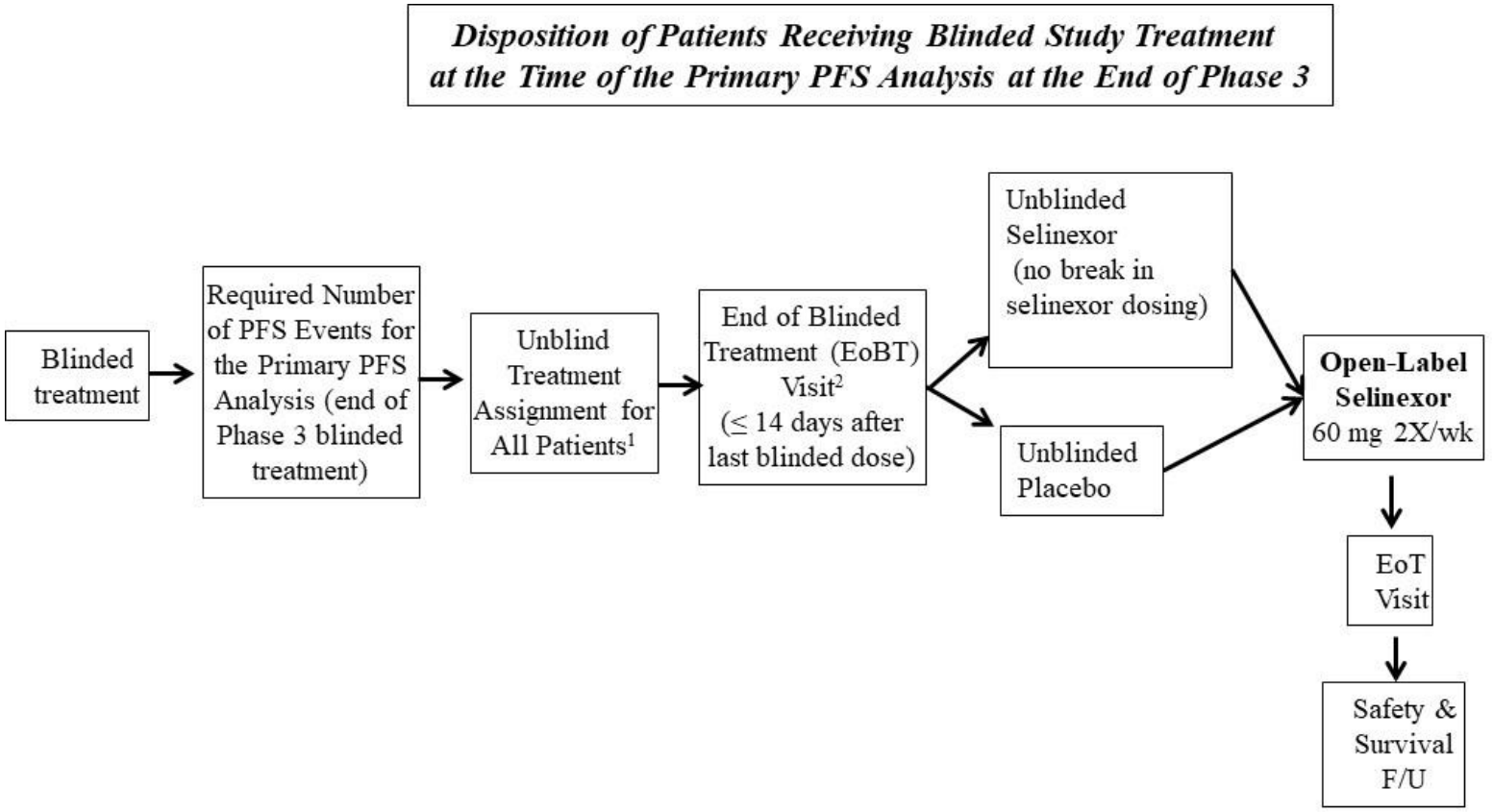
- 2:1 randomized/blinded (n=277: 92 pbo, 185 selinexor)
  - Stratified by prior eribulin vs no prior eribulin, prior trabectedin vs no prior trabectedin, and number of prior systemic therapies (2 vs ≥ 3)
- Interim analysis after 105 PFS events for possible sample size re-estimation
- Primary efficacy endpoint: PFS by RECIST v. 1.1
- Key secondary endpoints
  - OS for non-inferiority
  - OS for superiority
  - TTP
- Patients who have PD per RECIST v. 1.1 determined by the central reader will be unblinded; if in the placebo arm may cross over to open-label selinexor; 2) if in the selinexor arm and the patient may derive benefit from continued treatment, the patient may elect to continue selinexor but as open-label treatment
- Patients receiving blinded study treatment when all patients are unblinded at the primary PFS analysis at the end of Phase 3 may receive open-label selinexor until PD

Figure 2: Disposition of Patients Who Have PD Per RECIST v. 1.1 During Blinded Study Treatment and/or Who Discontinue Blinded Study Treatment



[1]Patients must remain on blinded study treatment until determination of PD from the central reader is obtained.
[2]Unblinding will take place within 14 days of the last blinded dose and may occur on or before the patient's EoBT Visit
[3]Prior to unblinding, patients and Investigators will be asked which study treatment (active [selinexor] or placebo) they believed the patient received.
[4]Exception: After their first PD on selinexor, the following patients may continue selinexor but as open-label treatment if the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment: A) patients randomized to the selinexor arm, and B) patients randomized to the placebo arm who cross over to open-label selinexor. Once these patients have a subsequent PD, they will discontinue open-label selinexor and be followed for survival.
[5]For patients in the selinexor arm who continue on selinexor, but as open-label treatment, there will be no break in the patient's twice-weekly dosing schedule.
[6]Patients who do not have PD determined by the central reader should continue on blinded study treatment. However, the Investigator may decide to discontinue these patients from blinded study treatment.
[7]Treatment assignment will not be unblinded until the primary PFS analysis at the end of Phase 3, except in the event of a severe SAE leading to discontinuation of study treatment that requires unblinding for clinical management and knowledge of the received study treatment is required for clinical management and treatment of the SAE.

Figure 3: Disposition of Patients Receiving Blinded Study Treatment at the Time of the Primary PFS Analysis at the End of Phase 3



[1]Unblinding will take place within 14 days of last blinded dose and may occur before or during the EoBT Visit. Prior to unblinding, patients and Investigators will be asked which study treatment (active [selinexor] or placebo) they believed the patient received.
[2]EoBT Visit (baseline for open-label selinexor treatment):

- Patients in the placebo arm: EoBT Visit ≤ 14 days after last blinded dose. EoBT Visit may be done on the day of patient's first open-label dose.
- Patients in the selinexor arm: EoBT Visit before next scheduled selinexor dose. EoBT Visit may be done on the day of patient's first open-label dose.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
AUC_{last}	area under the curve, first-last measurement
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Centigrade
CFR	Code of Federal Regulations
CHW	Cui, Hung, and Wang
cm	centimeter
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenzel
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CPGO	Clinical Practice Guidelines in Oncology
CCI	[redacted]
DDLS	dedifferentiated liposarcoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EoS	end of study
EQ-5D-5L	EuroQoL Group Health Questionnaire
F%	oral bioavailability

Abbreviation	Definition
°F	degrees Fahrenheit
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GMI	growth modulation index
GSH	glutathione
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
hr	hour
5-HT3	serotonin receptor subtype
IEC	independent ethics committee
IC_{50}	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Council for Harmonisation
HPLC/MS-MS	high performance liquid chromatography/ tandem mass spectrometry
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
kg	kilogram
LD	longest diameter
LDH	lactate dehydrogenase
LMS	leiomyosarcoma
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
MLS	myxoid/round cell liposarcoma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose

Abbreviation	Definition
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	overall response rate (CR + PR)
OS	overall survival
OS12	overall survival at least 12 months
PD	progressive disease
CCI	[redacted]
PET	positron emission tomography
PFS	progression-free survival
CCI	[redacted]
PK	pharmacokinetic
PP	per-protocol
PR	partial response
pRB	retinoblastoma protein
PT	prothrombin time
QLQ-C30	quality of life questionnaire-C30
QoL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAM	S-adenosylmethionine
SD	stable disease
SINE	selective inhibitor of nuclear export
SOC	system organ class (within AE context)
CCI	[redacted]
T-ALL	T-cell acute lymphocytic leukemia
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TLS	tumor lysis syndrome
t_{max}	time to peak plasma concentration
TRAE	treatment-related adverse event

Abbreviation	Definition
TSPs	tumor suppressor proteins
TTP	time to progression
ULN	upper limit of normal
WBC	white blood cell
WDLS	well-differentiated liposarcoma
wk	week
WHO	World Health Organization
XPO1	exportin 1

1. OVERVIEW

The nuclear export of most tumor suppressor proteins (TSPs) and other growth modulators inactivates their anti-cancer and regulatory functions. The vast majority of TSPs are exported from the nucleus *exclusively* by exportin 1 (XPO1, also called CRM1). Selinexor (KPT-330) is an orally bioavailable, selective inhibitor of nuclear export (SINE) that specifically blocks XPO1, leading to the nuclear accumulation and re-activation of TSPs and other growth modulators. The reactivation of multiple TSPs through inhibition of a non-redundant, single protein represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

Liposarcomas are among the most frequent type of soft tissue sarcoma, accounting for approximately 15-20% of all soft tissue sarcomas, and are most often located in the lower extremities or retroperitoneum. Liposarcomas are classified into three main biologic groups: well-differentiated liposarcoma (WDLS) and dedifferentiated liposarcoma (DDLS), myxoid/round-cell liposarcoma (MLS), and pleiomorphic liposarcoma. These subtypes range from WDLS, which tends to be slow-growing, to DDLS and MLS, which are more aggressive and have greater metastatic potential. While surgery is the primary therapy for localized liposarcomas, there remains a need for additional therapeutic options, to treat advanced, recurrent, or metastatic liposarcomas.

This Phase 2-3, randomized, double-blind, placebo-controlled study will consist of a Phase 2 portion to compare progression-free survival (PFS) obtained with selinexor versus placebo, to adjust PFS assumptions and sample size for Phase 3, followed by a Phase 3 portion to assess whether the oral, single-agent selinexor can improve PFS (versus placebo) rates in patients with liposarcoma.

2. LIPOSARCOMA

Soft tissue sarcomas are a group of heterogeneous malignancies with over 50 histological types with diverse biological behavior and often unique genetics. One of the most common subtypes is liposarcoma, which represents 24% of extremity sarcomas and 45% of retroperitoneal soft tissue sarcomas (Crago 2011). Liposarcomas are malignant mesenchymal tumors and are classified into three main biologic groups: (a) WDLS and DDLS, (b) MLS, and (c) pleiomorphic liposarcoma (Dickson 2013).

WDLS comprise 40%–45% of all liposarcomas and is classified as a low-grade neoplasm that is rarely metastatic and occurs most often in the retroperitoneum and limbs. WDLS malignancies have a tendency to recur locally (Conyers 2011). WDLS/DDLS are considered to be a biphasic disease: DDLS represents progression from low-grade to high-grade nonlipogenic morphology within a WDLS. In contrast to WDLS, DDLS is more aggressive with a metastatic rate of 10%–20% and overall mortality of 50%–75% (Conyers 2011).

Amplification of several oncogenes is associated with liposarcoma. MDM2 is the most frequent amplification in WDLS/DDLS (close to 100%) while CDK4 is amplified in over 90% of cases (Dei Tos 2000, Binh 2005, Nakayama 1995). MDM2 is involved in the destruction of the tumor suppressor protein p53 and CDK4 enhances progression through the G1 cell cycle checkpoint by inactivating the tumor suppressor protein retinoblastoma (pRB). Thus, co-amplification of MDM2 and CDK4 proteins may result in proliferation by blocking cell cycle arrest and apoptosis through combined effects upon the tumor suppressor p53 and the cell cycle (Conyers 2011). MLS is characterized by a translocation that results in the FUS-CHOP gene fusion that is present in over 95% of cases (Antonescu 2001, Crozat 1993). Receptor tyrosine kinases, particularly signaling through the PI3K/Akt pathway, appear to be involved in MLS oncogenesis (Conyers 2011).

Surgery is the primary treatment for localized liposarcoma, but approximately 40% of patients will eventually die from advanced disease (Gobble 2011). Advanced unresectable liposarcoma is relatively resistant to radiotherapy and chemotherapy, providing few options for these patients (Dickson 2013). Despite minimal responsiveness, most patients with liposarcoma currently receive anthracyclines and/or an alkylating agent. Olaratumab in combination with an anthracycline was granted accelerated approval in soft tissue sarcomas including liposarcoma based on an improvement in overall survival (OS) compared to doxorubicin alone.

Additional chemotherapeutic agents have recently shown PFS or OS benefits in randomized studies against the alkylating agent dacarbazine. In a recent Phase 3 study (Study SAR-3007) in patients with liposarcoma and leiomyosarcoma (LMS), trabectedin (Yondelis®) had a statistically significant reduction in the risk of progressive disease (PD), with a median PFS of 4.2 months versus 1.5 months with dacarbazine. There was no statistically significant difference in OS between the two arms. In a separate Phase 3 study, 452 patients with advanced soft tissue sarcoma were randomized to receive eribulin or dacarbazine. Treatment with eribulin (Halaven®) improved OS by 7.2 months compared with dacarbazine in patients with advanced LMS or liposarcoma.

Selinexor may represent a non-chemotherapy option for patients with liposarcoma. Because of the growth characteristics of liposarcoma, progression following selinexor or placebo in

the current study can be followed with the use of an anthracyline (eg, olaratumab plus doxorubicin), an alkylating agent, trabectedin, eribulin, or an experimental agent. Moreover, the study design (see Figure 1, Figure 2, and Figure 3) allows crossover from placebo to selinexor in order to provide patients with access to this experimental non-chemotherapeutic agent.

3. NUCLEAR EXPORT

3.1. Inactivation of Tumor Suppressor Proteins (TSPs) by Nuclear Export

Many important TSPs have been identified in cancer pathogenesis, including p53, p73, FOXO1 and 3a, IκB, BRCA1 and 2, APC, PP2A, and pRB (Turner 2012). TSPs mediate tumor suppression pathways via various functions including recognition of cellular (deoxyribonucleic acid [DNA]) damage, arrest of the cell cycle until repairs can be made, and induction of apoptosis in cells that have substantial DNA damage repair (Brown 2011).

The tumor-suppressing and anti-cancer activity of these proteins requires their presence in the nucleus. Conversely, export out of the nucleus can inactivate the abilities of TSPs to identify DNA damage and regulate cellular processes (Xu 2010). Cancer cells exploit normal nuclear export to inactivate TSPs and evade normal DNA-damage controls as well as anti-neoplastic therapy. The nuclear import (following synthesis on cytoplasmic ribosomes) and nuclear export of TSPs require specific shuttle proteins in order to traverse the nuclear envelope through the nuclear pore complexes (NPC) (Turner 2012). Although there are seven known nuclear export shuttle proteins (Exportins 1 – 7), exportin 1 (XPO1, also called CRM1) is the only known exportin protein for the vast majority of TSPs.

3.2. Inhibition of XPO1 in Human Cancer

Based on the postulated role of XPO1 in driving malignancy and chemotherapy resistance, XPO1 is promising as an oncologic therapeutic target (Turner 2012). XPO1 blockade causes the transient nuclear retention of TSPs and other growth modulators, re-establishing their tumor-suppressing and growth regulating effects on cancer cells and potentially reversing mechanisms leading to chemotherapy resistance, with clear implications for future combination therapies (Lain 1999, Kau 2003, Turner 2008). In normal cells, XPO1 inhibition transiently arrests the cell cycle without cytotoxicity followed by recovery after the inhibitor is removed (Lain 1999, van der Watt 2009, Gray 2007). In addition, the messenger ribonucleic acid (mRNA) cap-binding protein eIF4E requires XPO1 in order to exit the nucleus with its cargo mRNA proteins. The mRNAs coding for various short half-life oncoproteins such as c-MYC, MDM-2 and Cyclin D have m7-guanine caps and require eIF4E for nuclear export. XPO1 inhibition prevents the eIF4E-mediated mRNA nuclear export and, therefore, the translation of these proteins, leading to their down regulation providing additional anti-neoplastic activity.

Because restoration of TSP activity and reduction in oncogenic signals are relevant to essentially any cancer, XPO1 inhibition is expected to have activity against liposarcoma and many other malignancies (Table 3).

Table 3: Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway Affected	Effect of XPO1 Inhibition	Reference
p53 mutation	p73 activation, p21 activation	Ranganathan 2012
p53 and/or pRB destabilization	Nuclear p53 and pRB retention and stabilization	Knapp 2009, Kau 2003
MDM2 activation	MDM2 reduction, Nuclear p53 retention and activation	Kojima 2013 and unpublished data
Decreased pRB signaling	Decreased pRB phosphorylation and increased nuclear pRB, p14/p16 elevation	Fragomeni 2013
XPO1 overexpression	XPO1 reduction	Walker 2013
Bcr-Abl activation	PP2A activation	Walker 2013
c-Myc amplification	MYC protein reduction	Schmidt 2013
CDKN2A reduction	p53/p73 stabilization	Azmi 2013
KIT activation	KIT reduction	Ranganathan 2012
Bcl family overexpression	Bcl family reduction	Lapalombella 2012
NF-κB activation	IκB nuclear retention and activation	Lapalombella 2012
PIK3 or AKT activation	FOXO1, -3, -4 activation	Lapalombella 2012
Survivin-cytoplasmic	Survivin nuclear retention	Altura 2003, Cheng 2014

4. SELINEXOR (KPT-330)

4.1. Introduction

Several attempts to use XPO1 inhibitors as anti-cancer agents, based on the natural product leptomycin B, have failed due to secondary off-target effects of the drugs, which caused significant weight loss, diarrhea, and marked fatigue and asthenia in both animal studies and initial clinical studies (Mutka 2009, Newlands 1996, Roberts 1986). Modification of the structure of leptomycin B led to the development of parenterally administered compounds with improved pharmacokinetic (PK) properties and substantially improved therapeutic windows in preclinical studies (Mutka 2009), but clinical studies were never initiated.

Selinexor is an oral, first in class, slowly reversible, potent SINE compound that specifically blocks XPO1. Selinexor restores many of the TSPs to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, ie, for tumor cells, both *in vitro* and *in vivo*. All cell types exposed to SINE compounds *in vitro* undergo G1 ± G2 cell cycle arrest, followed by a 'genomic fidelity' review. Cells with damaged genomes are induced to undergo apoptosis. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor-suppressing pathways that lead to selective elimination of genomically damaged (ie, neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared. Further details about the mechanism of action of selinexor are provided in the selinexor Investigator's Brochure (IB).

4.2. Preclinical Data

4.2.1. Pharmacology

Selinexor has shown potent pro-apoptotic activity with a median inhibitory concentration, 50% (half maximal inhibitory concentration) (IC_{50}) of 90 nM across a panel of 46 tumor cell lines representing a broad spectrum of tumor types. As noted above, selinexor had little effect on normal lymphocytes or other non-transformed cells, which correlated with the low incidence in animals of the typical adverse drug reactions seen with most anti-cancer therapies, such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction. Selinexor and related SINE compounds have shown substantial efficacy, with dosing regimens that match those currently under investigation in humans, in a variety of mouse models of hematological and solid tumors. These include DLBCL, chronic lymphocytic leukemia, Mantle Cell Lymphoma, acute myeloid leukemia (AML), multiple myeloma, T-cell acute lymphocytic leukemia (T-ALL), neuroblastoma, melanoma and prostate, breast, lung and ovarian cancers.

Selinexor has shown potent *in vitro* and in vivo anti-sarcoma activity. Selinexor induced cell death through apoptosis in sarcoma cell lines, with nanomolar inhibitory concentrations in 11 of 12 lines. This cytotoxicity was associated with induction of p53 and p21 and reduction

in pRB expression. Furthermore, antitumor activity of selinexor was observed in two xenograft models of human liposarcoma (Nair 2013). Selinexor also completely suppressed tumor growth in human alveolar soft part sarcoma xenografts and this efficacy was associated with increased nuclear retention of p53 and p21 and reduced expression of survivin (Crochiere 2014).

