Clinical Study Protocol

SELNET-7-1 (SeliSarc)

Phase I/II randomized clinical trial of selinexor plus gemcitabine in selected advanced soft-tissue sarcomas

Study Number:	SELNET-7-1
Study Phase:	Phase I/II
Product Name(s):	Selinexor (KPT-330), gemcitabine
EudraCT Number:	2019-000652-33
IST Identifier:	IST-319
Indication:	Advanced soft-tissue sarcomas
Sponsor:	Asociación Europea y Latinoamericana Selnet para la Investigación en Sarcomas Calle de la Sierra de Pajarejo, 5, 5A 28023, Madrid, Spain
Sponsor-Investigator:	Dr. Javier Martín Broto – Hospital Universitario Fundación Jiménez Díaz (Madrid)
Collaborators:	• Grupo Español de Investigación en Sarcomas (GEIS) • Sarcoma as a model to improve diagnosis and clinical care of rare tumors through a European and Latin American multidisciplinary network (SELNET)
Selinexor Supplier/Drug Supplier and Funding Source:	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Additional Funding Sources:	None
Protocol Version and Date:	Version 5.0 of 17 February 2023

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.

INVESTIGATORS' AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. SELNET-7-1 version 5.0 and dated 17 February 2023 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices, ICH E6, and applicable EMA regulatory requirements.

Sponsor-Investigator's Signature: _____

Investigator's Name: **JAVIER MARTÍN BROTO**

Institution: **Hospital Universitario Fundación Jiménez Díaz**

Date:

Investigator's Signature: _____

Investigator's Name:

Institution:

Date:

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AV	arterioventricular
BIW	twice weekly
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence Interval
cm	centimeter
CR	complete remission
CRM1	chromosomal region maintenance protein 1
CSR	clinical study report
CST	Company-Sponsored Trial
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EAP	Expanded Access Program
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EU	European Union
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage-colony stimulating factor
GRP	growth regulatory protein
GSH	glutathione
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr	hour
HTLV	human T-cell lymphotropic virus
IC_{50}	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
eIF4E	mRNA cap-binding protein eukaryotic translation factor 4E
IL	interleukin
INR	international normalization ratio
IR	intermediate risk
IRB	Institutional Review Board
ISS	International Staging System
IST	Investigator-Sponsored Trial
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
kg	kilogram
LDH	lactic dehydrogenase
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minute
miRNA	microRNA
mL	milliliter
mITT	modified Intent-to-Treat
MM	multiple myeloma
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	minor response
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NHL	non-Hodgkin’s lymphoma
NK1R	neurokinin 1 receptor
NPC	nuclear pore complex
ORR	overall response rate (sCR + CR + VGPR + PR)

Abbreviation	Definition
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamics
PE	physical examination
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PP	per protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QW	once weekly
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	Relapsed/Refractory
RT	Richter's transformation
SAE	serious adverse event
SAM	S-adenosylmethionine
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SINE	selective inhibitor of nuclear export
SOC	standard of care; system organ class
SOP	standard operating procedure
STD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
TRAE	treatment-related adverse event
TSP	tumor suppressor protein
TTP	time to progression
ULN	upper limit of normal
US	United States
VGPR	very good partial response
WBC	white blood cell
XPO1	Exportin 1

1 PROTOCOL SYNOPSIS

Sponsor-Investigator/Institution: Asociación Europea y Latinoamericana Selnet para la Investigación en Sarcomas	**Investigational Product (s):** Selinexor (KPT-330), gemcitabine	**Developmental Phase:** Phase I/II
Title of Study: Phase I/II randomized clinical trial of selinexor plus gemcitabine in selected advanced soft-tissue sarcomas		
Protocol Number: SELNET-7-1 (SeliSarc)		
Protocol version: 5.0 of 17 February 2023		
EudraCT number: 2019-000652-33		
IST Identifier: IST-319		
Indication: Advanced soft-tissue sarcoma		

Rationale for the use of selinexor in sarcomas

Exportin-1 (XPO-1, also known as CRM1) is the main mediator of nuclear export in many cell types and it mediates leucine-rich nuclear export signal (NES)-dependent protein transport. Inhibition of XPO1-mediated nuclear export blocks the *''escape''* of multiple tumour suppressor proteins, turning off oncogenic signals and enhancing tumour suppression. Besides, XPO-1 overexpression has been associated with therapy resistance, reduced apoptosis and poor survival in solid tumours(1). In line with this observation, XPO-1 was described to be overexpressed in osteosarcoma(2), where it is associated with reduced progression-free survival (PFS) and overall survival (OS)(3). XPO-1 is the main target of the small molecule inhibitor selinexor(4).

Selinexor (KPT-330) is a *first-in-class*, highly specific, slowly reversible and orally bioavailable small-molecule inhibitor of XPO-1 that is approved in the USA for the treatment of patients with RRMM and DLBCL. This molecule was tested in a phase I clinical trial, in patients with advanced metastatic solid tumours, showing evident clinical benefit, as well as an acceptable safety profile. In this trial, among the 157 patients evaluated for efficacy, 1 patient had a complete response (CR), 6 patients had partial responses (PR) and 67 patients had stable disease (SD), with 27 patients reaching the stabilization at least for 4 months. In the translational study associated with this trial selinexor reduced cell proliferation and increased apoptosis, due to the nuclear accumulation of tumour suppressor proteins, such as p53 and FOXO3(5). Likewise, selinexor was tested in patients with advanced sarcomas, including STS and bone sarcoma, showing 21 patients SD, alongside with decreased tumour load (ranging from 5 – 23%) in 7 of them. The median PFS of selinexor was 4.2 months and 3.7 months, for patients with progressive liposarcoma or leiomyosarcoma, respectively. Selinexor pharmacokinetics was similar to previously published data and it was observed a better absorption in the fed state compared to fasting. Selinexor bioavailability was not affected by fat content. Biopsies taken pre- and post-treatment with selinexor (n=6) showed target inhibition of XPO-1, nuclear accumulation of p53, apoptosis by increased cleaved caspase, remarkable reduction in Ki-67 and cell content, and increased stroma. Furthermore, oral selinexor administered twice a week was well tolerated with manageable toxicities(6). Based on this data, a randomized, multicentre, double-blind, placebo-controlled

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phase II/III clinical trial, with oral selinexor, in patients with advanced unresectable dedifferentiated liposarcoma (DDLPS) (SEAL -NCT02606461) was performed.

Phase II-III data has been reported with the PFS being significantly longer with selinexor versus placebo: hazard ratio (HR) 0.70 (95% CI, 0.52 to 0.95; one-sided P = .011; medians 2.8 v 2.1 months), as was time to next treatment: HR 0.50 (95% CI, 0.37 to 0.66; one-sided P < .0001; medians 5.8 v 3.2 months)(7).

Furthermore, pre-clinical studies confirmed that selinexor targets the nuclear exportation of several tumour suppressor proteins, including APC, p21, p27, p53, Rb, FOXO proteins and FAS(4,8), sustaining the observations withdrawn from the clinical trials-associated translational studies. Selinexor avoids also survivin exportation to the cytoplasm, blocking its anti-apoptotic function(9). In general, the inhibition of nuclear exportation of all these proteins leads to reduced cell proliferation and increased apoptosis, in numerous types of solid tumours, including sarcoma(10). In sarcomas, selinexor proved to have a potent *in vitro* and *in vivo* activity, mostly by inducing G1 cell cycle arrest. Remarkably, in liposarcoma cell lines with *MDM2* and *CDK4* amplification, selinexor induced cell cycle arrest and apoptosis, independently of *TP53* expression or mutation. Nonetheless, p53 and p21 protein expression increased, suggesting a post-transcriptional regulatory effect(10). Of note, selinexor synergizes with Gemcitabine, in pancreatic cancer, enhancing apoptosis and inhibiting tumour growth.

Gemcitabine in the treatment of soft-tissue sarcoma

Gemcitabine is a deoxycytidine analogue used in the treatment of a large spectrum of tumours, including STS(11). This drug accumulates intracellularly, mainly through the nucleoside transporter hENT1, and undergoes a series of phosphorylations in order to become active. Then, Gemcitabine-tri-phosphorylated acts as a competitive substrate of deoxycytidine triphosphate, being incorporated, irreversibly and undetectably into DNA during replication. This incorporation inhibits DNA elongation, causing a solid G_1 cell cycle arrest and increasing cell death by apoptosis(12). Besides, Gemcitabine seems to enhance the activity of Fas/ Fas ligand pathway, inducing cell death and tumour regression, by an independent pathway(13). The form of gemcitabine with two phosphates attached (dFdCDP) also has activity; it inhibits the enzyme ribonucleotide reductase, which is needed to create new nucleotides. The lack of nucleotides drives the cell to uptake more of the components it needs to make nucleotides from outside the cell, which increases uptake of gemcitabine as well.

Nowadays, and in the metastatic setting of STS, gemcitabine is administrated as a single agent or in combination with docetaxel, showing special activity in leiomyosarcoma. Additionally, several clinical studies with gemcitabine in combination with other cytotoxic drugs, including dacarbazine(14) and paclitaxel(15), showed synergistic activity and proved the usefulness of gemcitabine in STS treatment. Nevertheless, gemcitabine was reported to be rapidly inactivated by cytidine deaminase (CDA) and numerous tumours developed resistance against this drug due to the loss of its transporters, lack of gemcitabine phosphorylation or by triggering gemcitabine-dependent angiogenesis. All these mechanisms of chemoresistance may justify the limited therapeutic effect of gemcitabine and therefore, new strategies are urgently required in order to improve intracellular gemcitabine and to potentiate its activity in STS. A quite stimulating and

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promising strategy is the combination of gemcitabine with selinexor, since this combination was shown to be synergistic in pancreatic cancer.

Rationale for the combination gemcitabine plus selinexor

A relevant finding derived from preclinical experiments is that Selinexor reduces mRNA and protein expression of DNA damage repair (DDR) gene products. In relation with that, selinexor has shown to be synergistic with DNA damage drugs. Moreover, eIF4e, an essential nuclear export of various proto-oncogenes as c-Myc, is thought to be involved since c-Myc regulates the transcription of other DNA damage repair genes. This biological effect of selinexor would prevent different repair signalling allowing rationale for combination with DNA damage agents as gemcitabine(16). *In vitro* experiments in sarcoma and other tumor cells have shown synergistic action with the combination of single (docetaxel, or gemcitabine) and double (cisplatin) strand breaks agents along with selinexor. These combinations showed increased cell death by cleaved caspase-3 and reduction of DNA damaged repair gene products. *In vivo* experiments, the combination of single strand break agent as docetaxel plus selinexor lowered DNA damage repair proteins expression while cisplatin or docetaxel did not produce DDR proteins reduction. Selinexor showed reduction in a wide range of DDR gene products as Rad51, CHEK1, MLH1, MSH2, MSH6, PMS2 and PARP1 and this effect was observed in several tumor types.

Importantly, the sequence turned out to be relevant and cytotoxicity was higher if DNA damage agent was first administered and then selinexor. Authors stated this could be related to the cycle arrest induced by selinexor, this would eventually prevent cells to enter in phase S which means less chemosensitivity.

Preclinical experiments *in vitro* and *in vivo* in pancreatic tumor models have shown synergistic action with the combination of gemcitabine and selinexor. In addition to the previous mentioned mechanism involving the DDR genes inhibition, authors found that nuclear retention of p27, the proapoptotic bax protein and the anti-apoptotic surviving, could explain the synergy seen between gemcitabine and selinexor(17).

Gemcitabine alone produces limited cytotoxicity which is in accordance with lack of apoptotic cell death seen in preclinical experiments with this drug in some cell lines. However, gemcitabine induces a significant increase of γH2AX immunoreactivity demonstrating DNA damage. Thus it is strategic to combine it with other drugs, as selinexor, that could increase apoptotic signalling through the blockade of DNA repair genes(16).

Nevertheless, gemcitabine can induce a p53 dependent apoptosis which is in relation to accumulation of pro-apoptotic proteins as bax. Selinexor could stabilize bax through the nuclear accumulation of nucleophosmin(18). This is another possible synergistic point with selinexor, through the retention of p53 in the nuclei(19).

Finally, FAS pathway can represent another potential synergistic mechanism since gemcitabine sensitizes FAS activation(13) and selinexor contributes as well to FAS activation(20). FAS could be a relevant prognostic factor in osteosarcoma(21) and in soft tissue sarcomas(22).

Taking together the previous information, we hypothesize that selinexor will have a synergistic effect with gemcitabine in sarcoma patients. The phase I trial will permit the selection of the best

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dose level for the phase II. The determination of predictive biomarkers to this combination will benefit the selection of future patients and will provide with the mechanism underlying the activity of selinexor plus gemcitabine.

Gemcitabine administration in sarcomas has been diverse. Mainly used in combination with doses ranging from 675 to 1800 mg/m^2 and infusion rates ranging from 30 minutes and 10 mg/m^2/min. This latter being the most frequently recommended. The GEIS scheme administered 1800 mg/m^2 of gemcitabine (10 mg/m^2/min) along with 500 mg/m^2 of dacarbazine every 2 weeks in advanced and progressing STS. Grade 3-4 neutropenia, anemia and thrombocytopenia was observed in 48%, 4% and 6 % respectively(15). In osteosarcoma patients progressing to standard treatments gemcitabine was administered at 800 mg/m^2/d on days 1 and 8 of cycle, (10 mg/m^2/min) along with rapamycin 5 mg (on a daily dose). With this scheme, the grade 3-4 neutropenia, anemia and thrombocytopenia were seen in 37%, 23% and 20% respectively.[28] The original combination of gemcitabine 900 mg/m^2/d on days 1 and 8 of cycle (10 mg/m^2/min) plus docetaxel 75 mg/m^2 on day 8 in advanced STS reported G3-4 neutropenia, anemia and thrombocytopenia was observed in 16%, 7% and 40% respectively(23). Finally, in the British randomized phase III trial, gemcitabine was administered at 675 mg/m^2/d on days 1 and 8 of cycle (90 min of infusion rate) along with docetaxel 75 mg/m^2 on day 8 of each cycle. The hematological grade 3-4 toxicity reported was neutropenia 20%, anemia 6% and thrombocytopenia 0%). Then the total dose per cycle is related with the extent of grade 3-4 hematological toxicity(24).

We estimate that the starting dose of 1000 mg/m^2 for gemcitabine is appropriate and we have considered two different infusion-rates for this dose in order to be more cautious in the dose-levels design for the phase I part. As thrombocytopenia could be the most frequent hematological toxicity for selinexor we estimate that the first level will be safe, but still, a -1 dose-level was considered.

Objectives and Endpoints:

Objectives	Endpoints
PHASE I	
Primary	
• To determine the maximum tolerated dose (MTD) or the recommended dose for phase II of selinexor plus gemcitabine.	• Based on Dose Limiting Toxicities (DLTs) observed during first cycle (day 1-21).
Secondary	
• To evaluate the safety profile according to CTCAE 5.0.	• Safety profile of the experimental treatment, through assessment of adverse event type,

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	incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 5.0
• To determine the overall response rate (ORR).	• Overall Response Rate (ORR): ORR is defined as the number of subjects with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) divided by the number of response evaluable subjects (according to RECIST 1.1 criteria).
• To evaluate efficacy according to Choi response.	• Efficacy measured through tumor response according to Choi criteria. The evaluation criteria will be based on the identification of target lesions in baseline and their follow-up until tumor progression.
• To evaluate the patients's quality of life (QoL).	• Quality of life will be measured with EORTC QLQ-C30.
PHASE II	
Primary	
• To evaluate the efficacy of the selinexor plus gemcitabine combination as measured by the progression-free survival rate (PFSR) at 6 months in patients with selected advanced soft-tissue sarcomas.	• Progression-free survival rate (PFSR): Efficacy measured by the PFSR at 6 months according to RECIST 1.1. PFSR at 6 months is defined as the percentage of patients who did not experience progression or death due to any cause since the first dose of experimental treatment until month 6 after treatment initiation.
Secondary	
• To evaluate overall survival (OS).	• Overall survival (OS): OS is defined as the time between the date of first dose and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive.