Results of a more recent study that investigated selinexor *in vitro* and *in vivo* using 17 cell lines and 9 sarcoma xenograft models confirm that selinexor has potent *in vitro* and *in vivo* activity against a wide variety of sarcoma models (Nakayama 2016). Furthermore, in liposarcoma cell lines with MDM2 and CDK4 amplification, selinexor induced G1-arrest and apoptosis irrespective of p53 expression or mutation and irrespective of pRB expression. Selinexor increased p53 and p21 expression at the protein but not ribonucleic acid (RNA) level, indicating a post-transcriptional effect.

4.2.2. Pharmacokinetics and Toxicology

The preclinical properties of selinexor were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). While PK studies were limited to male animals for all three species, toxicokinetic (TK) evaluations were conducted in both sexes for rats and monkeys as part of the selinexor toxicology studies, and no consistent sex-related differences were observed in either species. No accumulation was observed in any of the multi-dose toxicology studies with an every-other-day dosing regimen for selinexor. Overall, systemic exposure was generally dose-proportional in all TK studies that involved multiple dose levels. Higher maximum plasma concentration (C_{max}) and earlier time to peak plasma concentration (t_{max}) values were observed in monkeys that were fasted versus fed prior to dosing. Systemic exposure (area under the curve from first to last plasma measurement, AUC_{last}) to selinexor achieved with gelatin capsules was comparable to that achieved with oral suspension dosing, with lower C_{max} and later t_{max} values observed with capsules. Results were not affected by the feeding status in monkeys. Oral bioavailability (F%) of selinexor was remarkably consistent among the three species with average values of 66.5%, 61.2%, and 67.5% in mice, rats, and monkeys, respectively.

Nonclinical toxicology studies indicated that the major adverse drug reactions (dose limiting toxicities, DLTs) across all species are reduced appetite with anorexia-induced weight loss partially consistent with satiety induction. High calorie foods and glucocorticoids can mitigate weight loss in animals taking SINE XPO1 inhibitors.

See the selinexor IB for more information.

4.3. Clinical Experience

Phase 1 and Phase 2 studies are being conducted in advanced solid tumors and hematological malignancies (see the selinexor IB for a summary of clinical experience). To date, more than 2500 patients have received selinexor. Selinexor was generally well tolerated with supportive care given to prevent anorexia and fatigue. The aggressive use of appetite stimulants has reduced the severity of the anorexia and fatigue and improved the long-term tolerability of selinexor treatment. A maximum tolerated dose (MTD) of selinexor has been determined to be 65 mg/m^2 twice weekly (Days 1 and 3) in Phase 1 solid tumor patients. The recommended

Phase 2 dose of selinexor for use in this study is 60 mg (~35 mg/m^2) twice weekly which is below the MTD observed in Phase 1 solid tumor patients.

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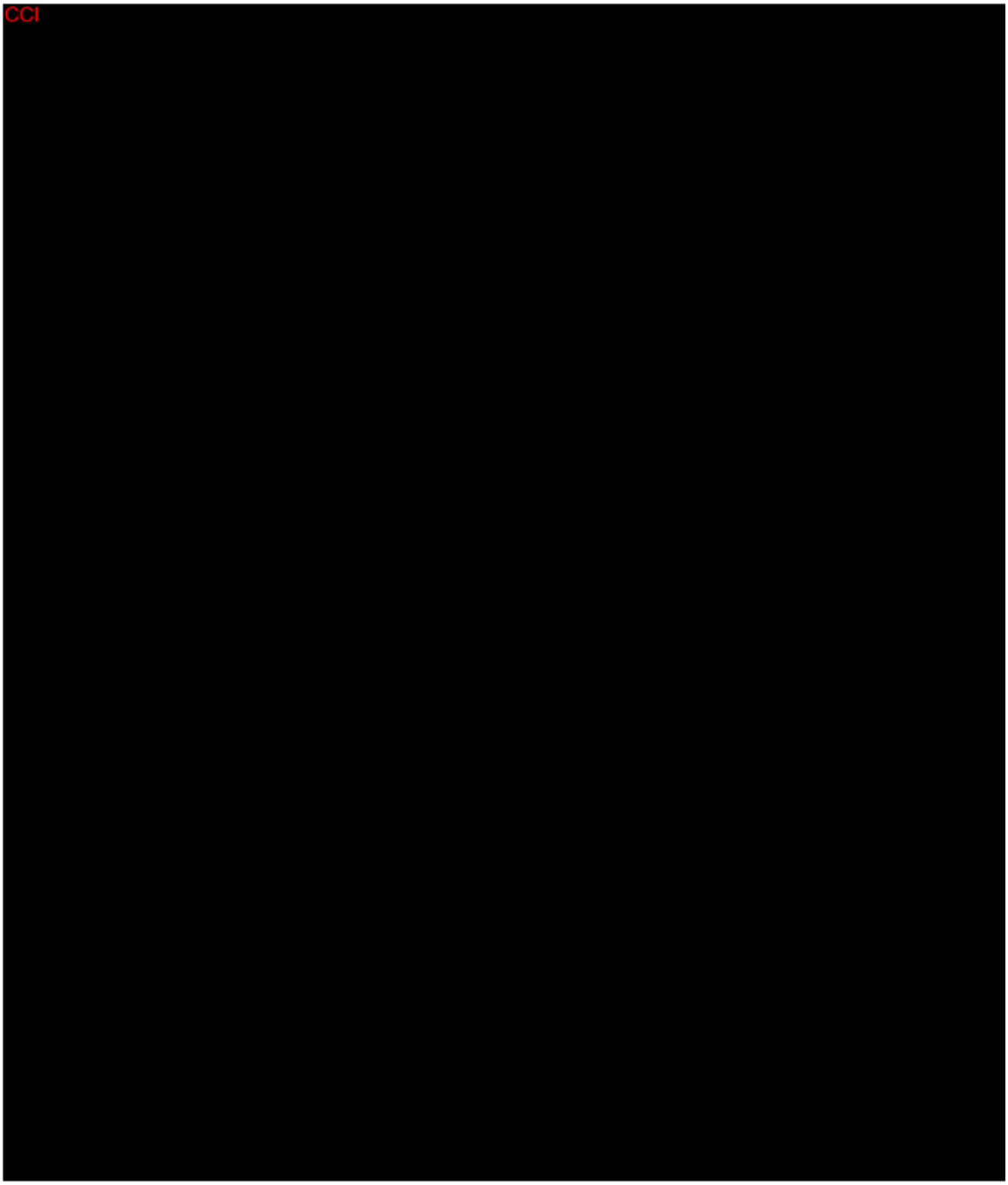

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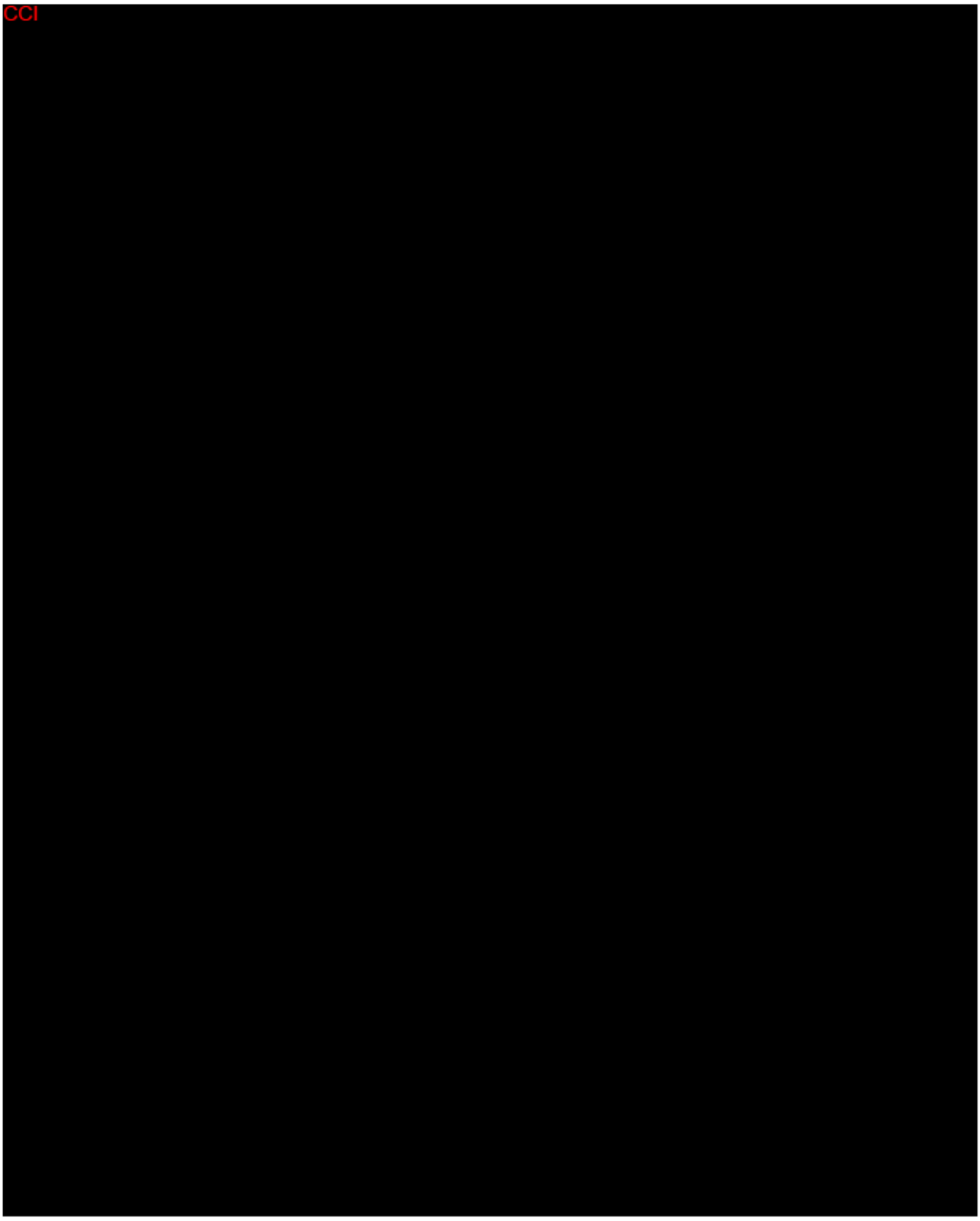

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5. RATIONALE FOR THE STUDY

Nonclinical data indicate that selinexor shows cytotoxic effects at nanomolar concentrations on a variety of sarcoma cell lines, whereas non-cancer cells show cytotoxic effects at much higher concentrations of selinexor. In murine xenograft models, three times a week oral treatment with selinexor inhibits the tumor growth of a variety of sarcomas including liposarcoma.

Selinexor treatment resulted in SD in 30 of 52 (58%) evaluable patients with liposarcoma in the sarcoma Phase 1 study KCP-330-003 (Section 4.3.1). The most commonly reported TRAEs were nausea, fatigue, thrombocytopenia, anorexia, and hyponatremia, which were primarily Grade 1 or 2 (Section 4.3.4.1). Nausea and anorexia were well controlled with antinausea medications and appetite stimulants. These data further support the development of selinexor for the treatment of liposarcoma.

5.1. Rationale for the Doses and the Dosing Regimen

To date, more than 2500 patients with advanced cancers have received selinexor orally in clinical studies of selinexor (Phase 1, 2, and 3), and of these, 1672 adult patients in Karyopharm-sponsored studies were evaluated for safety as of 31 March 2018.

Doses of 65 mg/m^2 twice weekly have cleared DLT assessment and this is the MTD in the Phase 1 dose escalation study in advanced solid tumors, KCP-330-002. It should also be noted that while a dose of 70 mg/m^2 cleared DLT in the AML arm of the Phase 1 study in patients with heavily pretreated hematological malignancies (KCP-330-001), escalating the dose beyond 70 mg/m^2 twice weekly is prohibited in any study.

In the present study, selinexor at a fixed oral dose of 60 mg (equivalent to ~35 mg/m^2) or matching placebo will be given twice weekly (eg, Day 1 Monday and Day 3 Wednesday or Day 1 Tuesday and Day 3 Thursday or Day 1 Wednesday and Day 3 Friday) during Weeks 1-6 of each 6-week (42-day) cycle for a total of 12 doses per cycle.

5.2. Rationale for Change in Response Criteria from WHO Response Criteria to RECIST v. 1.1 for the Primary Endpoint

The Phase 2 primary PFS endpoint was evaluated using the WHO Response Criteria (as specified in protocol Versions ≤ 4). The WHO Response Criteria were used based on input from the Sponsor's Liposarcoma Advisory Board. As RECIST Criteria have been traditionally used in sarcoma studies, including studies in liposarcoma, a prespecified analysis of PFS based on RECIST v. 1.1 was also conducted per protocol.

The preplanned analysis of PFS based on the WHO Response Criteria was conducted and the results of this blinded analysis (blinded to Sponsor and sites) were provided to the Data Safety Monitoring Board (DSMB).

In addition, a preliminary comparison of the PFS results by both WHO and RECIST v. 1.1 Criteria (48 PD events by WHO and 28 PD events by RECIST v. 1.1) for all eligible patients whose treatment assignments were unblinded in the Phase 2 portion of the study was carried out to inform the selection of the most clinically relevant response criteria for the Phase 3 portion of the study. Preliminary Phase 2 results, updated as of 11 August 2017, are

presented in Section 4.3.2. This analysis revealed that the WHO Response Criteria, which use a bi-dimensional evaluation of each lesion, resulted in the premature determination of clinically asymptomatic progression "events," typically involving small lesions, while overall tumor burden was stable (as previously reported by other Investigators [Therasse 2000]). Based on these results, the DSMB recommended that the analysis of the primary endpoint should use RECIST v. 1.1 Criteria, rather than WHO Response Criteria. The lead Investigators for the study, as well as the Sponsor, agreed with this recommendation.

Furthermore, the preliminary Phase 2 results using RECIST v. 1.1 Criteria were similar to those obtained in the Phase 1 study of selinexor in patients with sarcoma including liposarcoma (Gounder 2016). Based on these results and consistent with other studies in soft tissue sarcoma, RECIST v. 1.1 has been selected as the response criteria for the Phase 3 primary PFS endpoint.

5.3. Rationale for Change in the Primary Response Population

Due to the change in the primary response criteria at the end of Phase 2, the primary response population will now consist only of Phase 3 patients who were assessed for PD throughout the study using RECIST v. 1.1 Criteria. A formal analysis of all 56 eligible Phase 2 patients will be performed separately.

6. STUDY OBJECTIVES

6.1. Phase 2

6.1.1. Phase 2 Primary Objective

Assess and compare PFS of patients with advanced unresectable DDLS treated with selinexor (60 mg) or placebo twice weekly. PFS is defined as the time from date of randomization until the first date of PD, per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 (Eisenhauer 2009), or by death due to any cause.

6.1.2. Phase 2 Secondary Objectives

- Compare time to progression (TTP) on study treatment, per RECIST v. 1.1, with TTP on the patient's last prior systemic therapy.
- Determine the overall response rate (ORR: CR + PR), supported by duration of response (DOR). Responses will be defined by RECIST v. 1.1.
- Assess changes at 6 weeks in tumor glucose metabolism, density, and size using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) (diagnostic).
- Assess safety of each treatment arm.

6.1.3. Phase 2 Exploratory Objectives

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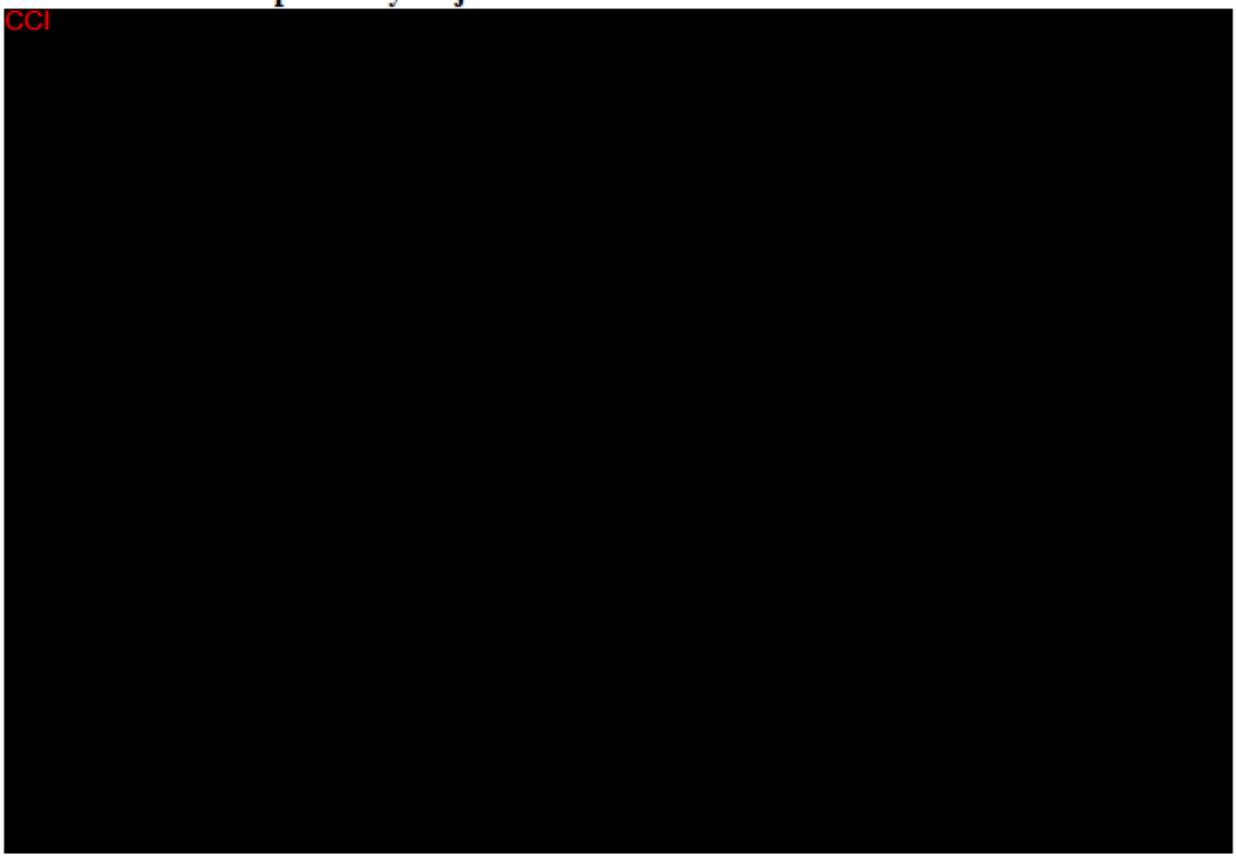

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6.2. Phase 3

6.2.1. Phase 3 Primary Objective

Assess and compare PFS of patients with advanced unresectable DDLS treated with selinexor (60 mg) or placebo twice weekly. PFS is defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause. Evaluation of the radiographic data for the PFS primary endpoint will be based on data from a scan review by the independent central reader (see additional details in Section 10.5.1).

6.2.2. Phase 3 Secondary Objectives

- Assess OS, measured from date of randomization until death due to any cause.
- Compare TTP on study treatment, per RECIST v. 1.1, with TTP on the patient's last prior systemic therapy.
- Assess Quality of Life (QoL) and patient-reported outcomes as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and the EuroQoL Group Health Questionnaire (EQ-5D-5L).
- Determine the ORR, supported by DOR. Responses will be defined by RECIST v. 1.1.

- Assess PFS according to the Investigator based on clinical and/or radiologic criteria.
- Assess safety of each treatment arm.

6.2.3. Phase 3 Exploratory Objectives

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7. STUDY DESIGN

7.1. Study Design Overview

This is a Phase 2-3, multicenter, randomized, double-blind, placebo-controlled study of patients diagnosed with advanced, unresectable liposarcoma. Approximately 334 total patients will be randomized to study treatment (selinexor or placebo) as described below.

Patients must provide written informed consent AND meet all the inclusion criteria and have none of the exclusion criteria, before any screening tests not routinely performed may be conducted. The study flow chart is shown in Figure 1 and the disposition of patients is shown in Figure 2 and Figure 3.