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• To evaluate efficacy according to Choi response.	• Efficacy measured through tumor response according to Choi criteria. The evaluation criteria will be based on the identification of target lesions in baseline and their follow-up until tumor progression.
• To evaluate the safety profile according to CTCAE 5.0.	• Safety profile of the experimental treatment, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 5.0.
• To evaluate the outcome of post protocol treatments.	• Clinical outcomes of post protocol treatments assessed by observation of such treatments in follow-up stage. Clinical outcomes of post protocol treatments assessed by observation of such treatments in follow-up stage.
• To evaluate the patients's quality of life (QoL)	• Quality of life will be measured with EORTC QLQ-C30.
Exploratory: translational study (Phase I and II)	
• To determine potential predictive biomarkers to the combination of selinexor plus gemcitabine in sarcomas in tumor blocks and peripheral blood samples.	• Potential biomarkers will be determined using gene expression analysis with HTG technology, protein expression with immunohistochemistry and analysis of plasmatic factors (ProcartaPlex Immunoassay).
• To understand the mechanisms and the cell signaling pathways related with response or resistance to the combination in FFPE tumor samples.	• Correlation of the different identified biomarkers with outcome will be analyzed.

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• To validate the translational study results in pre-clinical models of sarcoma.	• *In vitro* studies will be done with different STS cell lines.

Overall Study Design:

Phase I-II, non-randomized, single-arm, open-label, multicenter, international clinical trial.
Patients with advanced soft-tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor) will receive selinexor in combination with gemcitabine.
In the Phase I part safety and toxicity of the combination will be assessed using a 3+3 design. The recommended dose for the Phase II will be determined.

In the Phase II part there will be 2 different cohorts:

Cohort 1: Leiomyosarcoma (LMS)
Cohort 2: Malignant peripheral nerve sheath tumor (MPNST)

Number of Patients (planned): Phase I part 4-18; Phase II: 82 patients (88 including non-evaluable)

Study Population:

Patients with selected advanced (metastatic or locally advanced unresectable) soft-tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor).

Inclusion Criteria (Phase II):

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

1. Patients must provide written informed consent prior to performance of any study-specific procedures and must be willing to comply with treatment and follow-up. Informed consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient's routine clinical management (e.g. imaging tests), obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol.
2. Age: 18-80 years.
3. Histologic diagnosis of soft tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor) confirmed by central pathology review prior to enrollment with an archive tumor sample. A fresh paraffin embedded tumor tissue block must be provided for all subjects for biomarker analysis before and (when feasible) after treatment with investigational products.
4. Metastatic/advanced disease in progression in the last 6 months.

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5. Patients have previously received at least one previous line of systemic therapy.
6. Measurable disease according to RECIST 1.1 criteria.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
8. Adequate hepatic, renal, cardiac, and hematologic function.
9. Laboratory tests as follows:
    - Absolute neutrophil count ≥ 1,500/mm³
    - Platelet count ≥ 100,000/mm³
    - Bilirubin ≤ 1.5 mg/dL
    - AST and ALT ≤ 2.5 times upper limit of normal
    - Creatinine ≤ 1.5 mg/dL
10. Left ventricular ejection fraction ≥ 50% by echocardiogram or MUGA scan.
11. Females of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to enrollment and agree to use birth control measures during study treatment and for 3 months after its completion. Patients must not be pregnant or nursing at study entry. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

Exclusion Criteria (Phase II):

Patients meeting any of the following exclusion criteria are not eligible for this study:

1. Three or more systemic treatment lines (including both chemotherapy and targeted therapy) for advanced disease (localized unresectable or metastatic).
2. Patients who have received any other anti-cancer therapy or investigational product in the last 21 days prior to enrollment.
3. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer, adequately treated cervical carcinoma in situ, superficial bladder carcinoma) during the 5 years prior to randomization. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
4. Prior selinexor or another XPO1 inhibitor treatment.
5. Administration of a previous gemcitabine-containing treatment.
6. Any concurrent medical condition or disease (e.g. uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.

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7. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to Cycle 1 Day 1 (C1D1). Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
8. Pregnant or breastfeeding females.
9. Body surface area (BSA) <1.4 m^2 at baseline, calculated by the Du Bois(25) or Mosteller(26) method.
10. Life expectancy of less than 3 months.
11. Major surgery within 4 weeks prior to C1D1.
12. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or dysfunction that could interfere with absorption of study treatment.
13. 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).
14. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent.
15. Presence of brain or central nervous system metastases, unless they are controlled (patients with treated and stable metastasis are eligible).

Study Treatment/Treatment Groups, Dose, and Mode of Administration:

Selinexor

Pharmaceutical form: Tablet (20 mg tablets)
Route of administration: Oral use.

Gemcitabine

Pharmaceutical form: Concentrate for solution for infusion
Route of administration: Intravenous use.

Predefined dose levels (Phase I part)

Dose level	Selinexor weekly (given on days 1, 8 and 15 of each cycle)	Gemcitabine weekly (given on days 1, 8 of each cycle)
-1	60 mg	800 mg/m^2 (30 min)
1	60 mg	1000 mg/m^2 (30 min)
2	60 mg	1000 mg/m^2 (10 mg/m^2/min)
3	60 mg	1200 mg/m^2 (10 mg/m^2/min)
4	80 mg	1200 mg/m^2 (10 mg/m^2/min)

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Phase II:
For gemcitabine + selinexor:

- Selinexor will be given at 60 mg once per week orally days 1, 8 and 15 every 21 days
- Gemcitabine will be given at the dose 1200 mg/m^2 (10 mg/m^2/min) days 1 and 8 every 21 days

Cycles of 21 days.
Treatment cycles are unlimited and given until progression, unacceptable toxicity, or investigator's or patient's decision.

Duration of Treatment and Follow-up:

Phase I:

- Administrative start-up: 6 months
- First subject first visit (FSFV): November 2020
- Total recruitment period duration: 20 months
- Follow-up period (last patient in): 12 months

Phase II:

- First subject first visit (FSFV): April 2023
- Total recruitment period duration: 30 months
- Follow-up period (last patient in): 6 months
- Estimated end of study date: May 2026

Statistical Methods:

Phase I: 3+3 design
Phase II: Sample size for LMS and MPNST cohorts were calculated using Simon two-stage optimal designs (Section 13.2).

2 STUDY SCHEMATICS AND SCHEDULE OF ASSESSMENTS AND DOSING

Table 1: Schedule of Study Activities and Assessments (PHASE I)

Activity/Assessment	Screening [a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
ICF[c]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Central diagnostic confirmation in archived tumor[d]	X											
Clinical Assessments												
Height	X											
Weight	X	X	X	X	X			X			X	
Body Surface Area (BSA)[e]	X											
Vital signs[f]	X	X	X	X	X			X			X	
ECOG	X	X	X	X	X	X	X	X			X	
Physical examination	X	X	X	X	X	X	X	X			X	
12-lead ECG[g]	X				Perform if clinically indicated						X	
Echocardiogram or MUGA	X										X	
Laboratory Assessments												
CBC with differential[h]	X	X	X	X	X	X	X	X	X		X	
Complete serum chemistry[h]	X	X	X	X	X	X	X	X	X		X	
Coagulation test	X	X			X			X			X	

Activity/Assessment	Screening [a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
Urinalysis	X	X			X			X				
Pregnancy test (if applicable)[i]	X				X			X (even # cycles only)			X	
DLT period assessment												
Study samples[j]												
Tumor sample for diagnosis confirmation	X											
Tumor for translational research	X										X	
Blood for translational research	X	At each radiological assessment (every 6 weeks during the first 6 months of treatment, every 8 weeks after the first 6 months of treatment)									X	
Disease Assessments												
Scans (e.g. CT/MRI)for response assessments[k]	X	Every 6 weeks during the first 6 months of treatment, every 8 weeks after the first 6 months of treatment									X	X
Administration of selinexor		Days 1, 8, 15 every cycle										
Administration of gemcitabine		Days 1 and 8 every cycle										
Adverse events recording[l]	X	Throughout										
SAE reporting												
Concomitant medication recording	X	Throughout										
Nutritional consultation[m]	X	Perform if clinically indicated										
Telephone contact												X
Collection of information regarding antineoplastic therapy used after EoT												X

Activity/Assessment	Screening [a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
Quality of Life assessment[n]		X			X			Every 3 cycles (day 1)			X	

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; MUGA: multiple gated acquisition; PE: physical examination; SAE: serious adverse event

a) Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.
b) After discontinuation of selinexor if feasible and clinically indicated, evaluations should be performed every 2 months (8 weeks) for patients who have not progressed and every 3 months in progressed patients to assess durability of response. If sarcoma evaluations cannot be performed, at a minimum, a telephone call will be made to the patient (or the patient's family) to assess the survival status, status of the patient's sarcoma, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment (see Section 8.5.2).
c) ICF must be signed before any study-specific procedures are performed.
d) Central pathological confirmation: one archived formalin-fixed paraffin-embedded (FFPE) tumor block sample will be sent for central pathological confirmation before treatment initiation.
e) BSA should be calculated during Screening and as needed during the study.
f) Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination.
g) Patients must rest for at least 5 minutes prior to the ECG recording.
h) CBC with differential and complete serum chemistry will be performed on days 1, 8, and 15 on Cycle 1 and 2 and on days 1 and 8 in the rest of cycles.*=Limited serum chemistry: WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. Urea (mg/dL) = Blood urea nitrogen (mg/dL) × 2.14. Microscopy will only be performed if clinically indicated.
i) For females of childbearing potential; negative serum hCG or urine pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of even Cycles ≥2 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG or urine). Pregnancy testing may also be performed as clinically indicated during the study.

j) Translational samples: Tumor: One recent (not archived) (FFPE) tumor block sample mandatorily collected at baseline (minimum 6 tru-cuts); Blood: 2 10mL EDTA tubes of peripheral blood within 72 hours prior to starting treatment (baseline), two 10mL EDTA within ±72 h of each radiological assessment (TC scan, MRI) and two 10mL EDTA tubes of peripheral blood at the end of treatment (within 72 hours after progressive disease is documented). Another two 10mL EDTA tubes of peripheral blood when tumor response is observed. Plasma will be separated by a Ficoll-Paque protocol. Mononuclear cells will be also collected for further analysis.

k) CT scans or MRI will be performed every 6 weeks (±7 days). CT Scans will be performed every 8 weeks (±7 days) after 6 months of treatment. During Follow up CT scan or MRI will be done every 8 weeks (±7 days) if patient did not progress to assess durability of response. Screening CT Scan/MRI have to be done within 28 days prior treatment initiation.

l) All AEs that begin or worsen after the patient has provided informed consent will be recorded. SAEs must be reported to GEIS within 24 hours of first awareness.

m) Patients must be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study nurse and can be done on a phone call.

n) Quality of Life will be assessed with EORTC QLQ-C30. It will be performed on C1D1, C2D1 and then every 3 cycles and in EoT visit.

Table 2: Schedule of Study Activities and Assessments (PHASE II)

Activity/Assessment	Screening[a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
ICF[c]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X	X		X			X			X	
Body Surface Area (BSA)[d]	X											
Vital signs[e]	X	X	X		X			X			X	
ECOG	X	X	X		X	X		X			X	
Physical examination	X	X	X		X	X		X			X	
12-lead ECG[f]	X	Perform if clinically indicated									X	
Echocardiogram or MUGA	X										X	
Laboratory Assessments												
CBC with differential[g]	X	X	X		X	X		X			X	
Complete serum chemistry[g]	X	X	X		X	X		X			X	

Activity/Assessment	Screening[a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
Coagulation test	X	X			X			X				
Urinalysis	X	X			X			X				
Pregnancy test (if applicable)[h]	X				X			X (even # cycles only)			X	
Study samples[i]												
Tumor sample for diagnosis confirmation	X											
Tumor for translational research	X										X	
Blood for translational research	X	At each radiological assessment (every 6 weeks during the first 6 months of treatment, every 8 weeks after the first 6 months of treatment)									X	
Disease Assessments												
Scans (eg, CT/MRI)for response assessments[j]	X	Every 6 weeks during the first 6 months of treatment, every 8 weeks after the first 6 months of treatment									X	
Administration of selinexor (only on cohorts randomized to selinexor)		Days 1, 8, and 15 every cycle										

Activity/Assessment	Screening[a]	Cycle 1			Cycle 2			Cycles ≥3			End-of-Treatment (EoT) Visit	Durability of Response and Survival Follow-up (Every 2-3 months)[b]
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	≤30 Days Post-Last Dose	
		-3 days	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days			± 14 days
Administration of Gemcitabine		Days 1 and 8 every cycle										
Adverse events recording[k]	X	Throughout										
SAE reporting												
Concomitant medication recording	X	Throughout										
Nutritional consultation[l]	X	Perform if clinically indicated										
Telephone contact												X
Collection of information regarding antineoplastic therapy used after EoT												X
Quality of Life assessment[m]		X			X			Every 3 cycles			X	

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; MUGA: multiple gated acquisition; PE: physical examination; SAE: serious adverse event

a) Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.
b) After discontinuation of selinexor if feasible and clinically indicated, evaluations should be performed every 2 months (8 weeks) for patients who have not progressed and every 3 months in progressed patients to assess durability of response. If sarcoma evaluations cannot be performed, at a minimum, a

telephone call will be made to the patient (or the patient's family) to assess the survival status, status of the patient's sarcoma, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment (see Section 8.5.2).