Phase 2:

- Fifty-seven patients were randomized to selinexor (60 mg) or placebo in a 1:1 allocation.
- Randomization was stratified based on the following stratification factors for patients enrolled under protocol Versions ≤ 4: number of prior systemic therapies (1 versus ≥ 2) and prior eribulin use (prior eribulin versus no prior eribulin).

The preplanned analysis of PFS was performed and served as a guideline to inform the final design of the Phase 3 portion of the study. See Section 4.3.2 for the preliminary efficacy results for Phase 2.

Phase 3:

- Approximately 277 patients will be randomized to selinexor (60 mg) or placebo in a 2:1 allocation (~185 selinexor, ~ 92 placebo).
- Randomization will be stratified based on (a) prior eribulin use (prior eribulin versus no prior eribulin), (b) prior trabectedin (Yondelis®) use (prior trabectedin versus no prior trabectedin), and (c) the number of prior systemic therapies excluding eribulin and trabectedin (2 versus ≥ 3).

An interim analysis was conducted at 108 PFS events (see Section 14.1.1.2.1).

The Schedule of Assessments for Blinded Phase 2/Phase 3 Treatment and Open-label Selinexor are provided in Table 1 and Table 2, respectively.

Study treatment (selinexor or matching placebo) will be given twice weekly on Day 1 and Day 3 during Weeks 1-6 of each six-week (42-day) cycle, without interruption between cycles.

All radiographic responses will be determined by the central reader (see the *Imaging Manual* for more details).

PD per RECIST v. 1.1. will be determined by the central reader. Details for continuation of study treatment following PD and the primary PFS analysis and follow-up after discontinuation of study treatment are provided in Section 7.2.

Treatment will continue until one or more of the following occurs:

- PD, as defined by RECIST v. 1.1 (see exception for patients who may derive benefit from continued treatment with selinexor in Section 7.2.4)
- Clinical progression, as determined by the Investigator in consultation with the Sponsor (must be documented by radiographic imaging and assessed by the central reader)
- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Study treatment is discontinued at the discretion of the Investigator (see Section 11.2)
- Patient withdraws consent

Patients will be followed for survival (Section 9.1.8 and Section 9.2.6) until the end of the study, withdrawal criteria are met, or death.

Patients will also receive best supportive care to manage the main adverse drug reactions of selinexor, which are nausea, anorexia, and fatigue.

In order to minimize nausea, unless contraindicated, all patients must receive serotonin receptor subtype (5-HT3) antagonists (ie, ondansetron 8 mg or equivalent) starting on Day 1, before the first dose of blinded study treatment and continued, as needed, 2-3 times daily. In those patients in whom a 5-HT3 antagonist is contraindicated, olanzapine (5.0 mg at bedtime or 2.5 mg twice daily) is recommended based on Investigator experience during Phase 1 selinexor studies. Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) (NCCN CPGO) for antiemesis and anorexia/cachexia (palliative care).

Approximately 34 months will be required to complete the primary Phase 3 PFS analysis. The Phase 3 accrual period began immediately after enrollment of the Phase 2 portion was completed and will be approximately 30 months. The primary endpoint analysis will be performed approximately 4 months after enrollment of the last patient, once 209 PFS events have occurred, at which time all Phase 3 patients will be evaluable for assessment of the primary endpoint.

The Investigator may remove a patient from study treatment as described in Section 11. The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who discontinue study treatment are not eligible to re-initiate treatment at a later date.

Patients may decide to discontinue study treatment for any reason. Patients who decide to discontinue study treatment should be encouraged to continue in the study so that follow-up information on PD and survival status may be obtained. Patients who discontinue study treatment but continue follow-up will be followed for anti-neoplastic therapy initiation and CCI every 3 months. These patients will be included in the ITT analysis if they are in Phase 3. However, patients may withdraw consent and decline further participation in the study at any time.

7.2. Study Treatment Following PD and the Primary PFS Analysis and Follow-up After Discontinuation of Study Treatment

Patients should remain on blinded study treatment until the assessment of PD by the central reader.

Prior to unblinding, the patient and the Investigator will be asked which study treatment (active [selinexor] or placebo) they believe the patient received during blinded study treatment. See Section 10.7.2.

7.2.1. Study Treatment After Determination of PD by the Central Reader

Treatment assignment for patients who have PD per RECIST v. 1.1 (Eisenhauer 2009) determined by the central reader while receiving blinded study treatment will be unblinded. Note: WHO Response Criteria were used for Phase 2 patients whose treatment assignments were available at the time of the preplanned Phase 2 analysis.

Patients who have PD may proceed as follows:

- Patients in the placebo arm may cross over to open-label selinexor (60 mg twice weekly).
    - After their first PD on open-label selinexor, patients will discontinue study treatment and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor (see Section 7.2.4).
- Patients in the selinexor arm who have PD will discontinue blinded study treatment and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor (see Section 7.2.4).

7.2.2. Follow-up for Patients Without PD Who Discontinue Study Treatment

Treatment assignment for patients who do NOT have PD determined by the central reader will not be unblinded until the primary PFS analysis at the end of Phase 3.

Patients who do NOT have PD determined by the central reader and/or who discontinue blinded study treatment may proceed as follows:

- Patients should remain on blinded study treatment until the assessment of PD from the central reader is obtained.
- Patients who discontinue blinded study treatment at the discretion of the Investigator for reasons other than PD will be followed for survival. These patients are not allowed to receive open-label selinexor (see Section 11.3.1 for unblinding exceptions).

7.2.3. Study Treatment Following the Primary PFS Analysis

Treatment assignments for all patients will be unblinded when the required number of PFS events for the primary PFS analysis at the end of Phase 3 have been obtained.

Patients who are on blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 may proceed as follows:

- Patients in the placebo arm may cross over to open-label selinexor.
- Patients in the selinexor arm will continue selinexor but as open-label treatment.

All patients who have PD while receiving open-label selinexor will discontinue selinexor and be followed for survival, unless the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor (see Section 7.2.4).

7.2.4. Exception for Patients Who May Derive Benefit from Continued Treatment with Selinexor

After their first PD (determined by the central reader) on selinexor (either blinded or open-label) the following patients may elect to continue selinexor as open-label treatment if the Investigator, in consultation with the Sponsor, believes based on clinical judgement that the patient may derive benefit from continued treatment with selinexor:

- Patients randomized to the selinexor arm
- Patients randomized to the placebo arm who crossed over to open-label selinexor
- Patients randomized to the selinexor arm who continued selinexor as open-label treatment at the time of the primary PFS analysis

Once these patients have a subsequent PD, they will discontinue open-label selinexor and be followed for survival.

7.3. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be set up to review the safety of selinexor and to review any SAEs that occur during the study. The DSMB will develop and follow a data and safety monitoring plan and charter.

The DSMB will be composed of at least two oncologists (at least one of whom specializes in sarcoma) and a statistician. The DSMB will be provided with all reports of AEs including SAEs regardless of Investigator causality assessments.

DSMB meetings will occur on a periodic basis in accordance with the DSMB charter.

An independent unblinded statistician conducted the preplanned Phase 2 analysis, based upon calculated PFS by WHO Response Criteria and provided the results of this blinded analysis (blinded to Sponsor and sites) to the DSMB for review. In addition, a preliminary comparison of the PFS results by both WHO and RECIST v. 1.1 Criteria (48 PD events by WHO and 28 PD events by RECIST v. 1.1) for all eligible patients whose treatment assignments were unblinded in the Phase 2 portion of the study was carried out to inform the selection of the most clinically relevant response criteria for the Phase 3 portion of the study. Preliminary Phase 2 results, updated as of 11 August 2017, are presented in Section 4.3.2. Based on these results, the DSMB recommended that the analysis of the primary endpoint should use RECIST v. 1.1 Criteria, rather than WHO Response Criteria.

An independent statistician will produce unblinded Phase 3 results for the DSMB, conduct the interim analysis that is planned after 105 PFS events are observed, and provide the results of this blinded analysis to the DSMB for review. The Phase 3 interim analysis will be based upon PFS calculated by RECIST v. 1.1. Criteria and analyzed for treatment futility (non-binding) or sample size adjustment. The Sponsor (except for key team members as specified to monitor the conduct of the study] and the sites (eg, Investigators, staff, and patients) will remain blinded to the Phase 3 interim analysis results.

The chairperson of the DSMB will be provided with SAE reports, per the DSMB charter.

The charter of the DSMB will specify that this committee is charged with providing periodic reports to Karyopharm that contain recommendations that include, but are not limited to, (a) continuation of the study (or proposed changes to the study), and (b) termination of the study. The charter will also describe a procedure for adjusting sample size, if needed.

7.4. Stopping Rules

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 11: Discontinuation Criteria.

Adverse Event Stopping Rules:
The stopping rules in the previous version of the protocol have been revised based on the current selinexor safety profile and the decisions of the DSMB to continue the study without modifications. Stopping rules may be adjusted in the event of either the study re-opening to accrual or at any time during the conduct of the study and based on new information regarding the AE profile of selinexor. Accrual may be suspended due to unexpected AE findings that have not crossed a specified rule below.

Accrual will be temporarily suspended if, at any time, an excessive death rate, attributed to study treatment, as determined by the DSMB is observed.

7.5. Criteria for Evaluation

Disease assessments at the date of surgical or radiotherapy intervention may be censored in patients receiving such care, since these patients are receiving non-protocol specified therapy (ie, intervention), which may impact endpoint(s).

7.5.1. Primary Efficacy Endpoint

- Progression-free survival (PFS), defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause. Evaluation of the radiologic data for the primary PFS endpoint will be based on data from a scan review by the independent central reader.

7.5.2. Secondary Endpoints

7.5.2.1. Key Secondary Endpoints

- OS for non-inferiority, defined as the time from randomization until death due to any cause, for all randomized patients.
- OS for superiority, defined as the time from randomization until death due to any cause, for all randomized patients.

7.5.2.2. Secondary Efficacy Endpoints

- TTP, defined as the time from randomization to date of PD or death due to disease progression, whichever is earlier, per RECIST v. 1.1. Patients who remain progression free (whether they withdrew from the study or reached their maximum follow-up) will be censored at the date of their last disease assessment.
- ORR, defined as the proportion of patients who achieve complete response (CR) or partial response (PR), per RECIST v. 1.1.
- DOR, defined as the time from first occurrence of CR or PR until the first date of PD per RECIST v. 1.1 or death.
- Tumor glucose metabolism, density, and size using FDG-PET (Phase 2 only) and CT (diagnostic) after 6 weeks of treatment.
- PFS according to the Investigator, defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause as defined by the Investigator based on clinical and/or radiologic criteria.
- Time to next treatment (TTNT), defined as the duration of time from randomization to the date of the next anti-cancer therapy.

7.5.3. QoL Endpoint (Secondary Endpoint)

- QoL as measured by the EORTC QLQ-C30 total score and EuroQoL EQ 5D 5L category scores and total score.

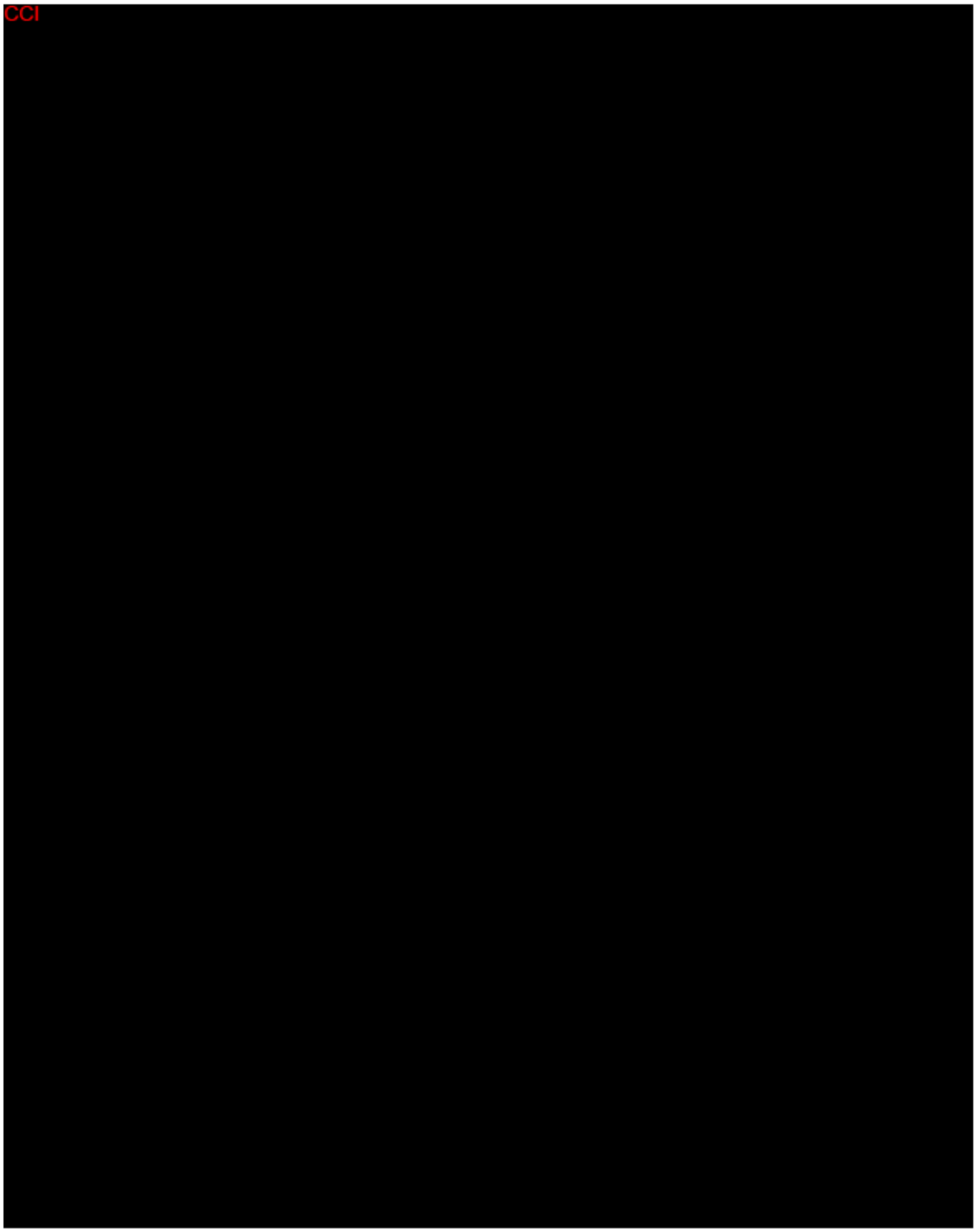
7.5.4. Safety Endpoints

Safety and tolerability will be evaluated by AE reports, physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, and laboratory evaluations. The CTCAE, v. 4.03, will be used for grading of AEs. Investigators will provide assessment of causality for all AEs as either related or not related to study treatment. An independent DSMB will review study safety, including any SAEs that occur (see Section 7.3).

7.5.5. Exploratory Endpoints

CCI

CCI



7.6. Screening and Registration

The Screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of randomization.

Key patient eligibility (inclusion/exclusion criteria) must be confirmed by the Sponsor for all patients participating in the study prior to randomization.

A Patient Enrollment Form will be sent from the site to the Karyopharm for evaluation. Upon confirmation of eligibility, Karyopharm will return the signed form to the site.

7.6.1. Study Patient Number

Each patient in this study will be assigned a unique patient number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason.

7.6.2. Rescreening

Rescreening is permitted in this study. If a patient fails any of the inclusion or exclusion criteria, a patient may be rescreened after a suitable period of time (the exact length is dependent upon the reason for the screen failure) per the documented agreement of Karyopharm and the Investigator. Any patient who is rescreened must be reconsented and will retain the same patient number. A patient may only fail screening once.

7.6.3. Screen Failures

Patients who sign an informed consent but are not randomized for any reason will be considered a screen failure. The reason for not being randomized will be entered on the eCRF. The demographic information (including screening number, informed consent date, and Inclusion/Exclusion pages) must also be completed for screen failure patients. No other data will be collected for patients who are screen failures, unless the patient experiences a SAE during the screening phase (see Section 13.2.2 for SAE reporting details).

These data will also be retained in the Investigator's study files and can be printed by the site in log format at the end of the study. The primary analysis for this study will be an intent-to-treat (ITT) analysis, therefore, screen failure data will not be analyzed.

7.6.4. Replacement of Patients

Patients who fail screening may be replaced.

Patients who withdraw from the study after randomization will not be replaced.

7.7. Randomization to Blinded Study Treatment

In Phase 2, patients were randomized to either selinexor (60 mg) or placebo in a 1:1 ratio. Randomization was stratified based on the following stratification factors for patients enrolled under protocol Versions ≤ 4: the number of prior systemic therapies (1 versus ≥ 2) and prior eribulin use (prior eribulin versus no prior eribulin).

In Phase 3, patients will be randomized to selinexor or placebo in a 2:1 ratio. Randomization will be stratified based on (a) prior eribulin use (prior eribulin versus no prior eribulin), (b) prior trabectedin (Yondelis®) use (prior trabectedin versus no prior trabectedin), and (c) the number of prior systemic therapies excluding eribulin and trabectedin (2 versus ≥ 3).

Specifically, randomization will be performed within each of the following 8 strata:

1. ≤ 2 prior systemic therapies without prior eribulin use or prior trabectedin use

2. ≤ 2 prior systemic therapies without prior eribulin use but with prior trabectedin use
3. ≤ 2 prior systemic therapies with prior eribulin use but without prior trabectedin use
4. ≤ 2 prior systemic therapies with both prior eribulin use and prior trabectedin use
5. ≥ 3 prior systemic therapies without prior eribulin use or prior trabectedin use
6. ≥ 3 prior systemic therapies without prior eribulin use but with prior trabectedin use
7. ≥ 3 prior systemic therapies with prior eribulin use but without prior trabectedin use
8. ≥ 3 prior systemic therapies with both prior eribulin use and prior trabectedin use

Randomization will be performed by a centralized system after confirmation of patient eligibility by the Sponsor (see Section 7.7).

Study treatment will be administered in a double-blinded manner until the analysis of the primary PFS endpoint at the end of Phase 3, with the following exceptions: 1) patients in the placebo arm who have PD while they are receiving blinded study treatment may cross over to open-label selinexor, or 2) patients in the selinexor arm who have PD but may derive benefit from continued treatment with selinexor may elect to continue selinexor, but as open-label treatment (see Section 7.2.4).

7.8. Blinding Procedures

All study staff will be blinded to the patient treatment assignments and study treatment will be administered in a blinded manner during blinded study treatment. To maintain the study blind, it is imperative that patient treatment assignments are not shared with the patients, their families, or any member of the study team, either at the study site or at Karyopharm until unblinding is permitted (See Section 11.3).

8. SELECTION OF PATIENTS

8.1. Number of Patients

Approximately 334 patients with advanced unresectable liposarcoma meeting all the eligibility criteria described below will be randomized to selinexor or placebo. In Phase 2, 57 patients were randomized to selinexor (60 mg) or placebo in a 1:1 allocation. In Phase 3, approximately 277 patients will be randomized to selinexor (60 mg) or placebo in a 2:1 allocation.

8.2. Recruitment

This multicenter study will be conducted at sites in North America and Europe; patients in Israel and/or Asia may also be included.

8.3. Inclusion Criteria

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Written informed consent in accordance with national, local, and institutional guidelines obtained prior to any screening procedures
2. Must be willing and able to comply with the protocol
3. Patients ≥ 12 years of age (patients <18 years of age are permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority).
4. Patients with a body surface area (BSA) ≥ 1.2 m^2 as calculated per Dubois 1916 or Mosteller 1987.
5. Documented histologic evidence of DDLS at any time from initial diagnosis to randomization AND current evidence of DDLS requiring treatment (documented evidence of disease progression from the most recent treatment):
   - Documentation of histologic evidence of DDLS requires the following:
     - This information will be provided based on prior diagnostic testing and is required for randomization.
     - Tissue (fresh or archival) will be provided for confirmatory histology at a central laboratory but confirmatory results are not required prior to randomization.
     - If archival tissue > 12 months old, the quality of the sample for confirmatory histology must be confirmed by the site histopathologist prior to randomization.
6. Must have measurable disease according to:
   - The bidimensional WHO Response Criteria (Miller 1981) (Phase 2 patients only)
   - RECIST v. 1.1 (Eisenhauer 2009) (Phase 3 patients only)
7. Radiologic evidence of progressive disease (PD) within 6 months prior to randomization. If the patient received other intervening therapy after PD is documented, further PD must

be documented after the completion of the intervening therapy, with the exception of patients who discontinued most recent treatment after no more than 1 dose.