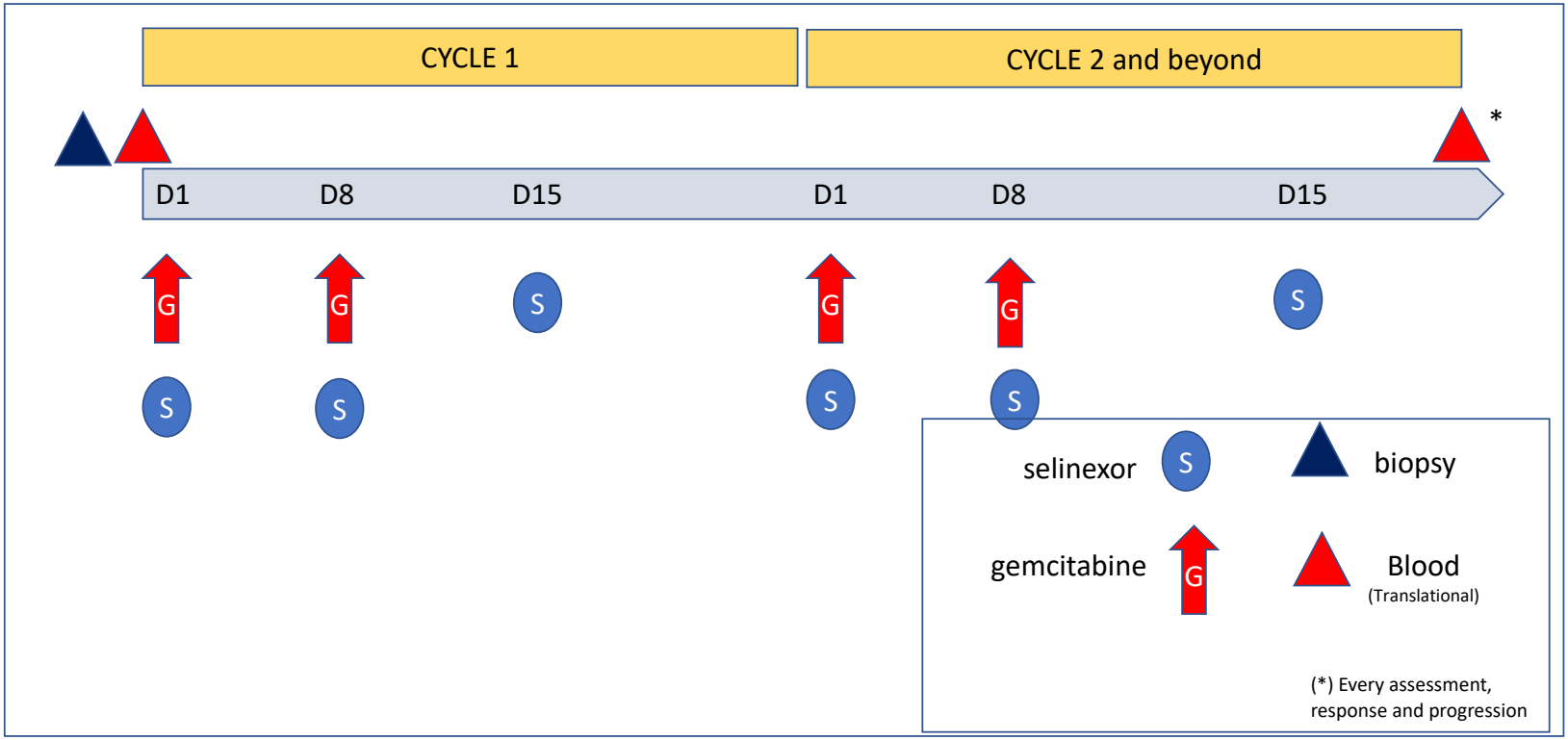
c) ICF must be signed before any study-specific procedures are performed.
d) BSA should be calculated during Screening and as needed during the study
e) Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination.
f) Patients must rest for at least 5 minutes prior to the ECG recording.
g) CBC with differential and complete serum chemistry will be performed on days 1 and 8, on Cycle 1 and 2 and on day 1 in the cycles ≥3. *=Limited serum chemistry: WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. Urea (mg/dL) = Blood urea nitrogen (mg/dL) × 2.14. Microscopy will only be performed if clinically indicated.
h) For females of childbearing potential; negative serum hCG or urine pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of even Cycles ≥2 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG or urine). Pregnancy testing may also be performed as clinically indicated during the study.
i) Central pathological confirmation: one archived formalin-fixed paraffin-embedded (FFPE) tumor block sample will be sent for central pathological confirmation before treatment initiation. Translational samples: Translational samples: Tumor: One recent (not archived) formalin-fixed paraffin-embedded (FFPE) tumor block sample mandatorily collected at baseline (minimum 6 tru-cuts); Blood: 2 10mL EDTA tubes of peripheral blood within 72 hours prior to starting treatment (baseline), two 10mL EDTA within ±72h of each radiological assessment (TC scan, MRI) and two 10mL EDTA tubes of peripheral blood at the end of treatment (within 72 hours after progressive disease is documented). Another two 10mL EDTA tubes of peripheral blood when tumor response is observed. Plasma will be separated by a Ficoll-Paque protocol. Mononuclear cells will be also collected for further analysis.
j) CT scans or MRI will be performed every 6 weeks (±7 days) . CT Scans will be performed every 8 weeks (±7 days) after 6 months of treatment. During Follow up CT scan or MRI will be done every 8 weeks (±7 days) if patient did not progressed to assess durability of response. Screening CT Scan/MRI have to be done within 28 days prior treatment initiation.
k) All AEs that begin or worsen after the patient has provided informed consent will be recorded. SAEs must be reported to GEIS within 24 hours of first awareness.
l) Patients must be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study nurse and can be done on a phone call.
m) Quality of Life will be assessed with EORTC QLQ-C30. It will be performed on C1D1, C2D1 and then every 3 cycles and in EoT visit.

Table 3: Dosing Schedule (Phase I Part and Phase II with Selinexor plus Gemcitabine)

Treatment	Week 1							Week 2							Week 3						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21
Selinexor	X							X							X						
Gemcitabine	X							X													

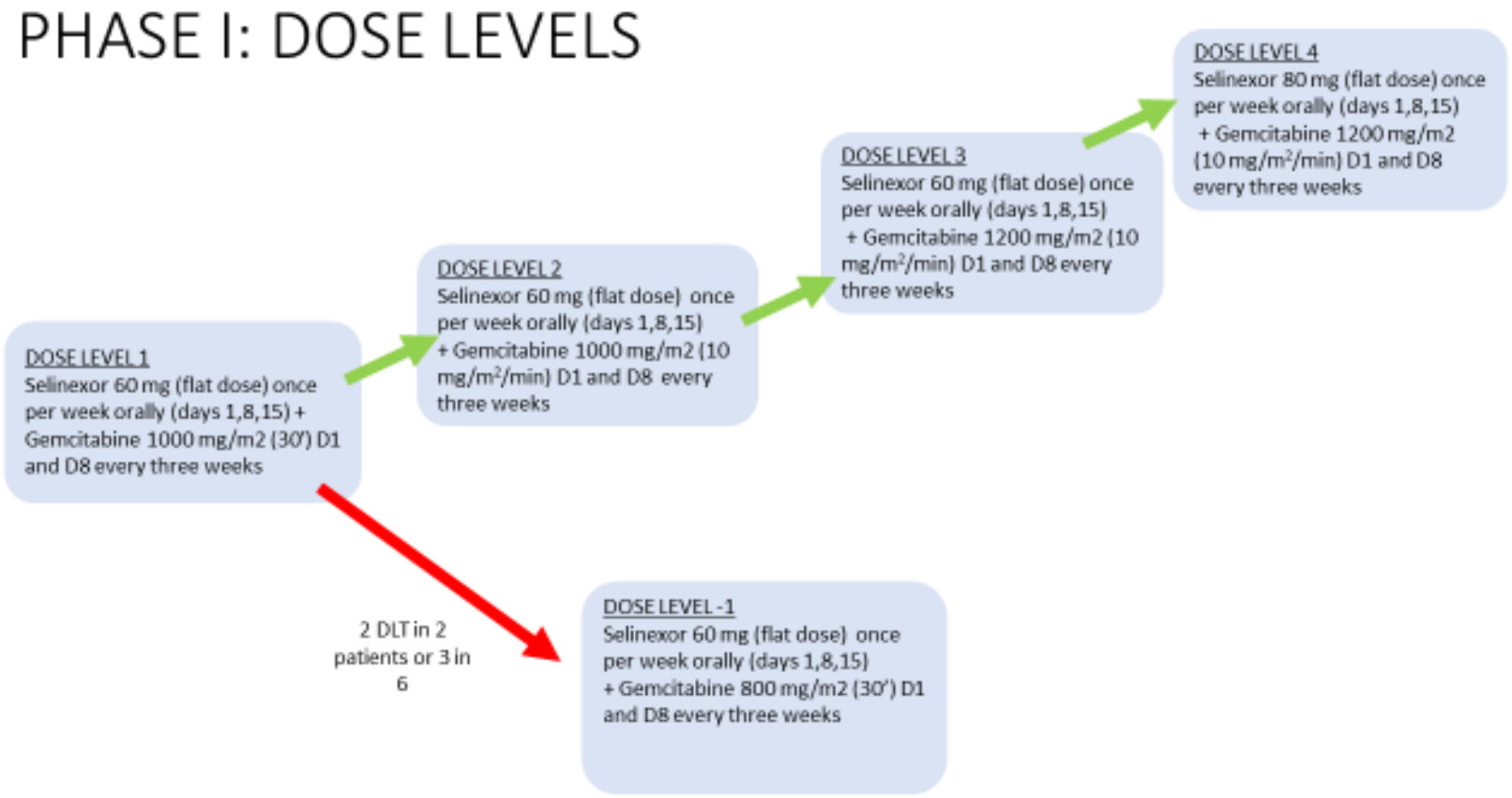
D: Study Day; X: dosing day.

Figure 1: Phase I Design



PHASE I DESIGN

Figure 2: Phase I Dose Levels



3 INTRODUCTION AND RATIONALE

3.1 Rationale for the Use of Selinexor in Sarcomas

Exportin-1 (XPO-1, also known as CRM1) is the main mediator of nuclear export in many cell types and it mediates leucine-rich nuclear export signal (NES)-dependent protein transport. Inhibition of XPO1-mediated nuclear export blocks the *"escape"* of multiple tumour suppressor proteins, turning off oncogenic signals and enhancing tumour suppression. Besides, XPO-1 overexpression has been associated with therapy resistance, reduced apoptosis and poor survival in solid tumours(1). In line with this observation, XPO-1 was described to be overexpressed in osteosarcoma(2), where it is associated with reduced progression-free survival (PFS) and overall survival (OS)(3). XPO-1 is the main target of the small molecule inhibitor selinexor(4).

Selinexor (KPT-330) is a *first-in-class*, highly specific, slowly reversible and orally bioavailable small-molecule inhibitor of XPO-1. This molecule was tested in a phase I clinical trial, in patients with advanced metastatic solid tumours, showing evident clinical benefit, as well as an acceptable safety profile. In this trial, among the 157 patients evaluated for efficacy, 1 patient had a complete response (CR), 6 patients had partial responses (PR) and 67 patients had stable disease (SD), with 27 patients reaching the stabilization at least for 4 months. In the translational study associated with this trial selinexor reduced cell proliferation and increased apoptosis, due to the nuclear accumulation of tumour suppressor proteins, such as p53 and FOXO3(5). Likewise, selinexor was tested in patients with advanced sarcomas, including STS and bone sarcoma, showing 21 patients SD, alongside with decreased tumour load (ranging from 5 – 23%) in 7 of them. The median PFS of selinexor was 4.2 months and 3.7 months, for patients with progressive liposarcoma or leiomyosarcoma, respectively. Selinexor pharmacokinetics was similar to previously published data and it was observed a better absorption in the fed state compared to fasting. Selinexor bioavailability was not affected by fat content. Biopsies taken pre- and post-treatment with selinexor (n=6) showed target inhibition of XPO-1, nuclear accumulation of p53, apoptosis by increased cleaved caspase, remarkable reduction in Ki-67 and cell content, and increased stroma. Furthermore, oral selinexor administered twice a week was well tolerated with manageable toxicities(6). Based on this data, a randomized, multicentre, double-blind, placebo-controlled phase II/III clinical trial, with oral selinexor, in patients with advanced unresectable dedifferentiated liposarcoma (DDLPS) (SEAL - NCT02606461) is currently ongoing. Phase II data has been presented recently and the median PFS on selinexor arm, by RECIST 1.1, was 5.6 months, compared with 1.8 in the placebo arm, supporting the continuation of the phase III part(27).

Furthermore, pre-clinical studies confirmed that selinexor targets the nuclear exportation of several tumour suppressor proteins, including APC, p21, p27, p53, Rb, FOXO proteins and FAS(4,8), sustaining the observations withdrawn from the clinical trials-associated translational studies. Selinexor avoids also survivin exportation to the cytoplasm, blocking its anti-apoptotic function(9). In general, the inhibition of nuclear exportation of all these proteins leads to reduced cell proliferation and increased apoptosis, in numerous types of solid tumours, including sarcoma(10). In sarcomas, selinexor proved to have a potent *in vitro* and *in vivo* activity, mostly by inducing G1 cell cycle arrest. Remarkably, in liposarcoma cell lines with *MDM2* and *CDK4* amplification, selinexor induced cell cycle arrest and apoptosis, independently of *TP53* expression or mutation. Nonetheless, p53 and p21 protein expression increased, suggesting a post-transcriptional regulatory effect(10).

3.2 Gemcitabine in the Treatment of Soft-Tissue Sarcoma

Gemcitabine is a deoxycytidine analogue used in the treatment of a large spectrum of tumours, including STS(11). This drug accumulates intracellularly, mainly through the nucleoside transporter hENT1, and undergoes a series of phosphorylations in order to become active. Then, Gemcitabine-tri-phosphorylated acts as a competitive substrate of deoxycytidine triphosphate, being incorporated, irreversibly and undetectably into DNA during replication. This incorporation inhibits DNA elongation, causing a solid G_1 cell cycle arrest and increasing cell death by apoptosis(12). Besides, Gemcitabine seems to enhance the activity of Fas/ Fas ligand pathway, inducing cell death and tumour regression, by an independent pathway(13). The form of gemcitabine with two phosphates attached (dFdCDP) also has activity; it inhibits the enzyme ribonucleotide reductase, which is needed to create new nucleotides. The lack of nucleotides drives the cell to uptake more of the components it needs to make nucleotides from outside the cell, which increases uptake of gemcitabine as well.

Nowadays, and in the metastatic setting of STS, gemcitabine is administrated as a single agent or in combination with docetaxel, showing special activity in leiomyosarcoma(28,29). Additionally, several clinical studies with gemcitabine in combination with other cytotoxic drugs, including dacarbazine(14) and paclitaxel(15), showed synergistic activity and proved the usefulness of gemcitabine in STS treatment. Nevertheless, gemcitabine was reported to be rapidly inactivated by cytidine deaminase (CDA) and numerous tumours developed resistance against this drug due to the loss of its transporters, lack of gemcitabine phosphorylation or by triggering gemcitabine-dependent angiogenesis(11,30–32). All these mechanisms of chemoresistance may justify the limited therapeutic effect of gemcitabine and therefore, new strategies are urgently required in order to improve intracellular gemcitabine and to potentiate its activity in STS. A quite stimulating and promising strategy is the combination of gemcitabine with selinexor, since this combination was shown to be synergistic in pancreatic cancer.

Rationale for the Combination Gemcitabine Plus Selinexor

A relevant finding derived from preclinical experiments is that selinexor reduces mRNA and protein expression of DNA damage repair (DDR) gene products. In relation with that, selinexor has shown to be synergistic with DNA damage drugs. Moreover, eIF4e, an essential nuclear export of various proto-oncogenes as c-Myc, is thought to be involved since c-Myc regulates the transcription of other DNA damage repair genes. This biological effect of selinexor would prevent different repair signalling allowing rationale for combination with DNA damage agents as gemcitabine(16). *In vitro* experiments in sarcoma and other tumor cells have shown synergistic action with the combination of single (docetaxel, or gemcitabine) and double (cisplatin) strand breaks agents along with selinexor. These combinations showed increased cell death by cleaved caspase-3 and reduction of DNA damaged repair gene products. *In vivo* experiments, the combination of single strand break agent as docetaxel plus selinexor lowered DNA damage repair proteins expression while cisplatin or docetaxel did not produce DDR proteins reduction. Selinexor showed reduction in a wide range of DDR gene products as Rad51, CHEK1, MLH1, MSH2, MSH6, PMS2 and PARP1 and this effect was observed in several tumor types.

Importantly, the sequence turned out to be relevant and cytotoxicity was higher if DNA damage agent was first administered and then selinexor. Authors stated this could be related

to the cycle arrest induced by selinexor, this would eventually prevent cells to enter in phase S which means less chemosensitivity.

Preclinical experiments *in vitro* and *in vivo* in pancreatic tumor models have shown synergistic action with the combination of gemcitabine and selinexor. In addition to the previous mentioned mechanism involving the DDR genes inhibition, authors found that nuclear retention of p27, the proapoptotic bax protein and the anti-apoptotic surviving, could explain the synergy seen between gemcitabine and selinexor(17).

Gemcitabine alone produces limited cytotoxicity which is in accordance with lack of apoptotic cell death seen in preclinical experiments with this drug in some cell lines. However, gemcitabine induces a significant increase of γH2AX immunoreactivity demonstrating DNA damage. Thus it is strategic to combine it with other drugs, as selinexor, that could increase apoptotic signalling through the blockade of DNA repair genes(16).

Nevertheless, gemcitabine can induce a p53 dependent apoptosis which is in relation to accumulation of pro-apoptotic proteins as bax. Selinexor could stabilize bax through the nuclear accumulation of nucleophosmin(18). This is another possible synergistic point with selinexor, through the retention of p53 in the nuclei(19).

Finally, FAS pathway can represent another potential synergistic mechanism since gemcitabine sensitizes FAS activation(13) and selinexor contributes as well to FAS activation(20). FAS could be a relevant prognostic factor in osteosarcoma(21) and in soft tissue sarcomas(22).

Taking together the previous information, we hypothesize that selinexor will have a synergistic effect with gemcitabine in sarcoma patients. The phase I trial will permit the selection of the best dose level for the phase II. The determination of predictive biomarkers to this combination will benefit the selection of future patients and will provide with the mechanism underlying the activity of selinexor plus gemcitabine.

Gemcitabine administration in sarcomas has been diverse. Mainly used in combination with doses ranging from 675 to 1800 mg/m^2 and infusion rates ranging from 30 minutes and 10 mg/m^2/min. This latter being the most frequently recommended. The GEIS scheme administered 1800 mg/m^2 of gemcitabine (10 mg/m^2/min) along with 500 mg/m^2 of dacarbazine every 2 weeks in advanced and progressing STS. Grade 3-4 neutropenia, anemia and thrombocytopenia was observed in 48%, 4% and 6 % respectively(15). In osteosarcoma patients progressing to standard treatments gemcitabine was administered at 800 mg/m^2/d on days 1 and 8 of cycle, (10 mg/m^2/min) along with rapamycin 5 mg (on a daily dose). With this scheme, the grade 3-4 neutropenia, anemia and thrombocytopenia were seen in 37%, 23% and 20% respectively(33). The original combination of gemcitabine 900 mg/m^2/d on days 1 and 8 of cycle (10 mg/m^2/min) plus docetaxel 75 mg/m^2 on day 8 in advanced STS reported G3-4 neutropenia, anemia and thrombocytopenia was observed in 16%, 7% and 40% respectively(23). Finally, in the British randomized phase III trial, gemcitabine was administered at 675 mg/m^2/d on days 1 and 8 of cycle (90 min of infusion rate) along with docetaxel 75 mg/m^2 on day 8 of each cycle. The hematological grade 3-4 toxicity reported was neutropenia 20%, anemia 6% and thrombocytopenia 0%). Then the total dose per cycle is related with the extent of grade 3-4 hematological toxicity(24).

Absence of signal of activity detected in osteosarcoma

In vitro studies of synergy were performed in osteosarcoma cell lines, for the combination of selinexor with gemcitabine. Our results indicated the absence of synergy between the two drugs, in the three lines of osteosarcoma that have been tested: MG63, SAOS2 and U2OS. Through cell viability assays, using the MTS reagent, antagonism for the combination has been observed in these lines at concentrations in the IC50 range. Specifically, the combination indices are 1.67 for MG63, 1.54 for SAOS2, and 1.23 for U2OS. Furthermore, in apoptosis assays using Annexin V-FITC/PI kits, the percentage of apoptotic cells is not significantly higher or lower between the monotherapies and the combination for MG63 and U2OS.

Osteosarcoma patients enrolled in the phase I part of SELISARC progressed quickly and, in contrast with other sarcoma subtypes treated, no signal of activity was detected.

Selinexor in malignant peripheral nerve sheath tumor (MPNST)

MPNST is a malignant neoplasm derived from peripheral nerve sheath with typically aggressive behavior. In up to 50% of MPNST cases there is a NF1 context and in 10% may emerge in previous irradiated places, the remaining 40% are sporadic MPNST. Plexiform neurofibroma is the characteristic precursor of MPNST in the NF1 syndrome. It has been also reported malignant transformation from epithelioid schwannoma, but this is clearly less frequent.

Pathological features are the presence of alternating areas of hypocellular and hypercellular (marbling appearance), with perivascular accentuation. Heterologous differentiation can be present in up to 10-15% of cases. Like dedifferentiated liposarcoma, rhabdomyoblastic features correlated with worse outcome(34). Uniform spindle cells with hyperchromatic thin nuclei is usually seen but epithelioid morphology can be present. Immunostaining can reveal positivity to SOX10 and s100 which is usually patchy while myogenin or desmin can be seen in rhabdomyoblastic elements. Loss of nuclear H3K27me3 in high grade sporadic and radiation associated MPNST is characteristic(35). Loss of INI1 can be seen in the subset of epithelioid MPNST(36).

Even when MPNST constitutes one of the 5 most frequent sarcoma subtypes of limbs and trunk wall, it represents an unmet need since the overall survival is still poor. Globally, the 5-year overall survival is around 40% considering all the MPNST cases and, in recent times, no significant difference has been detected between MPNST associated to NF1 or sporadic(37). Despite few relevant advances in the therapeutic field in the last decades, relevant advances in tumor biology and preclinical analysis have been reported.

NF1 loss is seen not only in MPNST linked to NF1 syndrome, but also in the majority of sporadic MPNST, suggesting that the loss of this tumor suppressor gene is a cornerstone in all MPNST. Genetic alteration of CDKN2A and TP53 are also detected in sporadic and radiation-related MPNST(38,39).

Somatic mutations in SUZ12 and EED that encodes components of the polycomb repressive complex 2 (PRC2) were communicated in sporadic and NF1-related MPNST(39,40). PRC2 acts as histone methyltransferase and marks chromatin for silencing. SUZ12 encodes a chromatin modifying protein and its loss stimulate growth in NF1 deficient gliobastoma cell. Moreover, SUZ12 ablation induces loss of trimethylation at lysine 27 of histone 3 (H3K27 me3) and an increase of H3K27me3 acetylation which entails bromodomain protein recruitment(41). Frequent co-alterations between SUZ12 and NF1 are seen in MPNST.

SUZ12 maps near NF1 in 17q11.2 and is commonly affected in microdeletions at the NF1 locus. Then the loss of NF1 function is an early driver event in MPNST pathogenesis. Additional genetic hits are loss of tumor suppressor genes as CDKN2A, TP53, RB1 or genes encoding PRC2 components as SUZ12 or EED. Then, selinexor might have an important role in the treatment of this disease preventing the efflux to cytoplasm of proteins encoded by some of these tumor suppressor genes.

Interestingly, a recent collected experience of 9 advanced MPNST patients treated with selinexor-based therapy reported 3 partial responses, 4 stabilizations and 2 progressions. Of 3 partial responses, 2 were treated with selinexor in monotherapy and 1 with the combination. Duration of response ranged from 3 to 8+ months. A patient with stable disease had a progression free survival of 13.5 months. The mean duration of disease control was 4.5 months(42). Probably tumor suppressor proteins relevant in MPNST are retained in the nuclei preventing the proliferative action in this aggressive sarcoma subtype.

Furthermore, gemcitabine is also an active drug in the context of MPNST, and this could indicate a potential synergistic effect in the context of this aggressive sarcoma(43).

3.3 Study and Dose Rationale

3.3.1 Dose Schedule Rationale

3.3.1.1 Selinexor Dosing

Based on the pharmacology, pharmacokinetics, pharmacodynamics (PDn), tolerability, and efficacy observed in clinical studies, the previously recommended dose for the use of single-agent selinexor in most cancer indications is 60 mg twice weekly (BIW), administered on Days 1 and 3 of each week, continuously. In patients with heavily pretreated MM, the combination of 80 mg selinexor plus 20 mg dexamethasone BIW was identified as the RP2D (Karyopharm internal report: Selinexor Exposure-Response White Paper, 06 April 2017) and this dose has been shown to be active in penta-refractory MM. As data has matured from two studies in relapsed / refractory myeloma (KCP-330-017 STOMP; NCT02343042 and XPORT-MM-028; NCT04414475), the dosing schedule for selinexor has evolved. As of 01 September 2022, a total of 95 patients received the selinexor + pomalidomide + dexamethasone (SPd) regimen. Dosing schedules ranged from 60 mg to 80 mg selinexor twice weekly (BIW) or 40 to 100 mg selinexor QW. Dexamethasone was dosed at 40 mg weekly, and pomalidomide was dosed 2 to 4 mg once daily (QD) on Days 1 through 21, administered in 28-day cycles (44). Among patients with pomalidomide-naïve or non-refractory MM in STOMP (n=44), overall response rate (ORR) was 57% and median progression-free survival (mPFS) was 12.2 months. Two expansion cohorts dosed with selinexor either at 40 mg QW (SPd-40) or 60 mg QW (SPd-60) in combination with pomalidomide 4 mg once daily (QD) on Days 1 through 21 and dexamethasone 40 mg QW were enrolled. Preliminary data available at the inception of this study suggested that the SPd-60 regimen conferred higher response rates and deeper responses compared to SPd-40. However, Grade 1/2 AEs and dose modifications were more frequent in the SPd-60 cohort compared to SPd-40 (45). With more data maturity, mPFS equalized between SPd40 and SPd 60. With sufficient follow-up data in patients treated with SPd-60 and SPd-40 in the STOMP and XPORT-MM-028 studies accumulated to identify SPd-40 as the optimal dose regimen of SPd based on benefit/risk assessment.

Based on the above data and latest risk/benefit analysis, the starting dose of selinexor will be 60 mg weekly, as listed in table 3.3.1.2.

3.3.1.2 **Gemcitabine Combination: Dose Levels**

The following dose levels have been determined to be tested in Phase I:

Dose level	Selinexor weekly (given on days 1, 8 and 15 of each cycle)	Gemcitabine weekly (given on days 1, 8 of each cycle)
-1	60 mg	800 mg/m^2 (30 min)
1	60 mg	1000 mg/m^2 (30 min)
2	60 mg	1000 mg/m^2 (10 mg/m^2/min)
3	60 mg	1200 mg/m^2 (10 mg/m^2/min)
4	80 mg	1200 mg/m^2 (10 mg/m^2/min)

After having completed the Phase I part, the recommended dose for Phase II is:

Selinexor will be given at 60 mg once per week orally days 1, 8 and 15 every 21 days.

Gemcitabine will be given at the dose 1200 mg/m^2 (10 mg/m^2/min) days 1 and 8 every 21 days.

4 STUDY OBJECTIVES

Table 4: Objectives and Endpoints

Objectives	Endpoints
PHASE I	
Primary	
• To determine the maximum tolerated dose (MTD) or the recommended dose for phase II of selinexor plus gemcitabine.	• Based on Dose Limiting Toxicities (DLTs) observed during first cycle (day 1-21).
Secondary	
• To evaluate the safety profile according to CTCAE 5.0.	• Safety profile of the experimental treatment, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 5.0.
• To determine the overall response rate (ORR).	• Overall Response Rate (ORR): ORR is defined as the number of subjects with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) divided by the number of response evaluable subjects (according to RECIST 1.1 criteria).
• To evaluate efficacy according to Choi response.	• Efficacy measured through tumor response according to Choi criteria. The evaluation criteria will be based on the identification of target lesions in baseline and their follow-up until tumor progression.
• To evaluate the patients's quality of life (QoL).	• Quality of life will be measured with EORTC QLQ-C30.

PHASE II	
Primary	
• To evaluate the efficacy of the selinexor plus gemcitabine combination as measured by the progression-free survival rate (PFSR) at 6 months in patients with selected advanced soft-tissue sarcomas.	• Progression-free survival rate (PFSR): Efficacy measured by the PFSR at 6 months according to RECIST 1.1. PFSR at 6 months is defined as the percentage of patients who did not experience progression or death due to any cause since the first dose of experimental treatment until month 6 after treatment initiation.
Secondary	
• To evaluate overall survival (OS).	• Overall survival (OS): OS is defined as the time between the date of first dose and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive.
• To determine the overall response rate (ORR).	• Overall Response Rate (ORR): ORR is defined as the number of subjects with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) divided by the number of response evaluable subjects (according to RECIST 1.1 criteria).
• To evaluate efficacy according to Choi response.	• Efficacy measured through tumor response according to Choi criteria. The evaluation criteria will be based on the identification of target lesions in baseline and their follow-up until tumor progression.
• To evaluate the safety profile according to CTCAE 5.0.	• Safety profile of the experimental treatment, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 5.0.
• To evaluate the outcome of post protocol treatments.	• Clinical outcomes of post protocol treatments assessed by observation of such treatments in follow-up stage. Clinical outcomes of post protocol treatments assessed by observation of such treatments in follow-up stage.
• To evaluate the patients' quality of life (QoL).	• Quality of life will be measured with EORTC QLQ-C30.
Exploratory: Translational study (Phase I and II)	

• To determinate potential predictive biomarkers to the combination of selinexor plus gemcitabine in sarcomas in tumor blocks and peripheral blood samples. • To understand the mechanisms and the cell signaling pathways related with response or resistance to the combination in FFPE tumor samples. • To validate the translational study results in pre-clinical models of sarcoma.	• Potential biomarkers will be determined using gene expression analysis with HTG technology, protein expression with immunohistochemistry and analysis of plasmatic factors (ProcartaPlex Immunoassay). • Correlation of the different identified biomarkers with outcome will be analyzed. • *In vitro* studies will be done with different STS cell lines.

5 STUDY DESIGN

This is a phase I-II, non-randomized, single-arm, open-label, multicenter, international clinical trial.

Patients with selected advanced soft-tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor) will receive selinexor in combination with gemcitabine.

In the Phase I part safety and toxicity of the combination will be assessed using a 3+3 design. The recommended dose for the Phase II will be determined.

In the Phase II part there will be 2 different cohorts:

Cohort 1: Leiomyosarcoma (LMS)
Cohort 2: Malignant peripheral nerve sheath tumor (MPNST)

Dose escalation levels (Phase I):

Dose level	Selinexor weekly (given on days 1, 8 and 15 of each cycle)	Gemcitabine weekly (given on days 1, 8 of each cycle)
-1	60 mg	800 mg/m^2 (30 min)
1	60 mg	1000 mg/m^2 (30 min)
2	60 mg	1000 mg/m^2 (10 mg/m^2/min)
3	60 mg	1200 mg/m^2 (10 mg/m^2/min)
4	80 mg	1200 mg/m^2 (10 mg/m^2/min)

After having completed the Phase I part, the recommended dose for Phase II is:

Selinexor will be given at 60 mg once per week orally days 1, 8 and 15 every 21 days.

Gemcitabine will be given at the dose 1200 mg/m^2 (10 mg/m^2/min) days 1 and 8 every 21 days.

5.1 Overall Study Design

5.1.1 Phase I Part

The dose escalation rules proceed as follows: escalating in cohorts of 3-6 patients per dose level. Three patients are treated at a given dose level. If at least 2 patients are observed to have dose-limiting toxicity (DLT), the prior dose level is defined as the maximum tolerable dosage (MTD) (unless only 3 patients have been treated at that level, in which case it is the tentative MTD). If 0 of the 3 patients are observed to have DLT, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above. If exactly 1 of the 3 patients treated show DLT, 3 additional patients are treated at the current dose level. If none of these additional 3 patients show DLT, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD.