8. Must have received at least 2 but no more than 5 prior systemic therapies for the treatment of liposarcoma.
9. Patients should have recovered from all major surgery, radiation or other interventions ≥ 21 days prior to randomization. Patients must have recovered from any clinically significant therapy-related toxicity to ≤ Grade 1 per CTCAE v. 4.03. Minor procedures, such as biopsies, dental work, or placement of a port or intravenous line for infusion, are permitted.
10. If patients received any previous systemic therapy, the last dose must have been ≥21 days prior to randomization (or ≥5 half-lives of that drug [whichever is shorter]), with all clinically significant therapy-related toxicities having resolved to ≤ Grade 1 CTCAE v. 4.03.
11. ECOG performance status ≤1 (Oken 1982)
12. Adequate laboratory functional values:
    - Adequate hematopoietic function:
        - Absolute neutrophil count (ANC) ≥1500/mm^3
        - Platelets ≥100,000/mm^3
        - Hemoglobin (Hb) ≥9 g/dL
        - Transfusions, hematopoietic growth factors, and hematinics are NOT permitted during screening
    - Adequate hepatic function:
        - Bilirubin ≤1.5 x upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤3 x ULN)
        - Alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) <3.0 x ULN (except patients with liver involvement of their liposarcoma who must have an AST and ALT ≤5 x ULN).
    - Adequate renal function: Serum creatinine of ≤ 1.5 mg/dL or estimated creatinine clearance of ≥ 30 mL/min, calculated using the Cockcroft and Gault formula (140 – Age) • Mass (kg)/ (72 • creatinine mg/dL); multiply by 0.85 if female (Cockcroft 1976).
13. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must agree to use highly effective contraception throughout the study and for 3 months following the last dose of study treatment. Highly effective methods of contraception are listed in Section 13.3.1.

8.4. Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Patients with liposarcoma of pure WDLS, myxoid/round cell or pleomorphic tumor histologic subtypes.
2. Significant cardiovascular impairment, defined as:

   a. Cardiac failure, New York Heart Association (NYHA) Class ≥ 3 according to the NYHA Functional Classification
   b. Unstable angina or myocardial infarction within 3 months of enrollment
   c. Serious and potentially life-threatening arrhythmia.
3. Patients with known central nervous system metastases.
4. Female patients who are pregnant or nursing.
5. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to randomization. Cancer treated with curative intent > 5 years prior to randomization and without evidence of recurrence is allowed.
6. Known active hepatitis B infection, as defined by seropositivity for hepatitis B surface antigen (HBs Ag); or known hepatitis C infection, as defined by seropositivity for hepatitis C antibody, with elevated liver aminotransferases (ie, above the levels specified in inclusion criterion #12) or any other evidence of active hepatitis.
7. Known human immunodeficiency virus (HIV) infection.
8. Any medical condition, such as an uncontrolled infection or uncontrolled diabetes mellitus (Type 2), which in the opinion of the Investigator would make study involvement unreasonably hazardous
9. Psychiatric illness that would prevent the patient from giving informed consent or being compliant with the study procedures
10. Patients unable to swallow tablets, patients with malabsorption syndrome, or any other GI disease or GI dysfunction that could interfere with absorption of study treatment
11. Inability or unwillingness to take supportive medications such as anti-nausea and anti-anorexia agents as recommended by the NCCN CPGO for antiemesis and anorexia/cachexia (palliative care).
12. Patients who had involuntary weight loss of ≥ 10% in the 3 months prior to randomization.
13. Participation in an investigational anticancer study ≤ 21 days prior to randomization.
14. A circulating lymphocyte count of >50,000/µL (for sites in France only)

9. STUDY ACTIVITIES

The assessments to be performed during blinded study treatment and treatment with open-label selinexor are listed in Section 9.1 and Section 9.2, respectively.

Additional assessments, including the following, may be performed throughout the study if clinically indicated:

- electrocardiograms (ECGs)
- urinalysis
- hematology
- complete or limited serum chemistry
- coagulation tests
- pregnancy testing
- nutritional consultation

After discontinuation of study treatment, all patients will be followed for survival (Section 9.1.8 and Section 9.2.6).

9.1. Description of Study Days: Blinded Treatment

Please note: screening visits may be combined at site discretion, in which case all screening must be completed within 14 days prior to the start of study treatment.

9.1.1. Visit 1 (within 21 days prior to C1 D1); Screening Visit 1

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF must be signed and dated by the patient and witnessed (as required by the IRB/IEC) prior to the first study-specific measures. For adolescent patients (permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority), a separate Assent Form must be signed by the patient at the time of informed consent. Procedures that are part of the clinical routine evaluations during the initial diagnostic work-up of the patient may be performed before the ICF is signed and dated (ie, procedures that are not specific to the conduct of the study). A copy of the ICF must be given to the patient or to the person signing the form on behalf of the patient. The Investigator or designee must record in the medical records of the patient the date when the study ICF was signed. The name and role of the witness should also be documented.

The following screening assessments must be completed within 21 days prior to C1 D1 (except as noted), as specified in Table 1*: Schedule of Assessments and Study Activities*.

The screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of randomization.

Rescreening is permitted in this study. See Section 7.6.2.

The study site should not repeat procedures completed as standard of care if they are within the screening window, and prior to signing the ICF. The data from these procedures are part of the medical history and may be used for study purposes.

The following procedures are to be performed:

- Sign written informed consent for blinded study treatment (note age on day consent is signed). Adolescent patients should also sign a written Assent Form
- Review inclusion and exclusion criteria
- Demography (year of birth, age, gender, race, and ethnicity [Hispanic origin])
- Complete medical history (Section 10.3)
- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Section 10.6.1.1)
- Weight, height, and BSA (Section 10.6.1.2)
- ECOG performance status assessment (Section 10.6.1.3)
- 12-lead ECG (Section 10.6.1.4)
- Urinalysis (Section 10.6.2.1)
- Hematology (Section 10.6.2.1)
- Complete serum chemistry (Section 10.6.2.1)
- Coagulation tests (Section 10.6.2.1)
- Tumor biopsy to provide tissue for confirmation of liposarcoma type by histology and presence of DDLS; the Investigator may omit this biopsy if appropriate archival (ie, of DDLS tissue) material is available. See Section 10.4.
- For Phase 3 only: Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest) (within 21 days prior to the first dose of blinded study treatment). CT (preferred) or MRI scan for tumor measurement; the same imaging modality should be maintained throughout the study.
- AEs and SAEs
- Concomitant medications

9.1.2. Visit 2 (within 14 days prior to C1 D1); Screening Visit 2

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. All baseline/screening CT/magnetic resonance imaging (MRI)/ PET scans, diagnosis and assessment of progression/extent of liposarcoma, QoL questionnaires, and confirmation of patient eligibility must be completed within 14 days prior to C1 D1.

The following procedures are to be performed:

- For Phase 2 only: Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest) (within 14 days prior to the first dose of blinded study treatment). FDG-PET and CT (diagnostic) scan for tumor density and SUV. If FDG-PET is contraindicated, CT

(preferred) or MRI scan should be used instead, so that, for a given patient, the same imaging modality is maintained throughout the study.

- Diagnosis and assessment of progression/extent of liposarcoma (RECIST v. 1.1, Appendix 2)
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (within 14 days prior to C1 D1) (Section 10.7.1)
- Serum human chorionic gonadotropin (hCG) pregnancy test (females of childbearing potential only, within 3 days before the first dose of blinded study treatment) (Section 10.6.2.2)
- Eligibility confirmation by the Sponsor (after screening procedures and before randomization)
- Randomization
- AEs and SAEs
- Concomitant medications

9.1.3. Visits 3-8 (Cycle 1: Days 1, 8, 15, 22, 29, and 36 [±1 days]); Return to the Clinic

There are six clinic visits (ie, Days 1, 8, 15, 22, 29, and 36) during the first six-week cycle (Cycle 1).

The following study assessments will be performed during Cycle 1, as specified in Table 1:

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 1, 8, 15, 22, 29, and 36) (Section 10.6.1.1)
- Weight (Days 1, 8, 15, 22, 29, and 36) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- 12-lead ECG (Day 1 only, CCI [redacted]) (Section 10.6.1.4)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Limited serum chemistry (Days 8, 15, 22, 29, and 36) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)
- Tumor biopsy, only if sufficient material was available from the screening biopsy (archival or fresh) for CCI testing (Day 22 only; may be taken Cycle 2 Day 1, see Section 9.1.4). See Section 10.4 and Section 10.11.3 for biopsy details. Note: This second biopsy (eg, either Cycle 1 Day 22 or Cycle 2 Day 1) should not be collected

from adolescent/pediatric patients for exploratory studies if there appears to be a potential for serious risk for the patient.

- CCI [redacted]
- CCI [redacted]
- Nutritional consultation (should occur on Day 1 before the first dose of blinded study treatment, or within the Screening Period). See Section 10.7.3.
- Study treatment: in clinic dosing and dispensing of for home use (Days 1, 8, 15, 22, 29, and 36)
- AEs and SAEs (throughout the cycle)
- Concomitant medications (throughout the cycle)

9.1.3.1. Phone Call with Patient: Cycle 1 Day 3 Only (+ 1 day)

A phone call will be made to the patient to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

9.1.4. Visits 9-11 (Cycle 2: Days 1, 15, and 29 [±2 days]); Return to the Clinic

There are three clinic visits (ie, Days 1, 15, and 29) for Cycle 2.

The following study assessments will be performed during Cycle 2, as specified in Table 1.

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 1, 15, and 29) (Section 10.6.1.1)
- Weight (Days 1, 15, and 29) (Section 10.6.1.2)
- Height and BSA (Day 1 only) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- 12-lead ECG (Day 1 only, CCI [redacted]) (Section 10.6.1.4)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Limited serum chemistry (Days 15 and 29 only) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)
- Female patients of childbearing potential only: pregnancy test (serum hCG or high sensitivity urine) prior to dosing on Day 1 only. A positive urine pregnancy test will be confirmed by a serum pregnancy test. (Section 10.6.2.2)
- Tumor biopsy, only if sufficient material was available from the screening biopsy (archival or fresh) for CCI [redacted] testing (Day 1 only and only if not obtained at Cycle 1 Day 22, see Section 9.1.3). See Section 10.4, and Section 10.11.3 for biopsy details. Note: This second biopsy (eg, either Cycle 1 Day 22 or Cycle 2 Day 1) should not be

collected from adolescent/pediatric patients for exploratory studies if there appears to be a potential for serious risk for the patient.

- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
  - Phase 2: FDG-PET and CT (diagnostic) scan approximately 6 weeks post-first dose (ie, Day 1 of Cycle 2). If FDG-PET is contraindicated, CT (preferred) or MRI scan should be used instead so that, for a given patient, the same imaging modality is maintained throughout the study.
  - Phase 3: CT (preferred) or MRI scan for tumor measurement approximately 6 weeks post-first dose (ie, Day 1 of Cycle 2); the same imaging modality should be maintained throughout the study
- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (Appendix 2) approximately 6 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycle 2), based on 6-week tumor scan.
- Treatment assignment query of patients and Investigators (only for patients with PD, query prior to unblinding) (Section 10.7.2).
- CCI
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Day 1 only, predose) (Section 10.7.1)
- Study treatment: in clinic dosing and dispensing of for home use (Days 1, 15, and 29)
- AEs and SAEs (throughout the cycle)
- Concomitant medications (throughout the cycle)

9.1.4.1. Phone Calls with Patient: Cycle 2 Days 10, 24, and 38 (+ 1 day)

A phone call will be made to the patient to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

9.1.5. Visits ≥ 12 (Cycles ≥ 3: Days 1 and 22 [±2 days]); Return to the Clinic

Patients enrolled in this study may continue from cycle to cycle without interruption.

The following study assessments will be performed for Cycles ≥ 3, as specified in Table 1.

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 1 and 22) (Section 10.6.1.1)
- Weight (Days 1 and 22) (Section 10.6.1.2)
- Height and BSA (Day 1 only) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Limited serum chemistry (Day 22 only) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)

- Female patients of childbearing potential only: pregnancy test (serum hCG or high sensitivity urine) prior to dosing on Day 1 only. A positive urine pregnancy test will be confirmed by a serum pregnancy test. (Section 10.6.2.2)
- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
    - Phases 2 and 3: CT (preferred) or MRI scan for tumor measurement approximately12, 18, and 24 weeks after start of study treatment (ie, Day 1 of Cycles 3, 4, and 5), and approximately every 12 weeks thereafter (ie, Day 1 of odd-numbered Cycles ≥ 7); the same imaging modality should be maintained throughout the study
- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (2) when tumor (CT/MRI) scans are performed. Assessments are to be performed approximately 12, 18 and 24 weeks after start of study treatment (ie, Day 1 of Cycles 3, 4 and 5), and approximately every 12 weeks thereafter (ie, Day 1 of odd-numbered- Cycles ≥ 7), based on tumor scans.
- Treatment assignment query of patients and Investigators (only for patients with PD; query after PD but prior to unblinding) (Section 10.7.2).
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Day 1 only, predose) (Section 10.7.1)
- Study treatment: in clinic dosing and dispensing of for home use (Days 1 and 22)
- AEs and SAEs (throughout the cycles)
- Concomitant medications (throughout the cycles)

9.1.5.1. Phone Calls with Patient: Cycles ≥ 3 Days 10, 17, 31 and 38 (+ 1 day)

A phone call will be made to the patient to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

9.1.6. End of Blinded Treatment Visit; Return to the Clinic

At the time a patient permanently discontinues blinded study treatment or has PD prior to unblinding of all patients at the end of Phase 3 (ie, when the required number of PFS events for the primary PFS analysis are observed), a visit should be scheduled as soon as possible (within 14 days), at which time all of the assessments listed for the End of Blinded Treatment (EoBT) Visit will be performed. Study procedures will be performed ≤ 14 days after the last dose of study treatment, as specified in Table 1. An EoBT CRF page will be completed, giving the date and reason for stopping the study treatment. Patients lost to follow-up should be recorded as such on the appropriate eCRF.

For patients proceeding to open-label selinexor, the EoBT Visit will serve as the baseline for the open-label treatment phase. After the unblinding following the PFS analyses, patients in the selinexor arm who are continuing on selinexor but as open-label treatment must complete their EoBT Visit before their next scheduled selinexor dose.

- Informed consent for open-label selinexor (only for patients proceeding to open-label selinexor) and Assent Form for adolescent patients (permitted only in countries in

which adolescents have been approved by the national/local regulatory/ethical authority)

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Section 10.6.1.1)
- Weight, height, and BSA (Section 10.6.1.2)
- ECOG performance status assessment (Section 10.6.1.3)
- 12-lead ECG (Section 10.6.1.4)
- Urinalysis (Section 10.6.2.1)
- Hematology (Section 10.6.2.1)
- Complete serum chemistry (Section 10.6.2.1)
- Coagulation tests (Section 10.6.2.1)
- Serum hCG pregnancy test (females of childbearing potential only). Females of childbearing potential who are proceeding to open-label selinexor must have a negative serum hCG pregnancy test at the EoBT Visit (or within 3 days before the first dose of open-label selinexor). (Section 10.6.2.2)
- Tumor biopsy for patients who were in the placebo arm and are crossing over to open-label selinexor only. If the patient has archival material (ie, of DDLS tissue) collected at Screening, Cycle 1 Day 22, or Cycle 2 Day 1 within 12 months prior to the first dose of open-label selinexor, that sample may substitute for the biopsy. Patients in the selinexor arm who continue on selinexor but as open-label treatment are not required to have an additional tumor biopsy at the EoBT Visit. See Section 10.11.3.
- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
    - Phases 2 and 3: CT (preferred) or MRI scan for tumor measurement (if ≥ 4 weeks since last prior scan AND required to document disease or clinical progression) for assessment of liposarcoma. Patients in the placebo arm who have clinical progression must have subsequent radiographic progression determined by the central reader in order to receive open-label selinexor.
- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (2) if tumor (CT/MRI) scan is performed.
- Treatment assignment query of patients and Investigators (if not performed at a previous visit; query after PD but prior to unblinding) (Section 10.7.2).
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Section 10.7.1)
- AEs/SAEs
- Concomitant medications
- Information on any antineoplastic therapies used since discontinuation of blinded study treatment

9.1.7. Safety Follow-up Phone Call (30 Days [+7 days] after last dose of study treatment)

Only for patients NOT proceeding to open-label selinexor.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for an EoBT Visit, will be contacted for safety evaluations during the 30 days (+7 days) following the last dose of study treatment. Every effort should be made to contact the patient (or the patient's family) by telephone or by sending appropriate correspondence (eg, certified letter or email).

During this patient contact the most important information to be obtained includes the following:

- Overall medical condition of the patient and status of their liposarcoma
- AEs, including follow-up on any AEs that were not resolved at the EoBT Visit
- Collection of information (including treatment type, response, and time of response for assessment of CCI) on any antineoplastic therapies used after discontinuation of blinded study treatment. For patients who progress on post-study treatment antineoplastic therapy, the Investigator should enter the date of progression from the medical record in the eCRF if that information is available to the Investigator.

9.1.8. Survival Follow-Up

Only for patients NOT proceeding to open-label selinexor.

After discontinuation of blinded study treatment, a call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's liposarcoma status, well-being, and information on any antineoplastic therapies used since discontinuation of study treatment (for assessment of CCI). If the patient has died, the patient's date of death will be collected, together with the reason for death, if possible.

Patients lost to follow up should be recorded as such on the eCRF-. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, eg, dates of telephone calls, registered letters, etc. (see Section 11.2).

9.2. Description of Study Days: Open-label Selinexor

Please note:

- EoBT Visit serves as baseline of Open-Label Selinexor; The EoBT Visit may occur on the day of the patient's first open-label dose (OL-C1 D1 Visit) but must be $\leq$ 14 days of last blinded dose. OL C1 D1 must occur within 14 days of the EoBT Visit.
- Patients in the selinexor arm who continue selinexor but as open-label treatment must complete the EoBT Visit before their next scheduled selinexor dose to maintain continuity of selinexor dosing from blinded to open-label treatment.
- Physical examination assessments and laboratory assessments done at the EoBT Visit do not need to be repeated at OL C1 D1.

9.2.1. Visits OL1-6 (Cycle 1: Days 1, 8*, 15*, 22, 29*, and 36* [±1 days]); Return to the Clinic

There are six clinic visits (ie, Days 1, 8*, 15*, 22, 29*, and 36*) during the first six-week cycle (Cycle 1).

Visits (ie, Days 8, 15*, 29*, and 36*) are not required for patients who continue selinexor but as open-label treatment.

The following study assessments will be performed during Cycle 1, as specified in Table 2.

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 8*, 15*, 22, 29*, and 36*) Section 10.6.1.1)
- Weight (Days 8*, 15*, 22, 29*, and 36*) (Section 10.6.1.2)
- Limited serum chemistry (Days 8*, 15*, 22, 29* and 36*) (Section 10.6.2.1)
- Tumor biopsy, only for patients who cross over from blinded placebo to open-label selinexor and have sufficient material available from a biopsy sample obtained during blinded study treatment (pre- or post-dosing) within 12 months prior to the first dose of open-label selinexor (Day 22 only). Note: If the biopsy is not performed on Cycle 1 Day 22, it may be performed on Cycle 2 Day 1 (see Section 9.2.2). Patients in the selinexor arm who continue on selinexor but as open-label treatment are not required to have an additional tumor biopsy on Cycle 1 Day 22 of open-label treatment. See Section 10.11.3 for biopsy details.
- CCI
- CCI
- Nutritional consultation (should occur on Day 1 before the first dose of open-label selinexor) for patients in the placebo arm who cross over to open-label selinexor. The nutritional consultation is not required at C1 D1 of open-label selinexor treatment for patients in the selinexor arm who continue on selinexor but as open-label treatment. See Section 10.7.3.
- Selinexor: in clinic dosing and dispensing of for home use
- AEs and SAEs (throughout the cycle)
- Concomitant medications (throughout the cycle)

The following OL1 Visit (C1 D1) assessments will be performed only if they were not performed at the EoBT Visit:

- Informed consent for open-label selinexor and Assent Form for adolescent patients (permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority) must be signed on or before the OL1 Visit

before any study-specific procedures for treatment with open-label selinexor are conducted at the OL1 Visit (Day 1 only)

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Day 1) Section 10.6.1.1)
- Weight (Day 1) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- 12-lead ECG (Day 1 only) (Section 10.6.1.4)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L); Day 1 only, predose) (Section 10.7.1)

9.2.1.1. Phone Call with Patient: Cycle 1 Day 3 Only (+ 1 day)

A phone call will be made to the patient to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

9.2.2. Visits OL7-9 (Cycle 2: Days 1, 15, and 29* [±2 days]); Return to the Clinic

There are three clinic visits (Days 1, 15, and 29*) for Cycle 2.

Visit (ie, Day 29) is not required for patients who continue selinexor but as open-label treatment.

The following study assessments will be performed during Cycle 2, as specified in Table 2.

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 1, 15, and 29*) (Section 10.6.1.1)
- Weight (Days 1, 15, and 29*) (Section 10.6.1.2)
- Height and BSA (Day 1 only) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Limited serum chemistry (Days 15 and 29 only) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)
- Female patients of childbearing potential only: pregnancy test (serum hCG or high sensitivity urine) prior to dosing on Day 1 only. A positive urine pregnancy test will be confirmed by a serum pregnancy test. (Section 10.6.2.2)
- Tumor biopsy only for patients who cross over from blinded placebo to open-label selinexor and have sufficient material available from a biopsy sample obtained during blinded study treatment (pre- or post-dosing) within 12 months prior to the first dose

of open-label selinexor (Day 1 only and only if not taken at Cycle 1 Day 22, see Section 9.2.1). Patients in the selinexor arm who continue on selinexor but as open-label treatment are not required to have an additional tumor biopsy on Cycle 2 Day 1 of open-label treatment. See Section 10.11.3 for biopsy details.

- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
    - CT (preferred) or MRI scan for tumor measurement approximately 6 weeks post-first dose (ie, Day 1 of Cycle 2) to evaluate site of disease and distant sites (abdomen, pelvis, chest)
- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (2) approximately 6 weeks after the first dose of open-label selinexor (ie, Day 1 of Cycle 2), based on 6-week tumor scan.
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Day 1 only, predose) (Section 10.7.1)
- Selinexor: in clinic dosing and dispensing of for home use (Days 1, 15, and 29)
- AEs and SAEs (throughout the cycle)
- Concomitant medications (throughout the cycle)

9.2.2.1. Phone Calls with Patient: Cycle 2 Days 10, 24, and 38 (+ 1 day)

A phone call will be made to the patient to evaluate supportive care medications, concomitant medications, and AEs/SAEs, and to adjust supportive care as appropriate.

9.2.3. Visits OL ≥ 10 (Cycles ≥ 3: Days 1 and 22 [±2 days]); Return to the Clinic

Patients enrolled in this study may continue from cycle to cycle without interruption.

The following study assessments will be performed for Cycles ≥ 3, as specified in Table 2:

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Days 1 and 22) (Section 10.6.1.1)
- Weight (Days 1 and 22) (Section 10.6.1.2)
- Height and BSA (Day 1 only) (Section 10.6.1.2)
- ECOG performance status assessment (Day 1 only) (Section 10.6.1.3)
- Urinalysis (Day 1 only) (Section 10.6.2.1)
- Hematology (Day 1 only) (Section 10.6.2.1)
- Complete serum chemistry (Day 1 only) (Section 10.6.2.1)
- Limited serum chemistry (Day 22 only) (Section 10.6.2.1)
- Coagulation tests (Day 1 only) (Section 10.6.2.1)
- Female patients of childbearing potential only: pregnancy test (serum hCG or high sensitivity urine) prior to dosing on Day 1 only. A positive urine pregnancy test will be confirmed by a serum pregnancy test. (Section 10.6.2.2)
- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
    - CT (preferred) or MRI scan for tumor measurement approximately 12 weeks after start of open-label selinexor (ie, Day 1 of Cycle 3), and approximately

every 12 weeks thereafter (ie, Day 1 of odd-numbered Cycles ≥ 5) to evaluate site of disease and distant sites (abdomen, pelvis, chest); the same imaging modality should be maintained throughout the study

- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (2) when tumor (CT/MRI) scans are performed. Assessments are to be performed approximately 12 weeks after start of open-label selinexor (ie, Day 1 of Cycle 3), and approximately every 12 weeks thereafter (ie, Day 1 of odd-numbered Cycles ≥ 5), based on tumor scans.
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Day 1 only, predose) (Section 10.7.1)
- Selinexor: in clinic dosing and dispensing of for home use (Days 1 and 22)
- AEs and SAEs (throughout the cycles)
- Concomitant medications (throughout the cycles)

9.2.4. End of Treatment Visit (≤ 14 days after last dose of study treatment); Return to the Clinic

At the time a patient permanently discontinues selinexor a visit should be scheduled as soon as possible (within 14 days), at which time all of the assessments listed for the End of Treatment (EoT) Visit will be performed. Study procedures will be performed ≤ 14 days after the last dose of selinexor as specified in Table 2. An EoT CRF page will be completed, giving the date and reason for stopping the selinexor. Patients lost to follow-up should be recorded as such on the appropriate eCRF.

- Physical examination and vital signs (blood pressure, pulse, and body temperature) (Section 10.6.1.1)
- Weight, height, and BSA (Section 10.6.1.2)
- ECOG performance status assessment (Section 10.6.1.3)
- 12-lead ECG (Section 10.6.1.4)
- Urinalysis (Section 10.6.2.1)
- Hematology (Section 10.6.2.1)
- Complete serum chemistry (Section 10.6.2.1)
- Coagulation tests (Section 10.6.2.1)
- Serum hCG pregnancy test (females of childbearing potential only). (Section 10.6.2.2)
- Imaging to evaluate site of disease and distant sites (abdomen, pelvis, chest)
    - CT (preferred) or MRI scan for tumor measurement (if ≥4 weeks since last prior scan AND required to document disease or clinical progression) for assessment of liposarcoma.
- Assessment of progression/extent of liposarcoma by RECIST v. 1.1 (2) if tumor (CT/MRI) scan is performed.
- QoL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-5L) (Section 10.7.1)
- AEs and SAEs

- Concomitant medications
- Information on any antineoplastic therapies used since discontinuation of open-label selinexor

9.2.5. OL Safety Follow-up Phone Call (≤ 30 Days [+7 days] after last dose of study treatment)

At a minimum, all patients who discontinue study treatment, including those who refuse to return for an EoT Visit, will be contacted for safety evaluations during the 30 days (+7 days) following the last dose of study treatment. Every effort should be made to contact the patient (or the patient's family) by telephone or by sending appropriate correspondence (eg, certified letter or email).

During this patient contact the most important information to be obtained includes the following:

- Overall medical condition of the patient and status of their liposarcoma
- AEs, including follow-up on any AEs that were not resolved at the EoT Visit
- Collection of information (including treatment type, response, and time of response for assessment of CCI) on any antineoplastic therapies used after discontinuation of open-label selinexor. For patients who progress on post-study treatment antineoplastic therapy, the Investigator should enter the date of progression from the medical record in the eCRF if that information is available to the Investigator.

9.2.6. OL Survival Follow-Up

After discontinuation of treatment with open-label selinexor, a call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's liposarcoma status, well-being, and information on any antineoplastic therapies used since discontinuation of study treatment (for assessment of CCI). If the patient has died, the patient's date of death will be collected, together with the reason for death, if possible.

Patients lost to follow-up should be recorded as such on the eCRF. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, eg, dates of telephone calls, registered letters, etc. (see Section 11.2).

9.3. Unscheduled Visits

Unscheduled visits may be conducted at any time during the blinded or open-label portions of the study at the discretion of the Investigator. Additional testing (eg, blood testing or imaging scans) may be performed to ensure patient safety.

If unscheduled imaging scans are performed, they will be evaluated as described in Section 10.5.1.1. If PD is confirmed based on an unscheduled imaging scan, the options for study treatment described in Section 7.2.1 will apply.

10. METHODS OF ASSESSMENT

10.1. Inclusion/Exclusion Criteria

The patient must meet the all of the inclusion criteria (Section 8.3) and none of the exclusion criteria (Section 8.4).

Key patient eligibility (inclusion/exclusion criteria) will be confirmed by the Sponsor for all patients participating in the study prior to randomization (Section 7.6).

See Section 7.7 for randomization details.

10.2. Demographic Data

Patient demographics (including date of birth, sex, race, ethnicity, age at time of consent, and tumor type) will be collected at study entry.

10.3. Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline liposarcoma symptoms as well as a detailed history of prior procedures and prior cancer therapies (ie, chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery) including start and stop dates, best response, PD during or after therapy, as well as discontinuations due to intolerability or toxicity.

A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will also be collected.

10.4. Liposarcoma Histology

For all patients, tumor tissue will be analyzed by a central laboratory for confirmatory histology (ie, to characterize tumor histology and confirm the presence of DDLS); the results of the central histologic assessment are not required for randomization and initiation of treatment. A tumor biopsy will be collected during screening unless appropriate archival material is available. At the Investigator's discretion, appropriate archival material may substitute for the biopsy during screening. Appropriate archival material includes DDLS tissue collected as part of clinical standard of care within 12 months prior to the first dose of blinded study treatment or > 12 months if the quality of the sample for confirmatory histology is confirmed by the site histopathologist before randomization.

It sufficient tissue is available, a portion of the sample will be used for CCI testing (see Section 10.11.3).

If a pretreatment (screening) tumor biopsy sample (archival or fresh) was obtained for CCI [redacted]. Portions of this biopsy will be formalin-fixed and frozen-unfixed as described in the *Laboratory Manual*. Biopsies are required if feasible. The feasibility of the biopsy procedure, in terms of patient safety and tumor accessibility, will be determined by the Investigator. Note: This second biopsy (eg, either Cycle 1 Day 22 or Cycle 2 Day 1)

should not be collected from adolescent/pediatric patients for exploratory studies if there appears to be a potential for serious risk for the patient.

Biopsies should be performed per Institutional Guidelines and may be either a core needle biopsy or an open biopsy.

Please see the *Laboratory Manual* for additional details on collection, handling, and shipping of biopsy tissue.

10.5. Efficacy Assessments

10.5.1. Tumor Imaging

10.5.1.1. Types of Imaging

Two forms of imaging will be used to image tumors to evaluate site of disease and distant sites (abdomen, pelvis, chest):

- ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET and CT) will be used to combine the high anatomical detail of CT with the assessment of tumor glucose metabolic activity provided by FDG-PET imaging (for Phase 2 only and only for screening and the first post-dose scan). If FDG-PET is contraindicated for a given patient, then a CT scan, which is the preferred modality, should be used instead. If CT is also contraindicated, then an MRI scan should be used. Please note that, for a given patient, the same imaging modality should be maintained throughout the study, where appropriate. The schedule for FDG-PET and CT (diagnostic) is given in Section 10.5.1.2.
- CT imaging is considered to be the preferred modality for the clinical imaging of sarcoma and will be used for this study (Phase 2 starting with the second post-dose scan and Phase 3 starting with screening). If CT is contraindicated for a given patient, then MRI should be used instead. Please note that, for a given patient, the same imaging modality should be maintained throughout the study, where appropriate. The schedule for CT (preferred) or MRI is given in Section 10.5.1.2.

All scans, including unscheduled scans, must be transmitted as soon as possible to the central reader. Scans will be centrally assessed by an independent reviewer, as follows, for:

- Single-dimensional (longest cross-sectional dimension) measurements (response per RECIST v. 1.1)
- Two-dimensional (product of longest diameter and greatest perpendicular diameter) measurements (response per WHO Response Criteria)
- CCI [redacted]
- Tumor density and SUV determinations for assessment of tumor response defined as ≥ 10% reduction in tumor sum of longest diameters or > 15% reduction in tumor density or > 30% reduction in SUV (FDG-PET and CT scans for Phase 2 only)

Additional details will be provided in the *Imaging Manual*.

10.5.1.2. Imaging Schedules for Phases 2 and 3

Blinded Study Treatment

Phase 2

- FDG-PET and CT (diagnostic) at screening and approximately 6 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycle 2).
- CT (preferred) or MRI scan will be performed at approximately 12, 18, and 24 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycles 3, 4, and 5), then every 12 weeks (ie, Day 1 of odd-numbered Cycles ≥ 7) thereafter until PD or unblinding.

Phase 3

- CT (preferred) or MRI will be performed at Screening and approximately 6, 12, 18, and 24 weeks after the first dose of blinded study treatment (ie, Day 1 of Cycles 2, 3, 4, and 5), then every 12 weeks (ie, Day 1 odd-numbered Cycles ≥ 7) thereafter until PD or unblinding.

Open-label Selinexor

- CT (preferred) or MRI at approximately 6 and 12 weeks after the first dose of open-label selinexor (ie, Day 1 of Open-label Cycles 2 and 3), then every 12 weeks (ie, Day 1 of odd-numbered Cycles ≥ 5) thereafter until PD.

10.5.2. Diagnosis/ Assessment of Progression/ Extent of Liposarcoma

Assessment of liposarcoma per RECIST v. 1.1 will be performed following each tumor scan.

10.6. Safety Assessments

Safety evaluations will be conducted as described below. Refer to Table 1, Table 2, and Section 9 for the timing of all safety assessments.

10.6.1. Clinical Safety Assessments

10.6.1.1. Physical Examination and Vital Signs

The physical examination will be performed according to the standards at each institution.

Physical examination, including vital signs, will be performed on the scheduled day, even if study treatment is being interrupted. Physical examinations should include general appearance, dermatological, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdominal, lymph nodes, musculoskeletal, and neurological examinations.

All vital signs will include:

- Body temperature (°C or °F)
- Systolic and diastolic blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. Blood pressure should be assessed on the same arm throughout the study.

Information about the physical examination must be present in the source documentation at the study site. The result of the physical examination prior to the start of study treatment must be included in the Relevant Medical History/Current Medical Conditions eCRF. Clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE eCRF.

10.6.1.2. Height, Weight, and BSA

Height (without shoes) in centimeters (cm) and weight (indoor clothing without shoes) in kilograms (kg) will be measured. BSA will be calculated by the Dubois (Dubois 1916) or Mosteller (Mosteller 1987) method to verify that BSA > 1.2 m^2 to ensure that an individual patient's selinexor dose would not exceed 70 mg/m^2 twice weekly. If the patient's weight fluctuates substantially, BSA should be re-calculated at each treatment visit. BSA should be re-calculated prior to any selinexor/placebo dose change.

10.6.1.3. ECOG Performance Status

ECOG performance status assessments (Oken 1982) will be performed during the study to assess how the disease affects the daily living abilities of the patients (Appendix 3).

10.6.1.4. Electrocardiography

Standard 12-lead ECGs will be performed. The ECGs performed on Day 1 of Cycles 1 and 2 during blinded study treatment are to be performed just prior to the blood sample taken 2 hours postdose (approximately at the expected t_{max} of plasma selinexor). ECGs may also be performed as clinically indicated during the study.

Patients must rest for at least 5 minutes prior to any ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The time the ECG was performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using either Bazett's or Fredericia's formula.

10.6.1.5. Concomitant Medications

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented for each patient at screening and C1 D1. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study treatment through the end of the study. All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded in the eCRF.

Necessary supportive care such as appetite stimulants, anti-emetics and anti-diarrheal medication, etc., will be allowed (see Section 12.2.5).

10.6.1.6. Adverse Events

Information regarding AEs and SAEs will be collected. See Section 13.1.2.

10.6.2. Laboratory Safety Assessments

10.6.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed by the sites' local laboratories. In addition, laboratory tests will be collected and analyzed on the scheduled day, even if study treatment is being interrupted. More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion and these should be recorded on the Unscheduled Visit eCRFs:

- **Hematology** (blood sample: ethylenediaminetetraacetic acid) will include hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, RBC count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.
- **Serum Chemistry** (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), total protein, albumin, creatinine kinase, uric acid.
  - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, and LDH.
  - If the total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
- **Coagulation tests** will include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- **Urinalysis** will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

Blood chemistry will be analyzed at each study center by a certified laboratory. The Investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values.

At any time during the study, abnormal laboratory values which are clinically relevant (eg, require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be documented in the eCRF. If any abnormal laboratory value or test result constitutes an AE, then these must be recorded on the AE eCRF. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a

clinically acceptable range (regardless of relationship to study treatment) or baseline. Any laboratory value that remains abnormal at the EoBT Visit (early discontinuation patients) or EoT Visit (open-label patients) and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline.

Toxicity will be assessed using the NCI CTCAE, v. 4.03.

Karyopharm must be provided with a copy of the laboratory certification and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Karyopharm must be provided with a copy of the certification and normal ranges for that laboratory.

10.6.2.2. Pregnancy Testing

Pregnancy testing will be performed for females of childbearing potential only. A negative serum hCG pregnancy test must be obtained at Screening within 3 days before the first dose of blinded study treatment. For females of childbearing potential who are proceeding to open-label selinexor a negative serum hCG pregnancy test must be obtained at the EoBT Visit (or within 3 days before the first dose of open-label selinexor). Test sensitivity for hCG must be ≥ 25 mIU/mL.

Pregnancy testing (serum hCG or high sensitivity urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 during both blinded and open-label treatment and at the EoT Visit (serum hCG). A positive urine pregnancy test will be confirmed by a serum pregnancy test.

Pregnancy testing may be performed if clinically indicated during the study.

10.7. Other Assessments

10.7.1. Quality of Life and Health-Related Outcomes

QoL questionnaires should be completed prior to study treatment administration on the days when QoL questionnaire is completed.

EORTC QLQ-C30: The QLQ-C30 is a validated, patient self-administered instrument for assessing the health-related QoL of cancer patients participating in international clinical studies. It is a questionnaire containing both multi-item and single scales, including five functional scales (physical, role, emotional, social and cognitive), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

EuroQoL EQ-5D-5L: The EQ-5D-5L is a validated, patient self-administered instrument used for multiple health conditions and treatments, to provide a simple descriptive profile and a single index value of health status.

10.7.2. Treatment Assignment Query

Prior to unblinding, the patient and the Investigator will be asked which study treatment (active [selinexor] or placebo) they believe the patient received during blinded study treatment.

Specifically:

- After PD but prior to unblinding, the patient and the Investigator will be asked which study treatment (active [selinexor] or placebo) they believe the patient received during blinded study treatment and their responses will be recorded.

- If blinded study treatment is discontinued without PD, query should be performed at the time that blinded study treatment is discontinued and prior to unblinding. See Section 11.3.

- If unblinding is required for clinical management of a clinically important SAE leading to discontinuation of study treatment and knowledge of the received study treatment is required for clinical management and treatment of the SAE, query should be performed prior to unblinding.

10.7.3. Nutritional Consultation

It is strongly recommended that the Investigator, or his/her designee, provide patients with a nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This consultation does not need to be performed by a nutritionist.

During blinded study treatment, the nutritional consultation should occur on C1 D1 before the first dose of blinded study treatment (or within the Screening Period).

During treatment with open-label selinexor, the nutritional consultation should occur on C1 D1 before the first dose of open-label selinexor for patients in the placebo arm who cross over to open-label selinexor. The nutritional consultation is not required at C1 D1 of open-label selinexor treatment for patients in the selinexor arm who continue on selinexor but as open-label treatment.

The nutritional consultation may be also performed at any time during the study, as necessary.

10.7.4. Collection of Information on Antineoplastic Therapy

Information on any antineoplastic therapies used after discontinuation of study treatment will be collected at the EoBT Visit (Section 9.1.6), the EoT Visit (Section 9.2.4), Safety Follow-up Calls (Section 9.1.7 and Section 9.2.5), and during Survival Follow-up (Section 9.1.8 and Section 9.2.6).

For patients who progress on post-study treatment antineoplastic therapy, the Investigator should enter the date of progression from the medical record in the eCRF if that information is available to the Investigator.