Dose-limiting toxicity (DLT) is usually defined as cycle 1 grade 3 or above toxicity, excepting grade 3 neutropenia unaccompanied by either fever or infection. More specifically, for this

clinical trial, DLT will be applied only to either of the following toxicities occurring **during the first treatment cycle (days 1-21):**

Hematological toxicity:

- Febrile neutropenia with documented Grade ≥3 infection or sepsis
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by hemorrhage >G1 bleeding
- Grade 4 neutropenia lasting 7 days or longer
-

Non-hematological toxicities:

Any grade 3-4 events, excluding:

- Nausea/vomiting/diarrhea unless uncontrolled by maximal antiemetic/ anti-diarrheal therapy
- Grade 3 fatigue persisting <14 days
- Grade 3 increased serum creatinine or electrolyte abnormalities deemed not clinically significant and which required no treatment
- Grade 3 transaminitis will not be considered Dose Limiting Toxicity unless this would entail a delay in the treatment administration.

5.1.2 Phase II Part

Sample size calculations for LMS and MPNST cohorts are described in Section 13.2.
(46)(47)(48)(49)(46)(50)(51)

5.2 Total sample size of the phase II part

2 cohorts:

(1) LMS: 38 evaluable patients (41 including non-evaluable)

(2) MPNST: 44 patients (47 including non-evaluable)

Total: 82 patients (88 including non-evaluable)

6 STUDY POPULATION

6.1 Study Population

Patients with advanced (metastatic or locally advanced unresectable) soft-tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor).

6.2 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for this study (Phase II):

1. Patients must provide written informed consent prior to performance of any study-specific procedures and must be willing to comply with treatment and follow-up. Informed consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient's routine clinical management (e.g. imaging tests), obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol.
2. Age: 18-80 years.
3. Histologic diagnosis of soft tissue sarcoma (leiomyosarcoma or malignant peripheral nerve sheath tumor) confirmed by central pathology review prior to enrolment with an archive tumor sample. A fresh paraffin embedded tumor tissue block must be provided for all subjects for biomarker analysis before and (when feasible) after treatment with investigational products.
4. Metastatic/advanced disease in progression in the last 6 months.
5. Patients have previously received at least one previous line of systemic therapy.
6. Measurable disease according to RECIST 1.1 criteria.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
8. Adequate hepatic, renal, cardiac, and hematologic function.
9. Laboratory tests as follows:
    - Absolute neutrophil count ≥ 1,500/mm³
    - Platelet count ≥ 100,000/mm³
    - Bilirubin ≤ 1.5 mg/dL
    - AST and ALT ≤ 2.5 times upper limit of normal
    - Creatinine ≤ 1.5 mg/dL
10. Left ventricular ejection fraction ≥ 50% by echocardiogram or MUGA scan.
11. Females of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to enrollment and agree to use birth control measures during study treatment and for 3 months after its completion. Patients must not be pregnant or nursing at study entry. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

6.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible for this study (Phase II):

1. Three or more systemic treatment lines (including both chemotherapy and targeted therapy) for advanced disease (localized unresectable or metastatic).
2. Patients who have received any other anti-cancer therapy or investigational product in the last 21 days prior to enrollment.
3. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer, adequately treated cervical carcinoma in situ, superficial bladder carcinoma) during the 5 years prior to randomization. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
4. Prior selinexor or another XPO1 inhibitor treatment.
5. Administration of a previous gemcitabine-containing treatment.
6. Any concurrent medical condition or disease (e.g. uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.
7. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to Cycle 1 Day 1 (C1D1). Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
8. Pregnant or breastfeeding females.
9. Body surface area (BSA) <1.4 m^2 at baseline, calculated by the Du Bois(25) or Mosteller(26) method.
10. Life expectancy of less than 3 months.
11. Major surgery within 4 weeks prior to C1D1.
12. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or dysfunction that could interfere with absorption of study treatment.
13. 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).
14. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent.
15. Presence of brain or central nervous system metastases, unless they are controlled (patients with treated and stable metastasis are eligible)

7 STUDY TREATMENTS AND TREATMENT ASSIGNMENT

7.1 Treatments Administered

Selinexor
Pharmaceutical form: Tablet (20 mg tablets).
Route of administration: Oral use.

Gemcitabine
Pharmaceutical form: Concentrate for solution for infusion.
Route of administration: Intravenous use.

Selinexor has to be taken before gemcitabine infusion.

7.1.1 Selinexor

Selinexor will be provided as tablets for oral administration in blister packs (see IST Pharmacy Manual for more information). Selinexor tablets will contain 20 mg of the active pharmaceutical ingredient (API).

Study treatments must be dispensed only by a pharmacist or appropriately qualified staff. Study treatments are to be dispensed only to patients enrolled in this study.

7.1.2 Gemcitabine

Gemcitabine is a commercially available product and should be stored, reconstituted and discarded per manufacturer's instructions.

Gemcitabine will be administered at different dose levels during Phase I:

Dose level -1: Gemcitabine 800 mg/m^2 (30 min) D1 and D8 every three weeks

Dose level 1: Gemcitabine 1000 mg/m^2 (30 min) D1 and D8 every three weeks

Dose level 2: Gemcitabine 1000 mg/m^2 (10 mg/m^2/min) D1 and D8 every three weeks.

Dose level 3: Gemcitabine 1200 mg/m^2 (10 mg/m^2/min) D1 and D8 every three weeks

Dose level 4: Gemcitabine 1200 mg/m^2 (10 mg/m^2/min) D1 and D8 every three weeks

7.2 Study Treatment Labeling and Storage

7.2.1 Labeling

All labels will include conditions for storage, lot number, and other information required by the European medicine Agency (EMA), International Council for Harmonization (ICH), and/or Annex 13, and all local regulations for investigational medications.

7.2.2 Storage

Refer to the IST Pharmacy Manual for selinexor storage.

Gemcitabine should be stored as described in the prescribing information.

7.3 Study Treatment Dosing and Administration

7.3.1 Dispensing Directions

Dispensing instructions for selinexor will be provided in the IST Pharmacy Manual.

For doses of oral selinexor to be taken on nonclinical days, patients will be provided with an adequate supply of selinexor for self-administration at home until at least their next scheduled study visit. Patients will be provided with a take home diary to complete on home dosing days; the patient diary will be reviewed at each clinic visit.

7.3.2 Dosing Information

7.3.2.1 Selinexor

Refer to the IST Pharmacy Manual for details of selinexor formulation, preparation, and administration.

Selinexor tablets should be taken orally with at least 120 mL (half a glass) of water at approximately the same time each day. It can be taken with or without food. Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

For doses of selinexor that are to be taken on nonclinical days, the patient will be provided with selinexor by the site pharmacy and selinexor may be self-administered by the patient on an outpatient basis.

7.4 Method of Assigning Patients to Treatment Groups

For phase I part no randomization will performed. All subjects will be treated with the two drugs (selinexor, gemcitabine).

For phase II part, patients will be assigned to either LMS cohort or MPNST cohort depending on their confirmed diagnosis.

7.5 Dose Schedules for Evaluation

7.5.1 Selinexor + Gemcitabine (Phase II)

- Selinexor will be given at 60 mg once per week orally days 1, 8 and 15 every 21 days.
- Gemcitabine will be given at the dose 1200 mg/m^2 (10 mg/m^2/min) days 1 and 8 every 21 days.

7.6 Study Phases and Determination of RP2D

7.6.1 Phase 1: Dose Escalation Phase

The dose schedule for evaluation during the Dose Escalation Phase I is presented in Figure 2.

7.6.1.1 **Treatments to be Escalated**

The dose of gemcitabine and selinexor will be escalated using a standard 3 + 3 approach as follows:

Dose level	Selinexor weekly (given on days 1, 8 and 15 of each cycle)	Gemcitabine weekly (given on days 1, 8 of each cycle)
-1	60 mg	800 mg/m^2 (30 min)
1	60 mg	1000 mg/m^2 (30 min)
2	60 mg	1000 mg/m^2 (10 mg/m^2/min)
3	60 mg	1200 mg/m^2 (10 mg/m^2/min)
4	80 mg	1200 mg/m^2 (10 mg/m^2/min)

The procedure for dose escalation to establish the MTD of the combination is provided in the following sections.

7.6.1.2 **Dose Escalation Procedures**

A standard 3 + 3 dose escalation schedule will be used for all escalations. Initially, 3 patients will be entered in each cohort at the scheduled starting dose level for that cohort. If a drug-related DLT (see 7.6.1.3) is not seen during the first cycle, the dose will be escalated for another group of 3 patients.

If 1 of 3 patients experiences a drug-related DLT, then 3 additional patients will receive that dose. If 1 of 6 patients experiences a drug-related DLT, the next scheduled dose level will be enrolled. If, at a given dose level, ≥2 patients experience a drug-related DLT, the MTD will have been exceeded, additional enrollment within that cohort will cease, and dose escalation will stop.

Subsequently, if a dose level proves intolerable (≥2 patients experience a DLT), enrollment will proceed at one dose-level lower. These rules are summarized in the table below.

Table 5: Dose Escalation Rules for Defining MTD

Number of Patients with Drug-Related DLT at a Given Dose Level	Dose Escalation Step
0 of 3	Proceed to next dose level
1 of 3	Treat 3 more patients at the same dose level
≥2 of 3	Dose escalation stops; MTD is next lower dose level
1 of 6	Proceed to next dose level
≥2 of 6	Dose escalation stops; MTD is next lower dose level
≤1 of 6 at the highest dose level	MTD

All patients will be considered evaluable for DLT unless they cannot complete the first cycle of therapy due to withdrawal of consent or disease progression. A patient who is not DLT-evaluable will be replaced.

7.6.1.3 Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is usually defined as cycle 1 grade 3 or above toxicity, excepting grade 3 neutropenia unaccompanied by either fever or infection. More specifically, for this clinical trial, DLT will be applied only to either of the following toxicities occurring during the first treatment cycle:

Hematological toxicity:

- Febrile neutropenia with documented Grade ≥3 infection or sepsis
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia complicated by hemorrhage > G1 bleeding
- Grade 4 neutropenia lasting 7 days or longer
-

Non-hematological toxicities:

Any grade 3-4 events, excluding:

- Nausea/vomiting/diarrhea unless uncontrolled by maximal antiemetic/ anti-diarrheal therapy.
- Grade 3 fatigue persisting <14 days.
- Grade 3 increased serum creatinine or electrolyte abnormalities deemed not clinically significant and which required no treatment)
- Grade 3 transaminitis will not be considered Dose Limiting Toxicity unless this would entail a delay in the treatment administration.

7.6.2 Determination of RP2D

The sponsor will collect and analyse the treatment and toxicity data from cycle 1 from every group of patients in the same dose level from the eCRF. The results will be evaluated by an Independent Data Monitoring Committee. This committee will give recommendations to escalate dose during phase I trial and to select the RP2D.

All sites, reviewers and Karyopharm will be informed of every decision taken.

7.6.3 Phase 2: Dose Expansion Phase

The dose for the phase II trial will be selected in the phase I.

Phase II is developed in one stage and therefore treatment and toxicity analysis will be performed when the specified number of patients has been completed in each cohort.

7.7 Missed or Vomited Doses

7.7.1 Missed Doses of Study Treatments

Missed doses should be managed as follows:

- **If a dose was missed**, If a dose was missed, and the patient realize in the first 48 hours, the patient will take the dose of this week. If the dose is delayed more than 48 hours, the dose of this week will be skipped (e.g. if the patient missed the dose of Monday, he will take this week Tuesday or Wednesday, no latter)
- **If a dose must be skipped** (e.g. due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

If a patient missed a full 1- or 2-week period of dosing for non-study treatment-related events (e.g. a required medical procedure or an unanticipated personal emergency), the days missed won't be replaced. For example, if patient missed Cycle 2 Day 8 to Cycle 2 Day 15, then the patient will start the next dosing on Cycle 3 Day 1 following the break. Similarly, if a patient misses Cycle 3 Day 1 to Cycle 3 Day 15, then the patient will start the next dosing on Cycle 4 Day 1.

7.7.2 Vomited Doses of Selinexor

If a dose of selinexor is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

7.8 Dose Modifications and Delays

To begin each cycle (Day 1), the following criteria must be fulfilled:

Table 6: Hematology and Biochemistry Day 1 Criteria (see also Table 7)

	VALUE
Neutrophil count	≥1.5 × 10^3 cells/µL (≥1500 cells/µL; ≥1.5 × 10^9/L)
Platelets	≥75 × 10 cells/µL
Haemoglobin	≥8.0 g/dL. Note: cycle can be started if a transfusion is indicated
AST and ALT	≤3.0 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases

Any treatment-related non-hematologic toxicity that is NCI-CTCAE, v5.0 Grade <3 or equivalent severity to baseline, unless toxicity consists of laboratory abnormalities (for

example, potassium, magnesium, or phosphate) that are managed per institutional standard or is judged as clinically not significant by investigator (e.g. alopecia).

All dose modifications will be captured in the medical files and registered in the Case Report Form.

Delays:

If dose delays of gemcitabine are indicated due to toxicity, selinexor can be maintained if the toxicity is not related with selinexor at investigator's discretion.

Treatment may be delayed for up to 21 days to allow a patient sufficient time for recovery from study drug-related toxicity.

Table 7: General Guidelines for Dose Modification Due to Hematologic Toxicity

Treatment day	Neutrophil count	Platelet	Gemcitabine dose (mg/m^2)	Selinexor
Day 1	>1000 / <1500/ml	>50000 / <75.000	Delay	Maintain at investigator discretion
Day 1	<500	< 50000	Delay	Delay
Day 8	>1000	>100000	Administer full dose	Maintain
Day 8	500-1000	>50000, < 100000	Administer 80% total dose	Maintain at investigator discretion
Day 8	< 500	Any	Omit/delay dose	Delay until G2 or less
Day 8	Any	<50000	Omit/delay dose	Delay until G2 or less
Day 15	>1000	>100000		Maintain
Day 15	500-1000	>50000, < 100000		Maintain at investigator discretion
Day 15	< 500	Any		Delay until G2 or less
Day 15	Any	<50000		Delay until G2 or less

In the case of toxicity, the day 8 administration of gemcitabine can be delayed to day 15 trying to preserve the dose intensity. If this strategy entails additional delays, then for the next cycle if the same toxicity is found , then the advice will be to omit the gemcitabine dose rather than additional delay.

Table 8: Dosage Reduction Guidelines for Gemcitabine Due to Hepatic Toxicities in Day +8

Investigation	Level	Gemcitabine dose (mg/m^2)	Selinexor
Bilirubin	<1.5 ULN	Administer	Maintain if < G3
AST /ALT	Grade ≥3 elevation	Delay (Max 21 days) until recovery to Grade ≤1 or pre-therapy baseline. After recovery, reduce 1 dose level (see 7.8.4) for all subsequent cycles. If recovery to Grade ≤1 does not occur, discontinue gemcitabine. A second dose reduction is allowed if Grade ≥3 elevations recur.	Maintain if < G3

7.8.1 Selinexor Dose Reduction Guidelines

Dose reductions and/or schedule modifications are allowed in order to optimize the antitumor activity and tolerability of selinexor. For some AEs, dose interruption and/or reduction is recommended. See Table 9 for pre-specified dose modifications for AEs related to study treatment and see Table 10 for dose reduction and interruption recommendations.

While drug-related major organ toxicities are not prominent, thrombocytopenia and a number of constitutional side effects can limit dosing with selinexor. Therefore, patients should also be treated with supportive care to reduce toxicities (see Section 7.12.2). In addition, it should be noted that the constitutional side effects often attenuate over the first 4 to 6 weeks of dosing. Finally, some patients with rapid tumor responses experience significant fatigue, nausea, malaise and/or asthenia after 1 or more doses of selinexor. This effect has not been associated with typical markers of TLS, but if suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

The CTCAE v 5.0 is used for grading the severity of AEs; the therapy modifications described in Table 10 are applied according to this severity grading. Toxicity will be documented as described in Section 9.1.3. If more than 1 type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay, as well as the reason, must be documented (Table 9 and Table 10).

Table 10 summarizes the starting dose (Dose Level 0) and preferred dose modifications for AEs listed in Table 10. General supportive care guidelines are provided in Section 7.12.1 and Section 7.12.2.

Table 9: Pre-specified Dose Modifications for AEs Related to Study Treatment

Selinexor Dose Modification[1]	Selinexor Dose Schedule
Dose level 0 (starting dose)	That derived from phase I
1st reduction	*Reduce by 20 mg.*
2nd reduction	*An additional 20 mg will be permitted*

[1]For some AEs, dose interruption rather than reduction is recommended. See Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

Adverse Event	Occurrence	Action
Hematologic Adverse Events		
Thrombocytopenia		
Platelet count 25 × 10^9/L to <75 × 10^9/L	Any	• Mantain selinexor. Consider reduction by 1 dose level at investigator discretion. • Consider additional supportive care and discuss with Sponsor's Medical Monitor
Platelet count 25 × 10^9/L to <75 × 10^9/L with concurrent bleeding	Any	• Interrupt selinexor • Restart selinexor at 1 dose level lower after bleeding has resolved • Consider additional supportive care and discuss with Sponsor's Medical Monitor
Platelet count <25 × 10^9/L	Any	• Interrupt selinexor • Monitor until platelet count returns to at least 50 × 109/L • Restart selinexor at 1 dose level lower • Consider additional supportive care and discuss with Sponsor-Investigator's Medical Monitor
Neutropenia		
ANC 0.5 to 1.0 × 10^9/L without fever	Any	• Initiate growth factor support

Adverse Event	Occurrence	Action
ANC <0.5 × 10^9/L OR febrile neutropenia	Any	• Interrupt selinexor • Monitor until ANC returns to ≥1.0 × 109/L • Restart selinexor at 1 dose level lower • Initiate growth factor support
Anemia		
Hb <8.0 g/dL	Any	• Administer blood transfusions and/or other treatments per clinical guidelines
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt selinexor • Monitor until Hb returns to ≥8.0 g/dL • Restart selinexor at 1 dose level lower • Administer blood transfusions and/or other treatments per clinical guidelines
Nonhematologic Adverse Events		
Hyponatremia		
Sodium ≤130 mmol/L	First	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at same dose
	Second	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at 1 dose lower
Fatigue		
Grade 2 lasting >7 days OR Grade 3	Any	• Interrupt selinexor and provide appropriate supportive care • Add methylphenidate • Monitor until fatigue resolves to Grade 1 or baseline • Restart selinexor at 1 dose level lower
Nausea and Vomiting (See Appendix 2)		
Grade 1 or 2 nausea OR Grade 1 or 2 vomiting	Any	• Maintain selinexor and initiate additional anti-nausea medications
Grade 3 nausea OR Grade ≥3 vomiting	Any	• Interrupt selinexor • Monitor until nausea or vomiting has resolved to ≤Grade 2 or baseline. • Initiate additional anti-nausea medications • Restart selinexor at 1 dose level lower
Diarrhea		
Grade 2	First	• Maintain selinexor and institute supportive care

Adverse Event	Occurrence	Action
	Second and subsequent	• Reduce selinexor by 1 dose level Institute supportive care
Grade ≥3	Any	• Interrupt selinexor and institute supportive care • Monitor until diarrhea resolves to Grade ≤2 • Restart selinexor at 1 dose level lower
Weight Loss and Anorexia		
Weight loss of 10% to <20% OR anorexia associated with significant weight loss or malnutrition	Any	• Interrupt selinexor and institute supportive care • Monitor until weight returns to >90% of baseline weight • Restart selinexor at 1 dose level lower
Other Nonhematologic Adverse Events		
Grade 3 or 4	Any	• Interrupt selinexor and institute supportive care • Monitor until resolved to ≤Grade 2 • Restart selinexor at 1 dose level lower

ANC=absolute neutrophil count; Hb=hemoglobin.

7.8.1.1 Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Patients may continue antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

7.8.1.2 Conditions Not Requiring Selinexor Dose Modification

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be interrupted or reduced in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g. urate) abnormalities that are 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.

7.8.2 Dose Increases

In select cases (e.g. for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased after discussions between the Sponsor-Investigator and Karyopharm. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the BSA for the patient will be calculated. In no case should the

dose of selinexor be increased to >100 mg twice weekly. Patients will be followed as long as possible until disease progression or death.

7.8.3 Gemcitabine Dose Modifications

As a general rule, for clinically significant Grade 3-4 toxicities, treatment with gemcitabine has to be delayed one week until recovery < Grade 2, and then restart at the same dose level.

If the toxicity recurs, delay again until recovery < Grade 2 and then restart at the next dose level.

Reductions only have to be done in the drug that is related with this toxicity.

Table 11: Dose Reduction Levels for Gemcitabine

Gemcitabine Level	Gemcitabine Dose Schedule
Starting dose	That derived from Phase I
1st reduction	Modify the administration rate from 10 mg/m^2/min to 30 min instead of dose reduction.
2nd reduction	To reduce gemcitabine dose by 200 mg/m^2 per dose
3rd reduction	To reduce additional 200 mg/m^2 per dose
4th reduction	To reduce additional 200 mg/m^2 per dose being the minimum dose of 600 mg/m^2 in 30 min administration.

7.9 Duration of Treatment and Follow-up

Treatment will be maintained until disease progression, death, unacceptable toxicity, patient's consent withdrawal or investigator decision. In the case of permanent discontinuation of one of the drugs due to toxicity, the patient may continue treatment with the other drugs, at the discretion of the investigator.

7.10 Study Treatment Accountability

Selinexor will be provided by the drug supplier, Karyopharm. Sites must request study treatment by submitting an order form to GEIS for the study treatment to be shipped to the site pharmacy. The Investigator or delegated pharmacy staff will verify and acknowledge receipt of all study treatment shipments by signing and returning all required forms.

Study treatment accountability and destruction records will be maintained by the Sponsor-Investigator.

Selinexor should not be used for any purpose outside the scope of this protocol, nor may selinexor be transferred or licensed to any party not participating in the clinical study. Data for selinexor are confidential and proprietary and shall be maintained as such by the Investigators.

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of unused material.

All drug supplies provided by the drug supplier must be kept in an appropriate, limited access, secure place until used or returned to the drug supplier for destruction. Drug supplies will be counted and reconciled at the site before being returned.

7.11 Treatment Compliance

The Investigator or other study staff will either directly administer or supervise study treatment given in the clinic and instruct the patient on study treatment self-administration, as appropriate.

Patients will be asked to bring their study treatment containers with them at each visit and compliance with protocol-defined study treatment intake at home will be checked by tablet count.

Compliance to oral study treatment taken at home will be assessed by the Investigator and/or study personnel at each visit and recorded in source documents after discussion with the patient and after performing study treatment accountability.

The Investigator/research staff will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the site's internal database and drug accountability logs along with the reasons for subsequent verification.

7.12 Supportive Care, Contraception Requirements, Concomitant Medications, and Restrictions

7.12.1 Required 5-HT3 Antagonists/Anti-emetics

In order to minimize nausea, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (e.g. ondansetron 8 mg or equivalent) unless contraindicated, starting on C1D1 before the first dose of selinexor and continued q 8 hours for days 1-3. . In addition for the first month olanzepine 2.5 mg po qm is also required. Olanzepine may be discontinued after the first month. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists (see Appendix 2).

7.12.2 Recommended Supportive Care for All Patients

Supportive measures for optimal medical care should be provided to all patients during participation in this study. In addition to the required prophylactic therapy with 5-HT3 antagonists (Section 7.12.1) supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (CPGO) (NCCN CPGO) should be used as clinically indicated at the discretion of the Investigator.

Supportive care guidelines for managing AEs are provided in Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor.

7.12.2.1 Infection

No prophylactic antimicrobial agent is recommended for most patients initiating therapy with selinexor. Patients with a history of recurrent infections or those at high risk for specific

infections may continue their prophylactic antimicrobial regimens without modification when initiating selinexor therapy.

In patients who develop fever or other signs of systemic infection, an appropriate antimicrobial should be initiated immediately. Selinexor should be suspended in any patient with a Grade 4 infection or sepsis (even in the absence of documented infection) until the patient's clinical condition is stabilized. Selinexor can then be restarted at the previous dose once the patient's clinical status has stabilized, even in the setting of continued IV (and/or oral) antimicrobial agents. Selinexor is not known to have any drug interactions with standard antimicrobials. Please also see Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor.

7.12.2.2 **Overdose**

As selinexor is metabolized by glutathione (GSH) conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in patients who 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.

7.12.3 Contraception Requirements

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. Women 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 must agree to use highly effective contraception listed below (i.e. 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

Please see Section 9.3.1 for additional safety information related to pregnancy.

7.12.4 Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s). 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, if applicable.

7.12.5 Permitted Concomitant Medication

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

7.12.6 Use of Blood Products

During treatment, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Sponsor-Investigator.

Appropriate anti-coagulation is allowed during the study (e.g. 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 2 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.

In this study, prophylactic granulocyte-colony stimulating factor (G-CSF) will not be recommended unless a previous G4 neutropenia had occurred.

7.12.7 Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study treatment should be held for ≥1 day before the start of palliative radiation therapy and ≥1 day following each dose of palliative radiation therapy. Study treatment shall not be discontinued solely due to palliative radiation.

7.12.8 Prohibited Medications

Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor-Investigator. Refer to the fact sheet for gemcitabine for the most current information on prohibited concurrent medications.

7.12.9 Restrictions for Study Treatment

7.12.9.1 Restrictions for Selinexor

Medications: There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen use must not exceed a total daily dose of 1 g.

Patients should not take GSH-, S-adenosylmethionine (SAM)-, or N-acetylcysteine-containing products during their participation in this study as these products may enhance the metabolism of selinexor. These agents are permitted if the patient has elevated liver function tests, but all natural products or supplements containing these agents should be avoided.

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

7.12.9.2 Restrictions for Gemcitabine

Refer to the full prescribing information for gemcitabine for the most current information for restrictions.

8 STUDY ASSESSMENTS

The next study assessments will be performed along the screening process, treatment period and follow up.

Each time point for the next assessment could be found in Tables 1 and 2 Schedule of Assessments.

Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

8.1 Informed Consent

Assessments may not be performed until the patient provides written informed consent (see Section 14.6.)

Patients that are pre-selected for participation in the study must sign an Informed Consent Form (IC) prior to performing any study procedures. Once patient signs the Informed Consent all specific study procedures can be performed.

The ICs are accompanied by a Patient Information Sheet (PIS) that explains the study and translational study procedures. Nevertheless, the Principal Investigator at the site or the delegated person should ensure that the patient has completely understood the study and no other clarification is needed before signing the consent.

8.2 Demographic and Baseline Characteristics Assessments

8.2.1 Demographics

Patient demographics (including date of birth, sex, race, ethnicity, and date of Informed Consent signature) will be collected.

8.2.2 Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline symptoms as well as a detailed history of prior cancer and their therapies (i.e. chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, PD during or after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. Evaluate the risk of TLS based on a clinical evaluation of comorbidity (such as presence of renal impairment or cardiac insufficiency).

Data from standard-of-care procedures will be part of the patient's medical history and may be used for study purposes.

8.3 Efficacy Assessments

8.3.1 Tumor Assessment

Tumor assessment will be performed by evaluation of CT scan and MRI images according to RECIST 1.1 and Choi criteria.

Screening imaging techniques (CT scan/MRI) have to be done within 28 days prior to study treatment initiation.

Tumor assessments will be done every 6 weeks (±7 days) during the first 6 months of treatment. Tumor assessments will be performed every 8 weeks (±7 days) after 6 months of treatment.

A central radiology reviewer will check measures to establish the best response and progression. Images will be sent by sites in DICOM format and coded with patient ID.

8.4 Safety Assessments

8.4.1 Adverse Events

Information regarding AEs and SAEs will be collected according to CTC 5.0. See Section 9.

8.4.2 Concomitant Medications

Concomitant medications will be documented for each patient at each scheduled visit. A detailed history of medications will be documented. At each study visit, patients will be asked whether they have taken any medication other than the study treatment (from screening 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, should be recorded.

Necessary supportive care such as appetite stimulants, anti-emetics, and anti-diarrheal, etc., is allowed (see Section 7.12.1, Section 7.12.2, and Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor.

8.4.3 Clinical Safety Assessments

8.4.3.1 Weight, Height, and BSA

Height (without shoes) in centimeters and weight (indoor clothing without shoes) in kilograms will be measured. BSA will be calculated by the Du Bois(25) or Mosteller(26) method to determine the volume of gemcitabine to be administered.

8.4.3.2 Physical Examination, Vital Signs, and ECOG Performance Status

Complete physical examinations should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations.

Symptom-directed physical examinations should include body systems as appropriate. These examinations will be performed according to the standards at each institution.

Information about the physical examinations must be present in the source documentation at the study site. Clinically relevant findings made after the start of study dosing, which meet the definition of an AE, must be recorded.

Vital signs include systolic and diastolic blood pressure, pulse measurements, and body temperature. Vital signs should be assessed pre-dose on the scheduled visit day, if possible. Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study.

The ECOG performance status assessments[39] will be performed during the study to assess how the disease affects the daily living abilities of the patients (<Appendix 1>).

8.4.4 Electrocardiography and Echocardiography

A standard 12-lead ECG will be performed. Patients must rest for at least 5 minutes prior to the ECG recording. The date and time the ECG was performed and the following parameters will be recorded: heart rate, PR interval, QT interval, QRS interval, and QT corrected using Fridericia's formula.[40] The Investigator will interpret the ECG using 1 of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant.

An echocardiogram or multiple gated acquisition (MUGA) scan to assess cardiac function and risk of cardiac dysfunction, including cardiomyopathy, will be performed. The same procedure (either MUGA or echocardiogram) that was performed at screening/baseline should be performed throughout the study. Preferably the same cardiologist/radiologist should read and report the outcome to minimize variability in results. Copies of all transthoracic echocardiograms and/or MUGA scans performed on patients who have a ≥20% decrease in left ventricular ejection fraction (LVEF) from baseline and whose cardiac ejection fraction is below the institution's lower limit of the normal range (LLN) will be required by the Sponsor-Investigator for review.

8.4.5 Laboratory Safety Assessments

8.4.5.1 Clinical Laboratory Tests

The next table presents the clinical laboratory tests that will be performed during the study.

Table 12: Clinical Laboratory Tests

Complete Blood Count with Differential (Blood sample: whole blood + EDTA)				
Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
WBC count	WBC differential[a]	Lymphocytes	Neutrophils	Platelets
Complete Serum Chemistry (Blood sample: serum)				
Sodium*	Potassium*	Chloride*	Uric acid	Urea or BUN*, [b]
Creatinine*	Glucose*	Calcium	Phosporus	Magnesium
ALT*	AST*	Alkaline Phosphatase*	Total bilirubin*	LDH*
Total protein	Albumin			
ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; EDTA: ethylenediaminetetraacetic acid; LDH: lactate dehydrogenase; RBC: red blood cell; ULN: upper limit of normal; WBC: white blood cell.				