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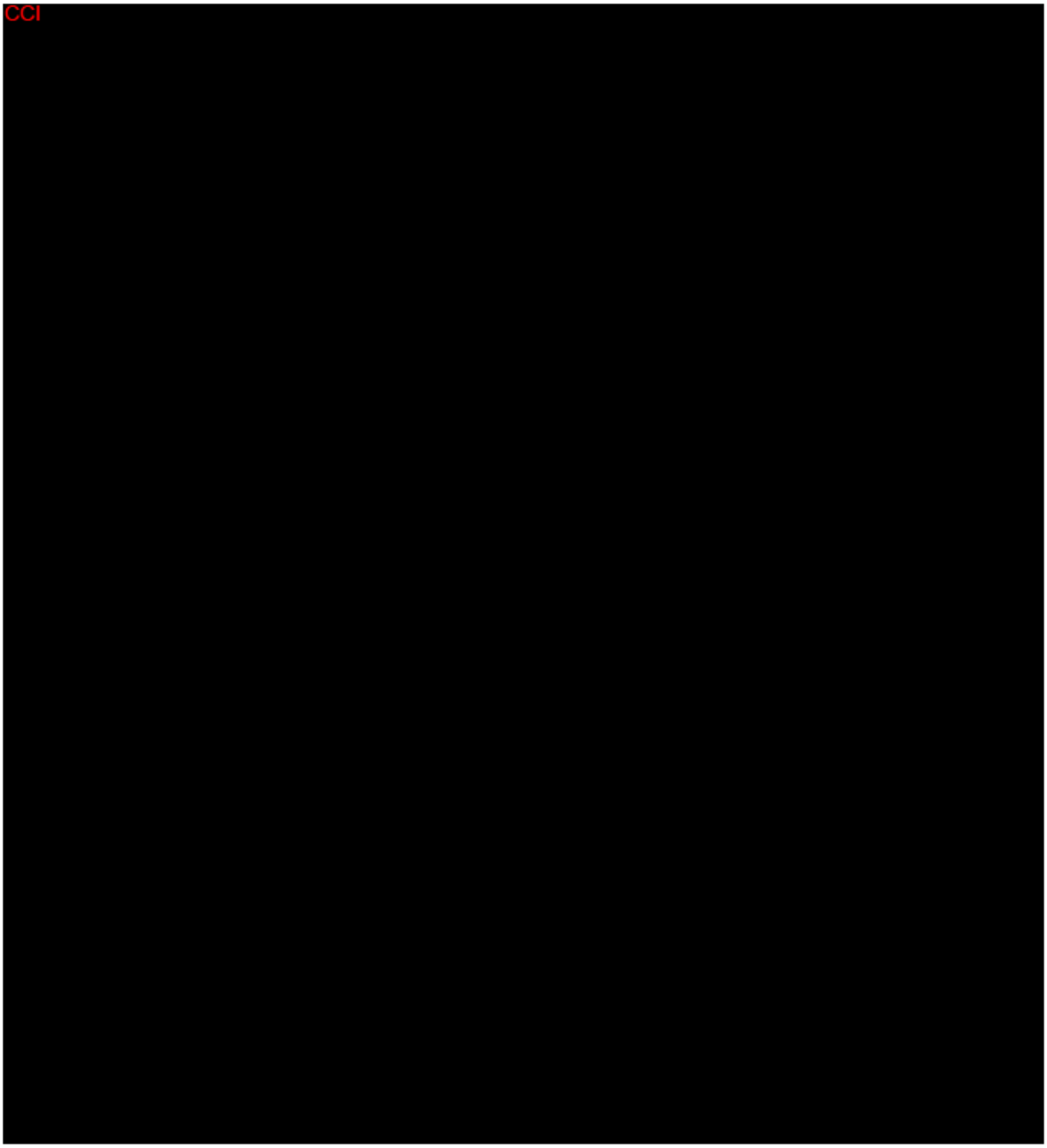

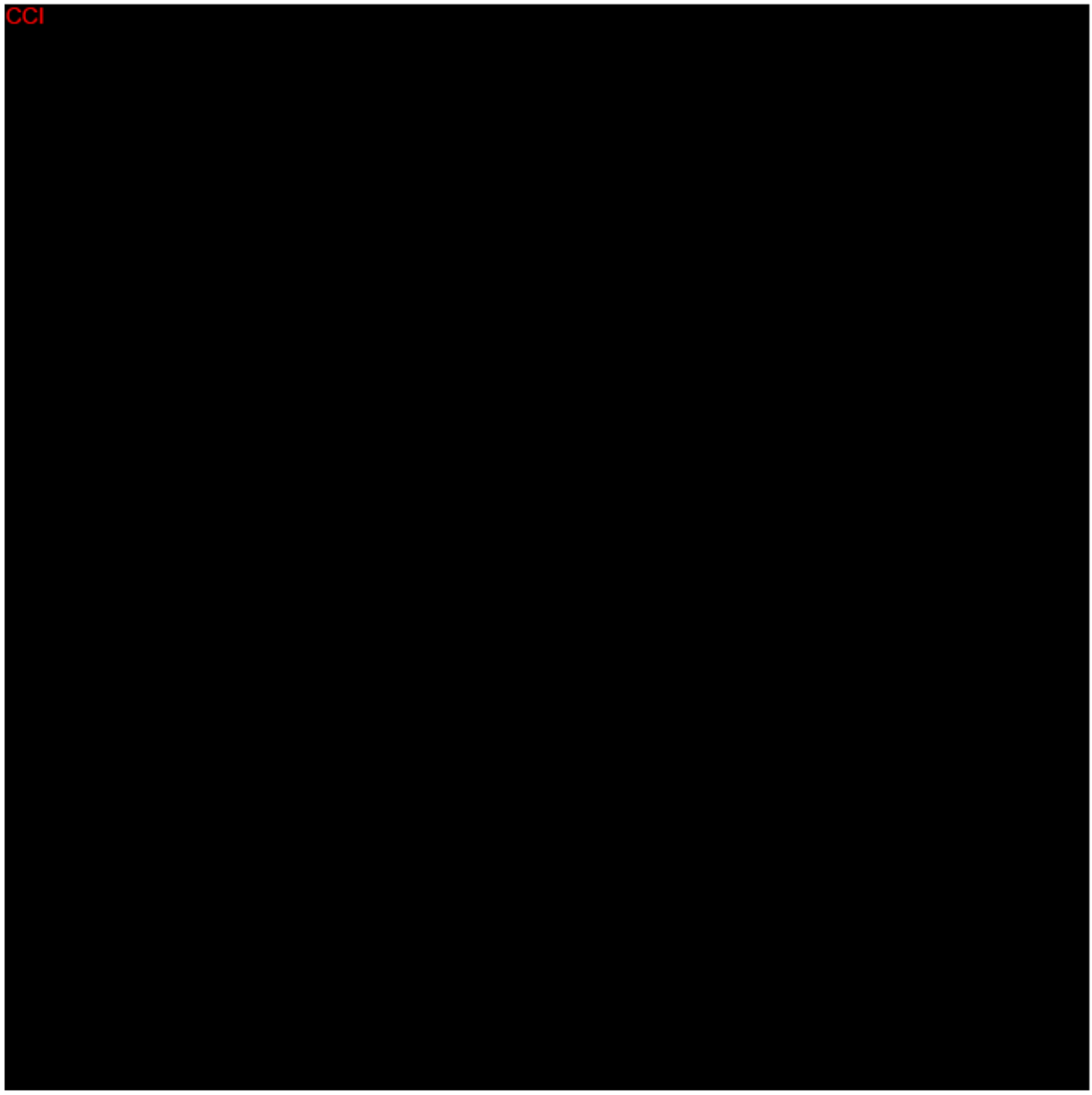
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11. DISCONTINUATION AND UNBLINDING CRITERIA

11.1. Early Termination of the Study

The study may be terminated at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. If this occurs, the Sponsor will notify IECs, IRBs, Investigators, and regulatory authorities.

11.2. Discontinuation of Study Treatment and/or Withdrawal of Patients from the Study

The Investigator may remove a patient from study treatment for any of the following reasons:

- PD as defined by the central reader by RECIST v. 1.1 (see exception for patients who may derive benefit from continued treatment with selinexor in Section 7.2.4)
- Clinical progression as determined by the Investigator in consultation with the Sponsor (must be documented by radiographic imaging and assessed by the central reader)
- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Significant deviations from inclusion/exclusion criteria
- Misuse of study treatment (eg, deliberate overdosing by patient)
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation, in the opinion of the Investigator.

The Investigator must remove a patient from study treatment for any of the following reasons:

- Patient withdraws consent to continue study treatment
- Pregnancy
- Use of radiation to treat the patient's liposarcoma (see Section 12.2.5.3)

Patients may discontinue study treatment for any reason. Patients who decide to discontinue study treatment should be encouraged to continue in the study so that follow-up information on PD and survival status may be obtained. Patients who discontinue study treatment but continue follow-up will be followed for anti-neoplastic therapy initiation and CCI every 3 months. These patients will be included in the ITT analysis if they are in Phase 3.

Patients may withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study.

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to three documented contact attempts will be considered lost to follow-up.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment/withdrawal from the study and record this information on the eCRF.

11.3. Unblinding

11.3.1. Unblinding of Treatment Assignment During Blinded Study Treatment

Patients who have PD per RECIST v. 1.1 will discontinue blinded study treatment and their treatment assignment will be unblinded. Unblinding will take place within 14 days of the last blinded dose and may occur on or before the patient's EoBT Visit (Section 9.1.6). Only the patient, the Investigator at the study site, and key Sponsor team members as specified to monitor the conduct of the study will be unblinded to the treatment assignment.

Treatment assignments for patients who discontinue blinded study treatment without determination of PD by the central reader (including patients who discontinue blinded study treatment for reasons other than PD) will not be unblinded until the primary PFS analysis at the end of Phase 3 and these patients are not allowed to receive open-label selinexor.

- **Exception:** Treatment assignment may be unblinded in the event of a clinically important SAE *only* if unblinding is required for clinical management of a clinically important SAE leading to discontinuation of study treatment and knowledge of the received study treatment is required for clinical management and treatment of the SAE. If the patient is on the placebo arm and PD has not been documented, the patient will not be eligible to receive open-label selinexor.

11.3.2. Unblinding of Treatment Assignment for All Patients at the Primary PFS Analysis at the End of Phase 3

Once the required number of PFS events for the primary PFS analysis at the end of Phase 3 are observed, unblinding of treatment assignment for all patients will take place and the primary PFS analysis will be conducted. Patients who did not have PD at the time of unblinding will 1) continue selinexor but as open-label treatment if they were in the selinexor arm, or 2) have the option to cross over to open-label selinexor if they were in the placebo arm.

11.4. Definition of End of Study

End of Study (EoS) will be upon completion of the follow-up period for the last patient treated in the study. Completion of follow-up for the last patient will occur when the last patient in the study has expired, has been followed for 24 months after enrollment, has been lost to follow-up, or has withdrawn consent, whichever occurs first.

12. TREATMENT

Selinexor (KPT-330) immediate release tablets for oral administration and matching placebo will be supplied in blister packs. Selinexor tablets will be provided in a coated tablet strength of 20 mg.

12.1. Dosing and Administration of Study Treatment

12.1.1. Labeling

Medication labels for each blister pack of selinexor and matching placebo tablets will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the randomization number but no information about the patient.

12.1.2. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the patient by authorized site personnel only. Dispensing instruction will be provided in the *Pharmacy Manual.*

12.1.3. Dosing Information

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water. Selinexor can be taken with or without food. For additional details on drug formulation, preparation, and administration, please refer to the *Pharmacy Manual* and the selinexor IB.

In order to avoid contact with skin, tablets must be swallowed whole and should not be crushed.

Blinded Study Treatment (Phases 2 and 3):

Selinexor and matching placebo will be administered as fixed blinded oral doses of three 20 mg tablets given twice weekly (eg, Day 1 Monday and Day 3 Wednesday or Day 1 Tuesday and Day 3 Thursday or Day 1 Wednesday and Day 3 Friday) on Weeks 1-6 of each 6-week (42-day) cycle until PD, intolerability, consent withdrawal, or unblinding. Patients with a BSA < 1.2 m^2 as calculated per Dubois 1916 or Mosteller 1987 will be excluded from the study. Selinexor will be administered as a flat-fixed dose, and not by body weight or BSA.

Open-Label Selinexor:

Patients on open-label selinexor will receive selinexor 60 mg twice-weekly during Weeks 1-6 of each 6-week (42-day) cycle.

The following 4 groups of patients may receive open-label selinexor:

(a) Patients in the placebo arm who have PD per RECIST v. 1.1 during blinded study treatment who elect to cross over to open-label selinexor

(b) Patients in the selinexor arm who have PD per RECIST v. 1.1 during blinded study treatment who may derive benefit from continued treatment with selinexor (see Section 7.2.4).
(c) Patients in the placebo arm who are receiving blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 who elect to continue to cross over to open-label selinexor
(d) Patients in the selinexor arm who are receiving blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 who elect to continue selinexor but as open-label treatment

C1D1 of treatment with open-label selinexor for all 4 groups of patients listed above must occur within 14 days of the patient's EoBT Visit. For patients in the selinexor arm during blinded study treatment who continue selinexor but as open-label treatment there will be no break in the patient's twice-weekly dosing schedule. These patients must complete the EoBT Visit before their next scheduled selinexor dose to maintain continuity of selinexor dosing from blinded to open-label treatment.

12.1.4. Dosing Instructions for the Study Participants

Study treatment will be provided for twice weekly dosing during Weeks 1-6 for all cycles. Patients will be provided adequate doses to take home to complete dosing until the next scheduled clinic visit. Patients will be asked to bring remaining study medicine, if any, when returning to the clinic for any scheduled or unscheduled visit.

The Investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment.

Supportive treatment for the management of known toxicities will be provided as needed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the eCRF. Compliance to study treatment will be recorded by study personnel after discussion with the patient and completion of drug accountability. Medication compliance will be monitored by the Investigator or a delegate and recorded in source documents. The date will be recorded as per the study treatment schedule. The Investigator or designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification of explanations for deviations. The Investigator or designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients and re-education when necessary.

12.2. Dose Reduction and Supportive Care Guidelines

12.2.1. Dose Modifications and Dose Delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The criteria for dose modifications for toxicities considered related to the study treatment, as well as

recommended supportive care, are outlined below and in Section 12.2. All interruptions or changes to study treatment administration must be recorded on the eCRF.

A dose reduction should be considered if the patient missed 2 consecutive doses or 3 nonconsecutive doses in a cycle due to an AE(s). The missed doses may be the result of a combination of AEs during the cycle (eg, Day 1 doses of Weeks 1 and 2 missed due to nausea, Day 1 dose of Week 3 missed due to fatigue). Following a dose reduction, dose re-escalation is allowed only after consultation with the Sponsor Medical Monitor.

Patients who require extended dose interruptions without disease progression (eg, unacceptable toxicities) will remain on study and continue with tumor scans per schedule of assessments as specified in Table 1 and Table 2.

Patients who withdraw from the study for a study-related AE or an abnormal laboratory value must be followed as described in Section 13.1.2. Based on observations from the Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range with activities from ~10 mg/m^2 to ≥ 60 mg/m^2. Based on observations in over 1000 patients treated with selinexor alone or in combination with other agents, fatigue, anorexia and weight loss associated with selinexor are highly variable and patient-specific. Therefore, in order to optimize specific antitumor activity and the patient's tolerability, we will allow for dose or schedule modifications as described in Section 12.2 below and in Table 9 (pre-specified dose/schedule modifications for AEs related to study treatment and supportive care/dose adjustment guidelines, respectively. Patients should also be treated aggressively with supportive care to reduce toxicities. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

For all ≥ Grade 3 hematological or Grade 3 non-hematological AEs that are NOT treatment related, after consultation with the Medical Monitor and at the discretion of the Investigator, dosing may be maintained provided that the patient can continue to take the agent by mouth.

For all Grade 4 non-hematologic toxicities, protocol-specified study treatment (selinexor/placebo) must be suspended and the Sponsor Medical Monitor consulted regarding options for continuation (ie requirements for resuming study treatment or permanent discontinuation).

Table 8: Pre-specified Dose/Schedule Modifications for Adverse Events Related to Selinexor/Placebo Treatment

	Dose/Schedule Modifications of Selinexor/Placebo[2]	
Dose Level[1]	**Total mg Selinexor/Placebo Per Week**	**Selinexor/Placebo Dose/Schedule**
Dose level 0 (starting dose)	120 mg	60 mg selinexor/placebo (3 tablets) twice weekly (Day 1, Day 3)
Dose level -1	100 mg	100 mg selinexor/placebo on Day 1 OR divided as 60 mg selinexor/placebo on Day 1 and 40 mg selinexor/placebo on Day 3
Dose level -2	80 mg	80 mg selinexor/placebo on Day 1 OR 40 mg selinexor/placebo on Days 1 and 3
Dose level -3	60 mg	60 mg selinexor/placebo on Day 1 OR divided as 40 mg selinexor/placebo on Day 1 and 20 mg selinexor/placebo on Day 3
Dose level -4	40 mg	40 mg selinexor/placebo on Day 1 OR 20 mg selinexor/placebo on Days 1 and 3

[1]For some AEs, dose interruption rather than reduction is recommended. See Table 9 for specific recommendations.
[2]All placebo doses will contain 0 mg of selinexor.

Table 9: Supportive Care and Dose Adjustment Guidelines for Selected Adverse Events

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Fatigue	
Grade 1	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8 g/dL (anemia Grade <3). Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting ≤7 days	As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.
Grade 2 lasting >7 days or Grade ≥3	Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for Hb <8 g/dL (Grade ≥3). Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level. Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.
Anorexia or Weight loss	
Grade 1 anorexia	Maintain dose. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®). For persistent symptoms, initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 1 weight loss Grade 2 anorexia	Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 2 weight loss Grade 3 anorexia, or Grade 3 weight loss	Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®) Initiate appetite stimulants as above,

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Nausea, Acute	
Grade 1 or 2	Maintain dose. Rule out other causes. Use standard additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. If persistent, use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia. Interrupt selinexor dosing until resolved to Grade ≤2 or baseline and reduce selinexor by 1 dose level. Patients with significant nausea/vomiting after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Provide supplemental oral and/or intravenous fluids if dehydration is present. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels <130-120 mmol/L without symptoms	Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). If (corrected) sodium is Grade ≤3 and continues to be asymptomatic, then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Rule out other causes including drug (eg, diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3 or 4	Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Rule out other causes including drug effects. For first occurrence: skip 1 dose and reduce selinexor by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents such as romiplostim 5 to 10 µg/kg SC weekly (preferred) or eltrombopag 100 to 150 mg QD. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, due to prior marrow-toxic therapy), or if there is thrombocytopenia Grade 2 to 4 at baseline, the Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored. Thrombopoietin stimulating agents are recommended.
Grade 4 without bleeding	Rule out other causes including drug effects. Interrupt selinexor until patient recovers to Grade 2 or baseline. Selinexor dosing may be reduced by 1 dose level (it is recommended to have only 1 dose modification per cycle) If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, due to prior marrow-toxic therapy), the Investigator in consultation with the Medical Monitor may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.
Grade ≥3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above.
Neutropenia	
Grade 3 or 4 neutropenia (afebrile) OR Febrile neutropenia	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils at least weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reinitiate selinexor therapy and colony stimulating factors per institutional guidelines. If recurrent, continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤2 or baseline levels, and reduce dose of selinexor 1 dose level.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Medical Monitor.	

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Tumor lysis syndrome	
If TLS risk factors are identified, provide prophylactic IV hydration and regular monitoring of hydration (especially when increasing the dose of selinexor), renal function, urine output, and clinical laboratory measures of interest for TLS (eg, phosphorus, potassium, calcium, LDH, uric acid). Consider administration of hypouricemic agents to reduce the risk of TLS. Hold selinexor in patient with hyperkalemia (≥7.0 mmol/L) and/or symptoms of hyperkalemia, an increase in uric acid, or other changes in biochemical blood parameters suggestive of TLS. Start IV hydration, and consider hypouricemic agent until levels return to normal. Selinexor can be reintroduced at the normal or reduced dose.	
Other selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Start treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Interrupt selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade ≥3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

IV: intravenous; NCCN: National Comprehensive Cancer Network; QD: once daily; PO: oral; SC: subcutaneous: TLS: tumor lysis syndrome.