*=Limited serum chemistry

a. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.
b. Urea (mg/dL) = Blood urea nitrogen (mg/dL) × 2.14.
c. Microscopy will only be performed if clinically indicated.

All laboratory safety assessments will be performed and analyzed at each site by a certified local laboratory. The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values. 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 End of Treatment (EoT) Visit and that is considered clinically meaningful 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 graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.

A copy of the laboratory certification and normal ranges for each parameter measured must be provided to the Sponsor.

8.4.5.2 **Pregnancy Testing**

For females of childbearing potential, a negative urine or serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. A serum hCG or urine pregnancy test is also required for these patients at the EoT Visit.

Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of pair Cycles (2, 4, 6, 8…) while on treatment. A negative pregnancy test must be documented prior to administration of study drug.

Pregnancy testing may also be performed as clinically indicated during the study.

8.5 Other Assessments

8.5.1 Nutritional Consultation

Patients must be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This consultation may be given by a study nurse and can be done by phone.

8.5.2 Durability of Response and Survival Follow-up Visit(s)

After discontinuation of selinexor/gemcitabine if feasible and clinically indicated, the following assessments should be performed at Durability of Response and Survival Follow-up Visits for patients who have not progressed to assess durability of response: clinical visit (when feasible), CT scan every 8 weeks. If these assessments cannot be performed, at a minimum, a telephone call will be made to the patient (or the patient's family) to assess the survival status, status of the patient's sarcoma, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment.

9 SAFETY DEFINITIONS, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 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.
- *Serious adverse event (SAE)*: Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e. 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; or defined by the Investigator as medically important. (See Section 9.2.3 for additional information about SAE reporting.)

9.1.2 Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent should be recorded by the Investigator, regardless of relationship to study drugs. AE registration in the eCRF should be continued for at least 30 days following the last dose of study treatment (i.e. 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 any AEs have occurred during the study, since the last visit. 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 and an 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.

9.1.2.1 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e. are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require

changes in study treatment), should be recorded as an AE. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening Visit) 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 recorded as an AE. A Grade 3 or 4 event (considered to be severe per the current version of NCI CTCAE) does not automatically indicate a SAE unless it meets the definition of serious as defined in Section 9.1.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such.

9.1.2.2 **Tumor Lysis Syndrome**

As of 31 March 2021, TEAEs of TLS were reported in a total of 10 patients; overall, 8 SAEs and 3 non-serious AEs were reported in these patients (one patient had two events). Of the 8 SAEs, 2 were reported from CST, 2 from IST and 4 from EAP. Three non-serious events of TLS were reported in 3 patients from CST. One patient from CST was reported to have experienced 2 TEAEs (1 SAE and 1 non-serious event) of TLS. Going forward all events of TLS will be upgraded to serious by the company irrespective of the reporter's seriousness.

The reported TEAEs of TLS occurred in patients with heavily pretreated haematologic malignancies (7 patients with MM, 2 patients with ALL, and 1 patient with AML). The event intensity was reported as Grade 3 in 6 events, Grade 4 in 3 events, and was reported as severe in 2 events. The outcomes were reported as recovered in 6 events and not recovered for 3 events; and were not reported in 2 events. Of the ten patients with reported TLS, the majority (6) received a combination treatment with selinexor and other agents, specifically: dexamethasone (2), dexamethasone and pomalidomide (2), bortezomib (1) and bortezomib and dexamethasone (1) (administration dates for bortezomib and dexamethasone were not reported). TLS is listed in the Warnings and Precautions sections of bortezomib and pomalidomide labels. Four patients received selinexor treatment only.

The following actions were taken with selinexor in these events: dose not changed (4), temporarily interrupted (3), action taken was not applicable (selinexor was withdrawn prior to the onset of the event (2), and treatment was withdrawn (2).

No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing selinexor EAP. Of the 10 patients, deaths were reported in 4; all deaths were reported to be from causes other than TLS, specifically due to the following Grade 5 events: respiratory failuire secondary to advanced MM (1); Sepsis (1); Respiratory failure, chemotherapy (non-selinexor) induced cardiomyopathy and ALL (1), Plasma cell myeloma (Disease progression) (1).

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, including MM, for potential signs and symptoms of TLS are most relevant.

See Table 10: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor for selinexor dose modification guidance.

9.1.3 Adverse Event Severity

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g. ‘severe’ headache). This is not the same as a “serious” AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If there is not a specific NCI CTCAE grading scale for an AE, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- **Grade 1:** Asymptomatic or Mild symptoms, clinical or diagnostic observations only, intervention is not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living(eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Fatal.

Note: Grade 4 AE should be only considered as life threatening if its occurrence places the patient at immediate risk of death. It does not include any AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

9.1.4 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.

9.2 Serious Adverse Events

See Section 9.1.1 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.

9.2.1 Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (i.e. an overnight stay to facilitate 24-hour urine collection) or other medical procedures are not considered SAEs. A 'serious' hospitalization is defined as 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 as in inpatient to the hospital (e.g. undesirable effects of any administered treatment) and must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period (see Section 9.2.3). Sudden or unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

9.2.2 Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the SAE Report Form provided by GEIS 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 SAE Report 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.

9.2.3 Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study drugs, occurring after the patient has signed informed consent until at least 30 days after the patient has stopped the study drugs must be reported to GEIS within *24 hours* of learning of its occurrence. The

investigational site personnel must use the SAE Report Form provided by GEIS for reporting any SAE.

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

Study CRO: Sofpromed Investigación Clínica, SLU

ensayos@sofpromed.com

Fax: +34 971 570 222

Any SAE observed after the 30-day follow-up period should only be reported to GEIS if the Investigator suspects that the SAE has causal relationship to the study drugs. 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 and an assessment should be made at each study 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 of the event.

Investigators are responsible as applicable for notifying their appropriate Health Authorities, Institutional Review Board or Local and Central Ethics Committees (EC) of all SAEs in accordance with local regulations.

Karyopharm will report applicable SAEs to other applicable regulatory authorities and Investigators utilizing selinexor, as may be required.

9.2.4 Suspected Unexpected Serious Adverse Reactions

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

9.2.5 Adverse Event Reporting

The Sponsor will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance twice per year in the form of line-listings in an excel spreadsheet.

Karyopharm, the drug supplier, will supply the cut-off dates of each requested line listing. The line listings will contain the following information: study ID, unique subject ID, adverse event term, serious event (yes or no), onset date (complete or partial), end date (complete or partial), action taken with selinexor, causality to selinexor, event ongoing (yes or no), outcome of AE, severity CTCAE Grade (1-5), subject dosed with selinexor (yes or no), date of first dose of selinexor, preferred term, system organ class (optional).

9.3 Procedures for Handling Special Situations

9.3.1 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.

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 (i.e. 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.

A list of highly effective methods of contraception is provided in Section 7.12.3.

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 of this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to GEIS by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by GEIS.

The pregnancy should be followed up to determine the 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.

All pregnancies occurring within 3 months after the patient's last dose of study drug must be reported to GEIS, regardless of whether the patient received the selinexor or other study drugs, withdraws from the study, or the study is completed. 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 (e.g. maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 9.2.3).

A pregnancy in a female partner of a male patient must be reported to GEIS 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 a selinexor-containing regimen.

9.3.2 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 GEIS on a SAE report form regardless of whether or not there is an associated AE or SAE.

9.3.2.1 **Overdose**

An overdose is a deliberate or accidental administration of study drugs to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, GEIS 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 recorded. Information regarding the overdose is to be recorded on a SAE report form and sent to GEIS 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 GEIS 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.

9.3.2.2 **Abuse, Misuse, or Medication Error**

Abuse is the persistent or sporadic, intentional excessive use of selinexor 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 the study drug are to be recorded on a SAE report form and sent to GEIS 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 GEIS within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

9.3.2.3 **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 the selinexor are to be recorded on a SAE report form and sent to GEIS 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 GEIS within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

10 DISCONTINUATION CRITERIA

10.1 Early Termination of the Study

The study may be terminated at the 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.

The Sponsor, in conjunction with appropriate regulatory authorities, would then decide if the study should be modified or terminated.

10.2 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:

- Unacceptable AEs or toxicity that cannot be managed by supportive care (this must be linked in the study database to the AE or toxicity event to support discontinuation).
- Any 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:

- Disease progression
- Patient elects to discontinue study treatment
- Pregnancy

Patients may discontinue study treatment for any reason. Patients who choose 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 may elect to withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study.

The reason for the patient's discontinuation of study treatment must be clearly documented in the site source data and include supporting data (i.e. discontinuation for PD must be accompanied by data points in the database to support PD; additionally, if the reason for discontinuation is physician decision, ample justification must be provided and linked to PD values, AEs, etc.).

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

All patients will be followed until disease progression, they withdraw consent, are withdrawn from the study by the Investigator, have died, or have been lost to follow up.

11 STUDY VISITS

11.1 Description of Study Days

11.1.1 Screening

Screening will include the study procedures described below and will be performed within 28 days prior to the start of therapy (i.e. Day -28 to Day -1), as summarized in Study Schematics and Schedule of Assessments and Dosing

Table 1**: Schedule of Study Activities and Assessments (PHASE I)**

The Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF. Data from SOC procedures will be part of the patient's medical history and may be used for study purposes.

Screening may be divided into two (or more) clinic visits at the discretion of the Investigator. The procedures to be performed during screening are listed below assuming such a division, however the decision is up to the Investigator, as long as all procedures are performed and Randomization occurs on Day -3 to Day -1 (i.e. prior to the first day of study administration).

DAY -28 TO DAY -1 (FOR PHASE 1 AND PHASE 2)

- Sign written informed consent (note age on day consent signed)
- Demographics (date of birth, gender)
- Medical history
- Height
- Weight
- Body Surface Area
- Vital signs (BP, pulse, and temperature)
- ECOG
- Physical examination
- 12-lead ECG
- Echocardiogram or MUGA
- CBC with differential
- Complete serum chemistry
- Coagulation test
- Urinalysis
- Pregnancy test
- Tumor sample for diagnosis confirmation

- Tumor for translational research
- Blood for translational research
- Scans (e.g. CT/MRI)
- Adverse events recording
- SAE reporting
- Concomitant medication recording
- Nutritional consultation

11.1.2 Cycle 1

11.1.2.1 Study Procedures (Days 1-21)

These procedures will be followed for all cohorts:

Table 13: Study Procedures for Cycle 1

Procedure	Phase 1 (Days)	Phase 2 (Days)
Weight	1, 8, and 15	1 and 8
Vital signs (BP, pulse, and temperature)	1, 8, and 15	1 and 8
ECOG	1, 8, and 15	1 and 8
Physical examination	1, 8, and 15	1 and 8
CBC with differential	1, 8, and 15	1 and 8
Complete serum chemistry	1, 8, and 15	1 and 8
Coagulation test	1	1
Urinalysis	1	1
Adverse events recording	Throughout the cycle	Throughout the cycle
SAE reporting	Throughout the cycle	Throughout the cycle
Concomitant medication recording	Throughout the cycle	Throughout the cycle
Nutritional consultation	Perform if clinically indicated	Perform if clinically indicated
Quality of Life assessment	1	1

11.1.2.2 Study Treatment Dosing

- Selinexor administration (Days 1, 8, and 15)
- Gemcitabine administration (Days 1 and 8)

11.1.3 Cycle 2

The procedures will be followed for all cohorts:

11.1.3.1 Study Procedures

Table 14: Study Procedures for Cycle 2

Procedure	Phase 1 (Days)	Phase 2 (Days)
Weight	1	1
Vital signs (BP, pulse, and temperature)	1	1
ECOG	1, 8, and 15	1 and 8
Physical examination	1, 8, and 15	1 and 8
12-lead ECG	Perform if clinically indicated	Perform if clinically indicated
Echocardiogram or MUGA	Perform if clinically indicated	Perform if clinically indicated
CBC with differential	1, 8, and 15	1 and 8
Complete serum chemistry	1, 8, and 15	1 and 8
Coagulation test	1	1
Urinalysis	1	1
Pregnancy test	1	1
Adverse events recording	Throughout the cycle	Throughout the cycle
SAE reporting	Throughout the cycle	Throughout the cycle
Concomitant medication recording	Throughout the cycle	Throughout the cycle
Nutritional consultation	Perform if clinically indicated	Perform if clinically indicated
Quality of Life assessment	1	1

11.1.3.2 Study Treatment Dosing

- Selinexor administration (Days 1, 8, and 15)
- Gemcitabine administration (Days 1 and 8)

11.1.4 Cycle ≥3

11.1.4.1 Study Procedures

Table 15: Study Procedures for Cycles ≥3

Procedure	Phase 1 (Days)	Phase 2 (Days)
Weight	1	1
Vital signs (BP, pulse, and temperature)	1	1
ECOG	1	1
Physical examination	1	1
12-lead ECG	Perform if clinically indicated	Perform if clinically indicated
Echocardiogram or MUGA	Perform if clinically indicated	Perform if clinically indicated
CBC with differential	1 and 8	1
Complete serum chemistry	1 and 8	1
Coagulation test	1	1
Urinalysis	1	1
Pregnancy test	1 (even cycles only)	1 (even cycles only)
Adverse events recording	Throughout the cycle	Throughout the cycle
SAE reporting	Throughout the cycle	Throughout the cycle
Concomitant medication recording	Throughout the cycle	Throughout the cycle
Nutritional consultation	Perform if clinically indicated	Perform if clinically indicated
Quality of Life assessment	1 (every 3 cycles)	1 (every 3 cycles)

11.1.4.2 Study Treatment Dosing

- Selinexor administration (Days 1, 8, and 15)
- Gemcitabine administration (Days 1 and 8)

11.1.5 End-of-Treatment Visit (within 30 Days after Last Dose)

Study procedures will be performed within 30 days (+ 7 days) after the last dose of study treatment for all patients, including early termination patients, as summarized below.

- Weight
- Vital signs (BP, pulse, and temperature)
- ECOG
- Physical examination

- 12-lead ECG
- Echocardiogram or MUGA
- CBC with differential
- Complete serum chemistry
- Coagulation test
- Pregnancy test
- Blood for translational research
- Tumor sample for translational research (optional)
- Adverse events recording
- SAE reporting
- Concomitant medication recording
- Scans (if visit is not due to progression)
- Quality of Life assessment

11.1.6 Survival Follow-Up

After treatment discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's status, general health, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

If the patient has not progressed but ended treatment a scan (CT/MRI) will be performed every 8 weeks (±7days).

If the patient has progressed, a scan (CT/MRI) will be performed at least every 3 months.

12 TRANSLATIONAL STUDY

12.1 Biological samples

1. One formalin-fixed paraffin-embedded (FFPE) tumor block sample mandatorily collected at baseline (primary/ metastatic tumor, from surgery/biopsy). Tumor blocks should be collected within the 28 days prior to starting the treatment, except for patients that have a tumor sample in the last 3 months and have not been exposed to any line of treatment, within this time.

NOTE 1: Mandatory biopsies for the translational study must follow the following guideline: minimum of 6 Tru-Cut cylinders (14g-16g needle) divided into two tubes, which in turn will be included in separate paraffin blocks.

NOTE 2: Tumor samples will be centralized at central lab, in IBiS (Seville). Biological samples will be shipped directly from each local site to the central laboratory, via courier, within the first week after enrollment.

2. One formalin-fixed paraffin-embedded (FFPE) tumor block sample optional collected at the End of Treatment.

3. Two 10mL VACUETTE® TUBE K3E K3EDTA tubes of peripheral blood within 72 hours prior to starting treatment (baseline), two 10mL VACUETTE® TUBE K3E K3EDTA within ±72h of each radiological assessment (TC scan, MRI, or PET scan) and two 10mL VACUETTE® TUBE K3E K3EDTA tubes of peripheral blood at the end of treatment (within 72 hours after progressive disease is documented). Plasma will be separated by a Ficoll-Paque protocol. Mononuclear cells will be also collected for further analysis.