[a]For all Grade ≥3 hematologic or non-hematologic AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.
[b]For all selinexor-related AE's, if the below prescribed dose reductions/interruptions result in a stabilization of ≥4 weeks, a re-escalation may be considered after approval from the Medical Monitor.
All dose modifications should be based on the worst preceding toxicity.
Note: When toxicities due to selinexor have returned to baseline levels or the patient has stabilized, the dose of selinexor may be re-escalated in consultation with the Medical Monitor.

12.2.2. Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney. Therefore, no dose alteration of selinexor/placebo is required in patients with renal dysfunction.

12.2.3. Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have treatment interrupted until the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

12.2.4. Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the guidelines. Dosing does not need to be interrupted in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (eg, urate) abnormalities that is reversible with standard interventions
- Isolated values of Grade ≥ 3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed.

12.2.4.1. Missed or Vomited Doses

Missed and Delayed Doses
A maximum of 2 doses may be given per week.

If a dose was missed, the schedule of that week should be altered to accommodate two doses in that week with at least 36 hr between two consecutive doses.

If a dose must be skipped (eg, due to recommendation of Investigator), the next dose will be taken as per schedule. Doses should not be administered less than 36 hr apart and all missed and delayed doses should be documented.

Vomited Doses
If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than one hour after dosing, it will still be considered a complete dose.

If a patient missed a full week of dosing for non-study treatment related events (eg, a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced. For example, if patient missed dosing from Cycle 2 Day 7 to Cycle 2 Day 14, then the patient will re-start dosing on Cycle 2 Day 15.

12.2.5. Supportive Care and Concomitant Treatments

12.2.5.1. Required Prophylactic Therapy with 5-HT3 Antagonists

In order to minimize nausea, unless contraindicated, all patients should receive 5-HT3 antagonists (8 mg or equivalent) starting before the first dose of blinded study treatment and continued 2-3 times daily thereafter, as needed. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists.

12.2.5.2. Supportive Care

General Supportive Care Recommendations

Supportive measures for optimal medical care should be provided during participation in this clinical study. Based on clinical observations 1672 adult patients in Karyopharm-sponsored studies as of 31 March 2018, the main adverse drug reactions are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding. Besides the required 5-HT3 prophylaxis (Section 12.2.5.1), supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments may be administered as described below:

a. Appetite stimulants: megesterol acetate at a dose of 80-400 mg daily.

b. Centrally acting agents, such as olanzapine (5.0 mg at bedtime or 2.5 mg twice daily). Additional options, including D2 antagonists, can be found in the NCCN CPGO for antiemesis and anorexia/cachexia (palliative care).

c. Neurokinin 1 receptor antagonist (NK1R antagonist): aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

Supportive Care and Dose Adjustment Recommendations for Specific Selinexor-Related Adverse Events

Please see detailed recommendations in Table 9: Supportive Care and Dose Adjustment Guidelines.

12.2.5.3. Concomitant Medication and Treatment

Concomitant medication includes any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings.

Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, AEs and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed.

Contraception Requirements

For females of childbearing potential, a negative serum hCG pregnancy test must be obtained at Screening within 3 days before the first dose of blinded study treatment. For females of childbearing potential who are proceeding to open-label selinexor, a negative serum hCG pregnancy test must be obtained at the EoBT Visit (or within 3 days before the first dose of open-label selinexor).

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby.

Female patients should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study.

Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 3 months following the last dose of study treatment.

Highly effective methods of contraception are listed in Section 13.3.1.

Use of Blood Products

During treatment, patients may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the PI, Sponsor, and Medical Monitor.

Appropriate anti-coagulation is allowed during the study (eg, low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF), pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines, prior to entry and throughout the study.

Glucocorticoid Therapy

Glucocorticoids ≤ 20 mg oral prednisone (or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (ie, asthma, irritable bowel disease, etc.), as needed, but patients should preferably have been on a stable dose for at least two weeks before study entry.

Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study treatment should be interrupted for two days before the start of palliative radiation therapy and 2 days after palliative radiation therapy. Treatment shall not be discontinued solely due to palliative radiation. (Radiation may be needed to treat the patient's liposarcoma and would require discontinuation of study treatment.)

12.3. Restrictions and Precautions

Fasting: Patients should maintain an adequate diet.

Diet: There are no dietary restrictions in this study. Patients should maintain adequate caloric and fluid intake.

Medications:

- **Acetaminophen** There are not any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with study treatment, EXCEPT on days on study treatment dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

- Patients should not take any products containing glutathione (GSH), S-adenosylmethionine (SAM), or N-acetylcysteine (NAC) during their participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 4 for a list of representative products. Patients must report all prescription and non-prescription medicines to the Investigator during this study.

12.4. Prohibited Medication

Acetaminophen must not exceed a total daily dose of 1 gram on days on dosing. On days when dose is not taken, there are no restrictions on the use of acetaminophen or acetaminophen-containing products

Patients should not take any products containing GSH, SAM, or NAC during their participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 4 for a list of representative products. Patients must report all prescription and non-prescription medicines to the Investigator during this study.

Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed.

Use of any immunosuppressive agents during the study must be approved by the Medical Monitor prior to use.

Other investigational agents should not be used in conjunction with study treatment but are allowed during Survival Follow-up.

12.5. Study Treatment Storage and Accountability

12.5.1. Drug Supply and Storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the selinexor IB.

The investigational drugs (selinexor and matching placebo) will be supplied by Karyopharm.

12.5.2. Study Treatment Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the Investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the monitor.

12.5.3. Disposal and Destruction

The study treatment supply can be destroyed at the investigative site or third party, as appropriate. Documentation of destruction is required if not undertaken by a Karyopharm third party facility.

12.6. Treatment Compliance

Compliance will be assessed by the Investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the source documentation. This information must be captured in the source document at each patient visit. The respective dose for investigational drug and any changes in dosing must be captured in the eCRF. Additionally, the exact time and date of dosing will be captured on the days of CCI sampling

13. SAFETY DEFINITIONS, RECORDING, AND REPORTING

13.1. Adverse Events

13.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Adverse event of special interest (AESI)*: Any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.
- *Serious adverse event (SAE)*: Any untoward medical occurrence that, at any dose, results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. (See Section 13.2.2 for additional information about SAE reporting.)

13.1.2. Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent will be recorded on the Adverse Events eCRF, regardless of whether dosing with study drug has commenced. AE monitoring should be continued for at least 30 days following the last dose of study treatment (ie, through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator). AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if AEs occur during the study. AEs may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in

severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

13.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (ie, are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment) should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline (at screening) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (severe per NCI CTCAE v. 4.03) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 13.1.1 and/or as per Investigator's discretion. A laboratory abnormality that results in a dose being interrupted or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

13.1.2.2. Other Adverse Events

13.1.2.2.1. Tumor Lysis Syndrome

As of May 2018, 8 TLS cases have been reported: 4 patients in Karyopharm-sponsored studies, 2 patients in Investigator-sponsored studies, and 2 patients in the expanded access program (compassionate use). Of the 8 patients, 5 had MM reported as their underlying cancer and 3 had hematological malignancies (including AML and acute lymphoblastic leukemia). The event onset latency ranged from 3 to 8 days (median 4 days). The total selinexor dose prior to event onset ranged from 40 mg to 320 mg (median 160 mg). The outcome was reported as recovered in 4 patients, not recovered in 2 patients, and the outcome was not reported in 2 patient. The Investigators assessed 7 of the events as related to selinexor. Of the 8 cases summarized above, there were 3 cases with Grade 5 TEAEs reported. The cause of death in each of these cases was reported as: respiratory failure secondary to advanced MM (Grade 5), sepsis (Grade 5), and respiratory failure, chemotherapy-induced cardiomyopathy and acute lymphoid leukemia (Grade 5). No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing expanded access program. Although the incidence of TLS is low (~0.3%), the causal relationship between selinexor treatment and TLS cannot be completely excluded. Early recognition of signs and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies for potential signs and symptoms of TLS are most relevant. See Table 9 for supportive care and Table 8 for selinexor dose modification guidance.

13.1.3. Adverse Event Severity

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 4.03 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If NCI CTCAE grading does not exist for an AE, the severity will be characterized as "mild," "moderate," "severe," or "life-threatening (corresponding to Grades 1 to 4) according to the following definitions:

- Grade 1 (Mild) events are usually transient and do not interfere with the patient's daily activities.
- Grade 2 (Moderate) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Grade 3 (Severe) events interrupt the patient's usual daily activities.
- Grade 4 events are Life-threatening.

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, 'severe' headache). This is not the same as a "serious" AE.

13.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as defined below.

- Not related: These events will lack a temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible. Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.
- Related: There is a temporal relationship of the event to the study treatment making a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

13.2. Serious Adverse Events

See Section 13.1.1 for the definition of an SAE. Please note that SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment must be reported (in addition to SAEs that occur after the first dose of study treatment).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (i.e., an overnight stay to facilitate 24-hour urine capture) or other medical procedures are not considered SAEs. However, a hospitalization meeting the regulatory definition for 'serious' is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital (eg, undesirable effects of any administered treatment) must be documented as an SAE.

Progression of the malignancy (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period (see Section 13.2.2). Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy, the finding should be reported as an AE or SAE, as appropriate, Section 13.1.1).

13.2.1. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the signing of the ICF until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the designated sponsor SAE Report Form in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator's site file.

All applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the SAE Report Form (in English).

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Attachment 1) for key data elements that are required for expedited reporting.

13.2.2. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department within *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

Fax: +1-617-334-7617 (USA)

+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

13.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

In addition, Karyopharm will communicate all cases of cerebellar toxicity, Grade 3 or higher, to regulatory authorities, central ethics committees (eg, IRBs), and Investigators, in the format of an expedited Safety Report, within 7 days of awareness of the event.

If required by local regulations, the Investigator is responsible for notifying his/her IRB or local ethics committee of all SAEs.

13.3. Procedures for Handling Special Situations

13.3.1. Pregnancy and Breastfeeding

Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

During both blinded and open-label treatment, female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

Highly effective methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:

  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

During both blinded and open-label treatment a pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the sponsor medical monitor of this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancies must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, regardless of whether the patient withdraws from the study or the study is completed, for 3 months after the patient receives his/her last dose of study treatment. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with selinexor-containing regimen.

13.3.2. Overdose, Abuse, Misuse, Medication Errors, and Occupational Exposure

All incidences of overdose, abuse, misuse, medication errors, and occupational exposure are required to be reported to Karyopharm Pharmacovigilance on an SAE report form, emailed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE.

13.3.2.1. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record and in the eCRF. Overdose is to be reported on an SAE report form to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

As selinexor is metabolized by GSH conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in overdose cases, if patients develop liver function test abnormalities, supportive measures such as SAM or other drugs that can replace GSH might be considered as part of the overall management plan.

13.3.2.2. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with any study treatment are to be reported on an SAE report form to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

13.3.2.3. Occupational Exposure

Occupational exposure is the exposure to a study treatment as a result of one's professional or non-professional occupation.

All occurrences of occupational exposure with any study treatment are to be reported on an SAE report form to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

14. STATISTICAL METHODS

A statistical analysis plan (SAP) will be finalized prior to database lock. Any deviation from the statistical plan will be described in the final report.

14.1. General Considerations

This is a multicenter randomized double-blind Phase 2-3 study of the SINE selinexor given orally in patients with advanced unresectable liposarcoma.

Enrollment in Phase 2 has been completed and the preplanned analysis of PFS (after 40 PFS events were observed) was performed. Details are provided in Section 14.1.1.1.

There was no break between Phase 2 and Phase 3 enrollment.

In Phase 3, patients will be randomized in a 2:1 fashion to receive selinexor (60 mg) or placebo. Randomization details are provided in Section 7.7.

Patients in the placebo arm who have PD while they are receiving blinded study treatment will be allowed to cross over to open-label selinexor (see Section 7.2.1).

Patients who are on blinded study treatment at the time of the primary PFS analysis at the end of Phase 3 may proceed as follows:

- Patients in the placebo arm may cross over to open-label selinexor.
- Patients in the selinexor arm will continue selinexor but as open-label treatment.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% CIs, unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized with Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs as well as percentage of censored observations.

14.1.1. Determination of Sample Size

14.1.1.1. Determination of Sample Size for Phase 2

Enrollment in Phase 2 has been completed.

Fifty-seven patients were randomized to selinexor or placebo in a 1:1 allocation. Randomization details are provided in Section 7.7.

The preplanned analysis of PFS (after 40 PFS events were observed) was performed and served as a guideline to inform the final design of the Phase 3 portion of the study.

A summary of the preliminary efficacy results for Phase 2 is provided in Section 4.3.2.

14.1.1.2. Determination of Sample Size for Phase 3

Per protocol, the Phase 3 sample size was re-evaluated based on the Phase 2 results. Sample size calculations were conducted under the following assumptions:

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Based on these assumptions, approximately 277 eligible patients will be randomized 2:1 to receive either selinexor (60 mg twice weekly) or placebo, respectively in a blinded manner to observe 209 PFS events. Sample size may be re-estimated based on the interim analysis (see Section 14.1.1.2.1).

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14.1.1.2.1. Phase 3 Interim Analysis After 105 PFS Events

The interim analysis was conducted at 108 PFS events and the results were reviewed by the DSMB on September 25, 2019. The purpose of this interim analysis was for sample size re-estimation with an early stopping boundary for efficacy.

An external, unblinded statistician calculated and presented to DSMB members

CCI

Based on the safety and efficacy data, the DSMB recommendation was continuation of the study with no change to safety monitoring and no sample size adjustment.

All sample size calculations were conducted using EAST Version 6.4 or higher (East 2016).

14.1.2. Blinding and Randomization

Study treatment will be administered in a blinded manner. Randomization will be performed across study sites within the stratification factors, in order to maintain the required 1:1 (selinexor:placebo in Phase 2) or 2:1 (selinexor:placebo in Phase 3) randomization. Randomization will be performed by a centralized system after confirmation of patient eligibility by the Sponsor (see Section 7.6 and Section 7.7).

14.2. Analysis Population

14.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all patients who are randomized to study treatment in Phase 3. This population will be used for primary analyses of efficacy. Patients will be analyzed in the treatment arm to which they were randomized.

14.2.2. Per-Protocol Population

The per-protocol (PP) population will consist of all patients in the ITT population who have no major protocol violations, including mis-randomizations, that would compromise the assessment of efficacy; this would include receipt of sufficient study treatment (80% compliance or more). Major violations will be determined independently of knowledge of response to study treatment. This population will be used for supportive inferences concerning efficacy. Patients will be analyzed according to the treatment actually received.

14.2.3. Safety Population

The safety population will consist of all patients who have received any amount of study treatment. Patients will be analyzed according to the treatment actually received.

14.3. Data Analysis and Presentation

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

14.3.1. Disposition of Patients

A tabulation of patient disposition will be presented including the number in each analysis population, the number in each analysis population, the number censored at each of the PFS and OS analyses, the number lost to follow-up, the number that withdrew, and reason(s) for withdrawal.

A by-patient listing of patient disposition information including the reason for study withdrawal, where applicable, will be presented.

14.3.2. Demographic Characteristics

Demographic characteristics will be summarized by treatment arm, as well as overall, and will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic or Latino origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each arm and the total sample. No formal hypothesis testing of treatment differences will be performed.

14.3.3. Baseline Characteristics and Medical History

Baseline characteristics include ECOG performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and number of prior therapies. Baseline data will be summarized for each treatment group using summary statistics; no formal hypothesis testing of treatment differences will be performed.

Medical history and physical examination results at baseline will be tabulated by treatment.

14.3.4. Efficacy Analysis

Disease assessments at the date of surgical or radiotherapy intervention may be censored in patients receiving such care, since these patients are receiving non-protocol specified therapy (ie, intervention), which may impact endpoint(s).

Based on the preplanned analysis of PFS by WHO and RECIST v. 1.1 Criteria in the Phase 2 portion of the study, the response criteria for the primary analysis (PFS) were changed from WHO to RECIST v. 1.1 Criteria in Version 4.0 of the protocol. Consequently, data from the Phase 2 portion of the study will be excluded from the final efficacy analysis in order to maintain statistical integrity and preserve overall Type I error rate.

14.3.4.1. Efficacy Analysis for Phase 2

All Phase 2 analyses will be conducted among Phase 2 patients only.

Phase 2 Primary Endpoint Analysis:

The preplanned analysis of PFS after 40 PFS events was conducted with an 11 August 2017 data cut with 49 eligible patients whose treatment assignments were available. Patients were analyzed in the treatment arm to which they were randomized. The preplanned PFS analysis was conducted by both WHO and RECIST v. 1.1 Criteria and served as a guideline to inform the final design of the Phase 3 portion of the study. See Section 4.3.2 for a summary of the preliminary data.

The primary endpoint PFS for Phase 2 is defined as the time from date of randomization until the first date of PD, per RECIST v. 1.1, or death due to any cause. Evaluation of the radiographic data for the PFS primary endpoint will be based on data from a scan review by the independent central reader.

The formal primary Phase 2 PFS analysis will be performed on all 56 eligible patients randomized to study treatment in Phase 2 when their treatment assignments are unblinded. Patients will be analyzed in the treatment arm to which they are randomized.

PFS data will be summarized with Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations. The stratified log-rank test will be used to compare the PFS distributions between treatment arms.

Phase 2 Secondary Endpoint Analysis

Secondary efficacy variables will include the following, according to the definitions described in the objectives and study endpoints:

- TTP on study treatment compared with TTP on the patient's last prior systemic therapy
- ORR
- DOR
- Tumor glucose metabolism, density, and size using FDG-PET and CT (diagnostic) after 6 weeks of treatment.

Secondary time-to-event endpoints will be analyzed using the stratified log-rank test as described above.

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[redacted]

Phase 2 Sample Size Calculation and Statistical Power:

Enrollment in Phase 2 has been completed. Details are provided in Section 14.1.1.1.

14.3.4.2. Efficacy Analysis for Phase 3

The final efficacy analysis will be conducted among Phase 3 patients only.

Stratified log-rank tests will be used to compare the distributions of time-to-event endpoints (PFS, OS, DOR, TTP) between the two arms using a 1-sided test and alpha=0.025 level of significance, and to estimate event free rate at various time points (eg, 1- year rate, 2-year rate, etc.) along with 95% CIs. Stratification factors for the stratified log-rank test are those that were used for randomization. The Cui, Hung, and Wang (CHW) method (Cui 1999) will be used to account for interim testing and possible sample-size re-estimation to preserve the overall Type I error rate.

14.3.4.2.1. Phase 3 Primary Endpoint Analysis

The primary PFS analysis will be performed on the ITT population for Phase 3 patients in and on the PP population as a supportive analysis. The stratified log-rank test will be used to test the null hypothesis that the PFS distributions are the same for both treatment groups versus the alternative hypothesis that the duration of PFS for the selinexor arm is longer than the placebo arm using a 1-sided test and alpha=0.025 level of significance, adjusted using the CHW method.

Multivariable Cox proportional hazards model will be used to assess PFS, adjusted for stratification factor and other prognostic covariates. Model assumptions will be examined, and in the presence of non-proportional predictors, stratification or including a time-dependent variable of the non-proportional predictors will be considered as appropriate.

14.3.4.2.2. Phase 3 Secondary Key and Efficacy Endpoint Analysis

Secondary Key Endpoint Analysis

Key secondary variables will include the following, assessed in hierarchical fashion in the order presented (to preserve the overall Type I error for the study), according to the definitions described in the objectives and study endpoints:

- OS for non-inferiority
- OS for superiority

OS endpoints will be analyzed using the stratified log-rank test as described above. In sensitivity analysis for OS, the 2-stage estimation method will be implemented to assess the impact of cross-over on the effect of selinexor on OS (Latimer 2017, Latimer 2018).

Secondary Efficacy Endpoint Analysis

The comparison of TTP in the current study to TTP on the most recent prior therapy will be performed as time-to-event using a stratified log-rank test stratified by patient IDs to account for correlation within patient and adjusted for treatment arm. Note that TTP for the current study may represent censored results, therefore, to minimize the impact of censoring, this analysis may require maturation of the TTP data beyond the required time at which the number of events for the primary PFS analysis at the end of Phase 3 have occurred.

Comparison of ORR between the two treatment arms will be performed using the Cochran-Mantel-Haenszel (CMH) $\chi 2$ or exact test as appropriate, stratified by the randomization stratification factors. For OS, an additional descriptive comparison of the median OS from the randomized selinexor arm will be made to historical OS to the extent feasible, to assist in providing the proper context for the ITT analysis of selinexor versus placebo.

DOR and PFS according to the Investigator will be analyzed using the stratified log rank test as described above.

QoL Analysis

The QoL endpoint as assessed by the EORTC QLQ-C30 and EuroQoL EQ-5D-5L questionnaires will be analyzed as a total score, using a linear mixed effects model with fixed effect of treatment arm, randomization stratification factors, and the baseline value for the parameter in the model as a covariate, as well as random effect of subjects and repeated measures over time points. For EORTC QLQ-C30 the transformed score will be used, calculated according to the *EORTC QLQ-C30 Scoring Manual*. For the EuroQoL EQ-5D-5L questionnaire, the overall health score will be used.

14.3.4.2.3. Phase 3 Exploratory Endpoint Analysis

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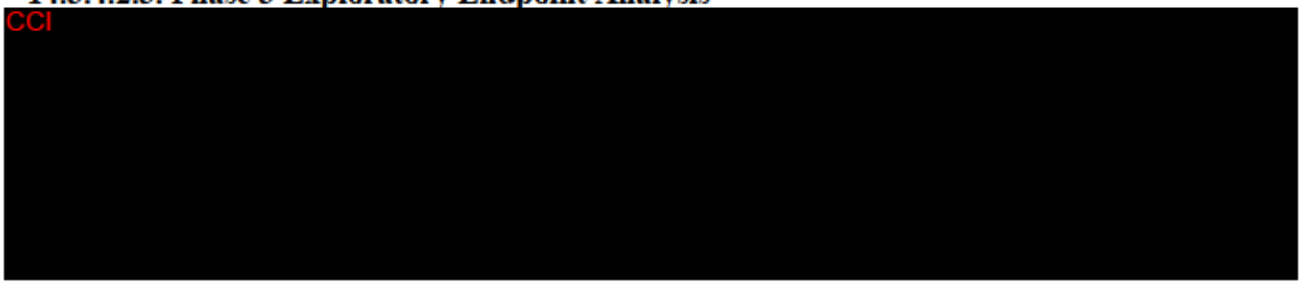

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14.3.6. Safety Analysis

Safety analyses will be performed on the Safety Population, which includes all patients who receive at least one dose of study treatment. Patients will be analyzed according to the treatment actually received.

Phase 2 safety data will be integrated with the Phase 3 safety data in the final safety analysis.

The safety and tolerability of selinexor will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations. CTCAE, v.4.03 will be used for grading of AEs. Investigators will provide their assessment as either related or not related to study treatment.

TEAEs, SAEs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment will be summarized by treatment group and in the overall safety population. TEAEs will be those that start or worsen on or after the first day of study treatment, through 30 days after last dose; related AEs will be those with an Investigator determination of related to treatment. Laboratory data will be analyzed by summary statistics over time, as well as by shift tables based on CTCAE v. 4.03 grades of severity.

14.3.6.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first dose of study treatment through 30 days following the last dose of study treatment, or any event considered drug-related by the Investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

AEs will be summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given AE (preferred term). The number and percentage of patients with any TEAE will be summarized for each treatment group, classified by SOC and preferred term. The number and percentage of patients with TEAEs assessed by the Investigator as related to treatment will also be tabulated. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner.

The causal relationship between the occurrence of an AE and the study treatment will be judged by the Investigator as either related or not related to study treatment. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

SAEs will also be tabulated.

All AEs (treatment-emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient and day on study. In addition, separate by-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

14.3.6.2. Laboratory Data

Clinical laboratory values will be expressed using conventional SI units.

For each treatment arm, the actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE criteria (eg, those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

14.3.6.3. Vital Signs and Physical Examinations

The actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on study evaluation will be summarized for vital signs.

By-patient listings of vital sign measurements will be presented in data listings.

Abnormal physical examination results at screening, and abnormal physical examination results (AEs) during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

14.3.6.4. Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

14.3.7. Procedures for Handling Missing Data

No imputation of missing efficacy data is planned for the primary analysis of efficacy endpoints. For patient reported QoL measurements, missing data will be handled as described in the *EORTC-QLQ-C30* and *EuroQoL EQ-5D-5L Scoring Manuals*. Additional sensitivity analyses will be done using the Jump to Reference (J2R) and last observation carried forward imputation approaches.

For time to event analyses, patients who have no efficacy evaluations will be considered as censored at time 0. For OS, patients will be censored on the date they were last known to be alive regardless of disease status.

For AEs, missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

14.4. Changes in the Conduct of the Study or Planned Analysis

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

14.5. Clinical Study Reports

A primary clinical study report (CSR) may be written based on all available patients' data following completion of the primary PFS analysis. The final CSR will be reported when all patients have completed the follow-up period, withdrawn consent, lost to follow-up, or have died.

15. DATA COLLECTION AND MANAGEMENT

15.1. Data Confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (eg has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

15.2. Site Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, Karyopharm personnel (or designated contract research organization) will review the protocol and CRFs with the Investigators and their staff. During the study, the monitor will visit the site regularly to check the completeness of patient records, accuracy of entries on the CRFs, adherence to the protocol and to Good Clinical Practice (GCP), progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The Investigator must also keep the original signed ICF (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Karyopharm monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Data Collection

This study will utilize Electronic Data Capture (EDC), the designated clinical site staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Clinical site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the Investigator staff.

The Investigator is responsible for assuring that the data entered into the eCRF is complete and accurate, and that entry and updates are performed in a timely manner.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

15.4. Database Management and Quality Control

Karyopharm personnel (or designated contract research organization) will review the eCRF data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, after discrepancies and missing values have been completed and the data have been verified to be complete and accurate, the database will be declared locked.

For EDC studies, after database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

16. ETHICAL AND ADMINISTRATIVE OBLIGATIONS

16.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations (CFR) Title 21), and with the ethical principles that originate from the Declaration of Helsinki.

16.2. Responsibilities of the Investigator and Good Clinical Practice

16.3. Institutional Review Boards/Independent Ethics Committees

The protocol and the proposed ICF(s) must be reviewed and approved by a properly constituted IRB/IEC before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Karyopharm monitors, auditors, designated agents of Karyopharm, IRBs/IECs and regulatory authorities as required.

16.4. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

In addition to the signing of informed consent by their parents, adolescent patients (permitted only in countries in which adolescents have been approved by the national/local regulatory/ethical authority) should sign written Assent Forms (witnessed, where required by law or regulation).

Informed consent for blinded study treatment must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). Informed consent for open-label selinexor must be obtained before any study-specific measures for open-label selinexor are conducted at the Open-label C1 D1 Visit. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

Karyopharm will provide to Investigators, in a separate document, proposed ICFs that are considered appropriate for this study and comply with the ICH GCP guideline and regulatory requirements. Any changes to the ICFs suggested by the Investigator must be agreed to by Karyopharm before submission to the IRB/IEC, and a copy of the approved version(s) must be provided to the Karyopharm after IRB/IEC approval.

Females of childbearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

16.5. Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Karyopharm. Signed ICFs and patient enrollment logs must be kept strictly confidential to enable patient identification at the site.

16.5.1. Study Documentation, Record Keeping and Retention of Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Karyopharm-sponsored study, each site will permit authorized representatives of Karyopharm and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

Data collection is the responsibility of the clinical study staff at the site, under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the eCRF system.

The Investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the clinical study unless Karyopharm provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

16.6. Publication of Study Protocol and Results

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and

finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.,

16.7. Discontinuation of the Study

Karyopharm reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

16.7.1. Audits and Inspections

Source data/documents must be available to inspections by Karyopharm or designee or Health Authorities.

16.8. Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR.

16.9. Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Karyopharm, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Karyopharm should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (eg, UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

17. REFERENCES

1. Altura RA, Olshefski RS, Jiang Y, Boué DR. Nuclear expression of survivin in paediatric ependymomas and choroid plexus tumours correlates with morphologic tumour grade. *British Journal of Cancer*. 2003;89(9):1743–1749.
2. Antonescu CR, Tschernyavsky SJ, Decuseara R, et al. Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: a molecular and clinicopathologic study of 82 cases. *Clin Cancer Res*. 2001 Dec;7(12):3977-87.
3. Azmi AS, Al-Katib A, Aboukameel A, et al. Selective inhibitors of nuclear export for the treatment of non-Hodgkin's lymphomas. *Haematol*. 2013(Jul);98(7):1098-1106.
4. Binh MB, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *Am J Surg Pathol*. 2005 Oct;29(10):1340-7.
5. Brown CJ, Dastidar SG, Quah ST, et al. C-terminal substitution of MDM2 interacting peptides modulates binding affinity by distinctive mechanisms. *PLoS One*. 2011;6(8):e24122.
6. Cheng Y, Holloway MP, Nguyen K, et al. XPO1 (CRM1) inhibition represses STAT3 activation to drive a survivin-dependent oncogenic switch in triple-negative breast cancer. *Mol Cancer Ther*. 2014 Mar;13(3):675-686.
7. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol*. 2007 May 1;25(13):1753-9.
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
9. Conyers R, Young S, Thomas DM. Review Article. Liposarcoma: molecular genetics and therapeutics. *Sarcoma* 2011. doi;10.1155/2011/483154.
10. Cousin S, Blay JY, Bertucci F, et al. Correlation between overall survival and growth modulation index in pre-treated sarcoma patients: a study from the French Sarcoma Group. *Ann Oncol.* 2013;24:2681-2685.
11. Crago AM, Singer S. Clinical and molecular approaches to well-differentiated and dedifferentiated liposarcoma. *Curr Opin Oncol*. 2011 Jul;23(4):373-378.
12. Crochiere ML, Kashyap T, Klebanov B, et al. Selinexor (KPT-330), a novel selective inhibitor of nuclear export (SINE), shows single agent efficacy against alveolar soft part sarcoma (ASPS) *in vivo*. *Cancer Res.* 2014 Apr;74(19 Suppl):5210.
13. Crozat A, Aman P, Mandahl N, Ron D. Fusion of CHOP to a novel RNA-binding protein in human myxoid liposarcoma. *Nature*. 1993 Jun 17;363(6430):640-4.

14. Cui L, Hung HMJ, and Wang, SJ. (1999), Modification of Sample Size in Group Sequential Trials. *Biometrics* 1999;55:853–857.

15. Dei Tos AP, Doglioni C, Piccinin S, et al. Coordinated expression and amplification of the MDM2, CDK4, and HMGI-C genes in atypical lipomatous tumours. *J Pathol*. 2000; Apr;190(5):531-6.

16. Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol.* 2013 (Jun 1);31(16):2024-2028.

17. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Medicine*. 1916;17:863-871.

18. East (2016) Software for design and monitoring of group sequential and adaptive trials; 6.4. Cytel, Inc., MA. www.cytel.com.

19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). *Eur J Cancer.* 2009:45:228-247.

20. Fragomeni RAS, Chung HW, Landesman Y, et al. CRM1 and BRAF inhibition synergize and induce tumor regression in BRAF-mutant melanoma. *Mol Cancer Ther*. 2013 Jul; 12(7):1171-1179.

21. Gobble RM, Qin L-X, Brill ER, et al. Expression profiling of liposarcoma yields a multigene predictor of patient outcome and identifies genes that contribute to liposarcomagenesis. *Cancer Res*. 2011;71(7):2697-2705.

22. Gounder, M.M., Zer, A., Tap, W.D., et al. 2016. Phase IB Study of Selinexor, a First-in-Class Inhibitor of Nuclear Export, in Patients With Advanced Refractory Bone or Soft Tissue Sarcoma. *J Clin Oncol* 2016; 34, 3166-3174.

23. Gray LJ, Bjelogrlic P, Appleyard VC, et al. Selective induction of apoptosis by leptomycin B in keratinocytes expressing HPV oncogenes. *Int. J. Cancer* 2007(Jun):120(11):2317-2324.

24. Kau TR, Silver PA. Nuclear transport as a target for cell growth. *Drug Discov Today*. 2003 Jan 15; 8(2):78-85.

25. Knapp AA, McManus PM, Bockstall K, Moroianu J. Identification of the nuclear localization and export signals of high risk HPV16 E7 oncoprotein. *Virology*. 2009 Jan:5; 383(1):60-68.

26. Kojima K, Kornblau SM, Ruvolo V, et al. Prognostic impact and targeting of CRM1 in acute myeloid leukemia. *Blood*. 2013;121(20):4166–4174.

27. Lain S, Xirodimas D, Lane DP. Accumulating active p53 in the nucleus by inhibition of nuclear export: a novel strategy to promote the p53 tumor suppressor function. *Exp Cell Res*. 1999;253(2):315-324.

28. Lapalombella R, Sun Q, Williams K, et al. Selective inhibitors of nuclear export show that CRM1/XPO1 is a target in chronic lymphocytic leukemia. *Blood*. 2012;120(23):4621–4634.

29. Latimer NR, Abrams KR, Lambert PC, et al. Adjusting for treatment switching in randomized controlled trials – a simulation study and a simplified two-stage method. *Stat Methods Med Res.* 2017;26(2):724–51.

30. Latimer NR, Abrams KR, Lambert PC, Morden JP, Crowther MJ. Assessing methods for dealing with treatment switching in clinical trials: a follow-up simulation study. *Stat Methods Med Res.* 2018;27(3):765–84.

31. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981 Jan 1;47(1):207-14.

32. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med.* 1987;317:1098.

33. Mutka SC, Yang WQ, Dong SD, et al. Identification of nuclear export inhibitors with potent anticancer activity *in vivo*. *Cancer Res*. 2009; 69(2):510-517.

34. Nair JS, Tap W, Vasudeva SD, et al. KPT-330, a selective small molecule inhibitor of nuclear export, is active in bone and soft tissue sarcoma. *Cancer Res*. 2013 Apr;73(8 Suppl):5210.

35. Nakayama R, Zhang YX, Czaplinski JT, et al. Preclinical activity of selinexor, an inhibitor of XPO1, in sarcoma. *Oncotarget*. 2016; 7:16581-16592.

36. Nakayama T, Toguchida J, Wadayama B, et al. MDM2 gene amplification in bone and soft-tissue tumors: Association with tumor progression in differentiated adipose-tissue tumors. *Int J Cancer*. 1995 Oct 20;64(5):342-6.

37. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue, Palliative Care, and Antiemesis. Available on line at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

38. Newlands ES, Rustin GJ, Brampton MH. Phase I trial of elactocin. *Br J Cancer*. 1996; 74(4):648-649.

39. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

40. Penel N, Demetri GD, Blay JY, et al. Growth modulation index as metric of clinical benefit assessment among advanced soft tissue sarcoma patients receiving trabectedin as a salvage therapy. *Ann Oncol*. 2013; 24:537-542.

41. Ranganathan P, Yu X, Na C, et al. Preclinical activity of a novel CRM1 inhibitor in acute myeloid leukemia. *Blood*. 2012;120(9):1765–1773.

42. Roberts BJ, Hamelehle KL, Sebolt JS, Leopold WR. *In vivo* and *in vitro* anticancer activity of the structurally novel and highly potent antibiotic CI-940 and its hydroxy analog (PD 114,721). Cancer *Chemother Pharmacol*. 1986;16(2):95-101.

43. Schmidt J, Braggio E, Kortuem KM, et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. *Leukemia*. 2013 Dec;27(12):2357-65.

44. Therasse PP, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000; 92:205-16.

45. Turner JG, Sullivan DM. CRM1-mediated nuclear export of proteins and drug resistance in cancer. Curr Med Chem. 2008;15(26):2648-55.

46. Turner JG, Dawson J, Sullivan DM. Nuclear export of proteins and drug resistance in cancer. *Biochem Pharmacol*. 2012;83(8):1021-1032.

47. Van der Watt PJ, Maske CP, Hendricks DT, et al. The Karyopherin proteins, CRM1 and Karyopherin beta1, are overexpressed in cervical cancer and are critical for cancer cell survival and proliferation. *Int J Cancer*. 2009 Apr 15;124(8):1829-40.

48. Walker CJ, Oaks JJ, Santhanam R, et al. Preclinical and clinical efficacy of XPO1/CRM1 inhibition by the karyopherin inhibitor KPT-330 in Ph+ leukemias. *Blood*. 2013; 22(17):3034–3044.

49. Xu D, Farmer A, Chook YM. Recognition of nuclear targeting signals by Karyopherin-beta proteins. *Curr Opin Struct Biol*. 2010;20(6):782-790.

18. APPENDICES

APPENDIX 1 World Health Organization (WHO) Tumor Response Criteria

(Adapted from Miller AB, et al., Reporting results of cancer treatment. Cancer. 1981;47:207 214.)

Characteristic	Criteria
Tumor Burden	No maximal number of lesions specified. No limitations specified per organ site
Measurability of lesions at baseline	1. *Measurable, bidimensional* (product of LD and greatest perpendicular diameter)[a] 2. *Nonmeasurable/evaluable* (eg, lymphangitic pulmonary metastases, abdominal masses)
Objective response	1. *Measurable disease* (change in sum of products of LDs and greatest perpendicular diameters, no maximum number of lesions specified) CR: disappearance of all known disease, confirmed at ≥ 4 wk PR: ≥ 50% decrease from baseline, confirmed at ≥ 4 wk. • Bidimensional: single lesion, greater than or equal to 50% decrease in tumor area (multiplication of longest diameter by the greatest perpendicular diameter); multiple lesions, a 50% decrease in the sum of the products of the perpendicular diameters of the multiple lesions. • Unidimensional: greater than or equal to 50% decrease in linear tumor measurement. • No new lesions or progression of any lesions. PD: ≥ 25% increase of one or more lesions, or appearance new lesions NC (SD): neither PR or PD criteria met 2. *Nonmeasurable disease* CR: disappearance of all unknown disease, confirmed at ≥ 4 wk PR: estimated decrease of 50%, confirmed at ≥ 4 wk PD: ≥ 25% in existent lesions of appearance of new lesions NC (SD): neither PR or PD criteria met 3. *Bone Metastases* CR: Complete disappearance of all lesions on x-ray or scan for at least four weeks. PR: Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least four weeks. PD: Increase in size of existent lesions or appearance of new lesions. NC (SD): Because of the slow response of bone lesions, the designation of no change should not be applied until ≥ 8weeks have passed from start of therapy. Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.

Characteristic	Criteria
Overall response	1. Best response recorded in measurable disease 2. NC in nonmeasurable lesions will reduce a CR in measurable lesions to an overall PR 3. NC in nonmeasurable lesions will not reduce a PR in measurable lesions
Duration of response	1. *CR*: From date CR criteria first met to date PD first noted. 2. *Overall Response*: From date of treatment start to date PD first noted. 3. In patients who only achieve a PR, only the period of overall response should be recorded

LD = longest diameter; CR = complete response; PR = partial response; PD = progressive disease; NC = no change; SD = stable disease.

[a]Lesions that can be measured only unidimensionally are considered measurable (eg, mediastinal adenopathy, malignant hepatomegaly).

APPENDIX 2 RECIST Version 1.1

(Modified from Eisenhauer 2009)

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to < 10mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD)

Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD)

At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions will also constitute PD.

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded since the treatment started.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Evaluation of Best Overall Response – Patient with Target (+/- non-target) disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR-Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Best Overall Response – Patient with Non-Target Disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR-Non-PD	No	Non-CR/Non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Method of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT (preferred) or MRI

CT (preferred) and MRI imaging might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be an adverse drug reaction of the treatment) and/or PD.

APPENDIX 3 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale Assessment

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655

APPENDIX 4 Glutathione (GSH)-, S-Adenosylmethionine (SAM)-, OR N-Acetylcysteine (NAC)-Containing Products (Representative List)

Glutathione		**N-acetylcysteine (NAC)**		**S-adenosylmethionine (SAM)**	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	glutathione	Antidote for acetaminophen overdose	acetylcysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	glutathione L-cysteine vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		
(Mega-) Liposomal Glutathione	glutathione				
Lypospheric GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				