NOTE 3: Blood samples will be collected and immediately shipped to central lab. Peripheral blood samples need to be processed within the first 24 hours after being collected.

NOTE 4: Peripheral blood samples cannot be collected at Fridays and the day before a holiday.

NOTE 5: Central laboratory needs to be informed every time that a blood sample is shipped, in order to book the cytometer. This point is mandatory and it should occur at the same time that the courier is requested.

12.1.1 Objectives

- To determinate potential predictive biomarkers to the combination of selinexor plus gemcitabine in sarcomas in tumor blocks and peripheral blood samples.
- To understand the mechanisms and the cell signaling pathways related with response or resistance to the combination in FFPE tumor samples.
- To validate the translational study results in pre-clinical models of sarcoma.

12.1.2 Methodology

A) HTG Molecular Oncology Biomarker Panel Assay:

Gene expression, in pre-treatment tumor samples, will be evaluated with HTG EdgeSeq Oncology Biomarker Panel (OBP) (HTG Molecular; Tucson, AZ, USA). Briefly, samples will

be prepared from FFPE (1.5µm section in a slide), through a chemical lysis without nucleic acids extraction. Then, a protection probe will bind specifically to the target RNA, which will be later eliminated by heat and base treatment. Subsequently, precise sequencing adaptors will be added to the library and this library will be amplified. Afterwards, the library will be quantified and normalized to a pool library and sequenced by Next-Generation Sequencing (NGS) with a HiSeq 2500 System. The data will be analyzed using the HTG EdgeSeq software and the results represented in terms of copy number alteration (CNA). Tumor samples will have more than 70% of tumor area and minimum of 13 mm^2 of area. Gene expression levels will be correlated with clinical data, to determine potential prognostic and/ or predictive biomarkers. Moreover, cell signaling pathways that may be predictive to treatment will be also determined, using gene expression profile. Cell signaling pathways results will be validated in *in vitro* studies. In bioinformatics analysis, particular interest will be putted in DDR-related genes/ cell signaling pathways, as predictive biomarkers of selinexor combination.

B) Gene expression validation of HTG Oncology Biomarker Panel assay results:
The results of gene expression, obtained with OBP panel, will be validated by qRT-PCR, using RNA extracted from FFPE samples. Of FFPE samples, three 20µm-thick sections will be obtained for total RNA extraction using the Recover All Total Nucleic Acid Isolation® kit (Ambion; Austin, USA), following the manufacturer's instructions. RNA concentration will be measured at 260 and 280nm using the Nanodrop® 1000 spectrophotometer (Thermo Scientific; Waltham, MA, USA). Next, the reverse transcription will be performed from 40ng of total RNA using the High Capacity cDNA Reverse Transcription Kit® (Applied Biosystems; Foster City, CA, USA) and following manufacturer's protocol. The changes on target genes expression will be determined in triplicate, by qRT-PCR, in 10µl reactions, containing: 2µl of the synthesized cDNA, 5µl of TaqMan Fast Universal PCR Master Mix (Applied Biosystems) and 1µl of the corresponding expression assay (Applied Biosystems). All PCR reactions will be carried out on a 7500 Fast Real Time PCR system (Applied Biosystems). The expression of these genes will be normalized to β2-microglobulin mRNA levels (Hs99999907_m1, Applied Biosystems). When necessary a different housekeeping gene will be used.

C) Protein expression analysis in FFPE samples:
The genomic alterations determined in FFPE samples will be also validated at protein level by immunohistochemistry (IHC), using complete sections of tumor blocks. The blocks will be revised by a pathologist expert in sarcomas and a hematoxylin-eosin staining will be performed on each block to check for the existence of the tumor. 3µm sections will be used for IHC. Immunodetection will be performed with the DAKO EnVision Visualization Method (DAKO), with diaminobenzidine chromogen as substrate. The sections will be counterstained with hematoxylin.

Peer Review: To improve the reliability of the IHC analysis, the results will be read by two pathologists, experts in sarcomas.

D) Protein expression analysis in plasma:
The protein levels of soluble factors (i.e. angiogenic factors, chemokines, cytokines and others), that proven to be potential predictive biomarkers in OBP assay, will be evaluated and validated, through a ProcartaPlex Immunoassay (ThermoFisher Scientific), using plasma samples collected at different time points during the treatment. Plasma will be isolated from peripheral blood, following a Ficoll-Paque protocol. The protein levels will be accessed by ELISA or ProcartaPlex Immunoassay following the manufacturer's instructions. The soluble factors levels will be correlated with clinical data, to determine potential prognostic and/ or predictive biomarkers, as well as to determine the alterations induced by treatment in these proteins.

E) Peripheral blood mononuclear cells counting:
Variations on peripheral blood mononuclear cells in response to treatment will be assessed by flow cytometry. Regulatory T-cells (Tregs) will be sorted as CD3, CD4, CD25, CD127 cells. Cytotoxic T-cells will be sorted as CD3, CD8 cells and helper T-cells (Th Cells) as CD3, CD4, CXCR3/ CCR4 cells. Mature B-cells will be sorted as IgM, CD19 cells and activated B cells as CD19, CD25, CD30 cells. Monocytes subsets will be sorted as CD14, CD16, CD64 cells, macrophages subsets as CD11b, CD68, CD86, CD163, CD206 cells, dendritic cells subsets as CD1c, CD83, CD141, CD209, MHC II cells and natural killers as CD3(-), CD16, CD56. Cell count number and ratios between cell populations will be correlated with clinical data.

F) Statistical Plan:
For variables with binomial distributions and categorical variables, frequency and percentages will be calculated. A Chi-square test and Fisher´s exact test will be used to compare categorical variables. For time-to-event variables (i.e. PFS or OS) Kaplan-Meier estimations will be used and to compare groups the Log-Rank test. To analyze the reduction of risk Cox Regression will be applied. The translational data will be correlated with clinical results.

12.2 Pre-clinical study

Cell lines:

a) Human leiomyosarcoma cell line SK-UT-1
b) Human primary leiomyosarcoma cell line AA
c) Human primary leiomyosarcoma cell line CP0024
d) Human primary leiomyosarcoma cell line ICP055
e) Human primary leiomyosarcoma cell line IEC005
f) Human primary UPS cell line IEC016
g) Human osteosarcoma cell line U2OS
h) Human osteosarcoma cell line SAOS-2
i) Human osteosarcoma cell line HOS
j) Human osteosarcoma cell line MG-63

12.2.1 Methods

Determination of IC50 proliferation indexes

Working cell lines will be seeded in 96-well plates and treated separately with increasing concentrations of selinexor (1x10-13 to 1x10-7), Gemcitabine (1x10-13 to 1x10-7) for 72 hours in order to analyze cell proliferation. Cell proliferation will be evaluated by MTT assay and the concentrations that inhibit 50% of cell growth (IC50) will be determined using nonlinear regression in Prism 5.0 (GraphPad Software).

***In vitro* studies of cell death**

The induction of late apoptosis will be evaluated after exposing the cell lines to selinexor and/or Gemcitabine. Cells will be seeded in 6-well plates and treated with concentrations in IC50 range. After the respective treatment (72 hours later), cells will be further staining with Propidium Iodide and Annexin-V. The percentage of cells undergoing apoptosis will be determined in a BD FACSCANTO II flow cytometer. Moreover, protein will be extracted in

order to evaluate the presence of cleaved Caspase-3 and cleaved PARP-1, by SDS-PAGE/ Western blotting.

***In vitro* validation of the transcriptional activity in response to treatment**

The transcriptional profile determined in the translational study (OBP panel) will be validated in the cell line panel. Cells will be treated, for 72 hours, with selinexor and Gemcitabine I in monotherapy or in combinations, using concentrations in the IC50 range. For qRT-PCR, total RNA will be isolated by the TRIzol® (Invitrogen Corp., Carlsbad, CA) -chloroform method, from all cell lines, according to the manufacturer's protocol. One microgram of total RNA will be submitted to reverse transcription using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems™ - Thermo Fischer Scientific., Carlsbad, CA), in the presence of MultiScribe™ Reverse Transcriptase and a random primer scheme for initiating cDNA synthesis. The cDNA obtained will be amplified and quantified by real-time quantitative PCR, using the GoTaq® qPCR Master Mix Kit (Promega, Madison, WI). The relative expression of target genes will be normalized to β2 microglobulin (β2M) and the expression in each sample, compared to the control (RNA pool: Universal Human Reference RNA; Agilent Technologies, Santa Clara, CA, USA). Individual quantification of gene expression will be performed using the comparative CT method (CT) and the relative expression will be calculated as $2^{-\Delta CT}$.

The results obtained in the translational study using the OBP panel of HTG Molecular will be also validated at protein levels by SDS-PAGE/ WB and immunofluorescence (IF).

***In vitro* validation of Multicarta Plex results**

Potential predictive biomarkers and changes in protein expression of soluble factors, determined through a ProcartaPlex Immunoassay (ThermoFisher Scientific), in the translational study will be validated by ELISA assay. For this purpose, it will be used cell medium collected from cell culture supernatants, before treatment and after 72 hours treatment. ELISA will be performed following manufacturer's instructions.

***In vivo* experiments**

Experiments in *in vivo* models of sarcoma are not scheduled; however, if any result or mechanisms needs be evaluated or validated in PDX models of sarcoma, the protocol will be amended and the corresponding ethics committee submitted for approval.

13 PLANNED STATISTICAL METHODS

13.1 General Considerations

All the sample size calculations have used Type II error of 80% and one sided, type I error of 5%.

GEIS will have the responsibility of the statistical analysis. The software package used for statistical analysis will be SPSS Statistics (version 20).

For variables with binomial distributions, frequencies and percentages will be calculated with their corresponding 95% CIs.

To compare categorical variables, Fisher's exact or $\chi 2$ tests will be used where applicable.

Time-to-event variables (overall survival and progression-free survival) will be measured from the date of therapy onset and will be estimated according to Kaplan-Meier survival analysis.

Comparisons between the variables of interest will be done with the log-rank test.

Multivariate analyses with the variables that appear to be significant in the univariate analyses will be done according to the Cox proportional hazard regression model.

The validity of proportional hazard assumption will verified by adding a time- dependent variable to each model to confirm that the hazard ratio for each covariate do not increase or decrease over time.

All p values reported will be two-sided, and significance is defined as a p value lower than 0.05.

13.2 Determination of Sample Size

Sample Size Estimation for Leiomyosarcoma (Single-Arm Cohort)

Sample size is obtained for the primary endpoint of 6-month progression-free survival rate, and estimated accrual 24 months. A 6-m PFSR of 20% will be considered not promising whereas of 45% will be considered promising in this population. With a type I error α of 0.05 and a power of 0.90, 38 patients were estimated in this cohort. With Simon's two-stage Optimal design(46), at least 5 cases over the 16 first patients (stage 1) should have ≥ 6-m PFS. Then additional 22 patients would be accrued up to 38 patients. If at least 12 patients had a 6-m PFS or longer, further investigation of the drug is warranted.

Bibliographic support

In comparative studies with advanced leiomyosarcoma, in PALETTE trial comparing pazopanib vs placebo, the median of PFS reported with approved drugs was around 4.5 months with a calculated 6-month PFSR of 37%(47). Similarly, in phase III trial comparing trabectedin vs dacarbazine, the median of PFS for the trabectedin was 4.2 months, significantly better than 1.5 months for dacarbazine. The calculated 6-month PFSR for the active drug was 37% while it was 14% for dacarbazine. The only phase III conducted in advanced soft tissue sarcoma with gemcitabine combination was addressed in first line obtaining 46.4% of 6-month PFSR, in second or further line this should be less than 40%.[3] Interestingly, a recent case-series focusing on advanced leiomyosarcoma reported in leiomyosarcoma with molecular-aberrant related therapies a median PFS of 5.8 months

whereas in leiomyosarcoma without aberration-related therapies the median PFS was 1.9 months with a calculated 6-month PFSR of 12%(48).

More recently, a new benchmark recommended by EORTC for advanced/metastatic leiomyosarcoma has been shared. For second or further lines, the updated threshold for activity in leiomyosarcoma is a 6-month PFS rate of >30%(49). Thus, the statistical assumptions are based on this data.

Sample Size Estimation for Malignant Peripheral Nerve Sheath Tumor (Single-Arm Cohort)

Sample size is obtained for the primary endpoint of 6-month progression-free survival rate, and estimated accrual 24 months. A 6-m PFSR of 15% will be considered not promising whereas of 35% will be considered promising in this population. With a type I error α of 0.05 and a power of 0.90, 44 patients were estimated in this cohort. With Simon's two-stage Optimal design(46), at least 4 cases over the 19 first patients (stage 1) should have ≥ 6-m PFS. Then additional 25 patients would be accrued up to 44 patients. If at least 11 patients had a 6-m PFS or longer, further investigation of the drug is warranted.

Bibliographic support

MPNST is classically considered more resistant to chemotherapy than other common subtypes of soft tissue sarcoma, and there is no threshold released by EORTC nor by other cooperative groups for the systemic treatment activity of MPNST. The classic benchmark would fit with the expectation of PFS at 6 months(50). One compilation of advanced MPNST treated with systemic therapies, reported a median PFS of 3.3 months for second lines showing a dismal prognosis in MPNST progressing after anthracycline-based chemotherapy(51).

13.3 Analysis Populations

13.3.1 Intent-to-Treat Population

The intent-to treat population is formed by all the patients providing informed consent and with a centrally confirmed diagnosis of leiomyosarcoma, UPS, MPNST or ASPS.

Progression-free survival rate at 6 months (the primary objective), overall survival and progression-free survival will be measured with the intention-to-treat population.

13.3.2 Per Protocol Population

The per-protocol population is defined as the subset of the intention-to-treat population with measurable disease at study entry per RECIST. Patients in this population also received at least 21 days (one cycle) of treatment and had at least one radiological assessment. Otherwise the patient was not considered assessable (the exception will be early progression or death, for which patients will be included).

13.3.3 Safety Population

Safety population is defined as all the patients receiving at least one dose of any of the study drugs.

13.4 Demographics and Baseline Characteristics

The following demographic data will be collected:

- Date of birth
- Gender
- Date of initial diagnosis
- Stage at diagnosis (localized/locally advanced/metastatic)
- Size at diagnosis (mm)
- Site of primary tumor
- Previous surgery (Yes/No)
- Date of metastatic disease
- Relevant medical history

In baseline the following data will be collected:

- ECOG
- Concomitant medication
- Stage at study initiation (locally advanced/metastatic)
- Site of metastasis
- Number of previous lines of systemic therapy for advanced disease
- Date of progression for study inclusion

13.5 Efficacy Analysis

- Progression-free survival rate (PFSR): Efficacy measured by the PFSR at 6 months according to RECIST 1.1. PFSR at 6 months is defined as the percentage of patients who did not experience progression or death due to any cause since the first dose of experimental treatment until month 6 after treatment initiation.
- Overall survival (OS): OS is defined as the time between the date of first dose and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive.
- Overall Response Rate (ORR): ORR is defined as the number of subjects with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) divided by the number of response evaluable subjects (according to RECIST 1.1 criteria).
- Efficacy measured through tumor response according to Choi criteria. The evaluation criteria will be based on the identification of target lesions in baseline and their follow-up until tumor progression.
- Clinical outcomes of post protocol treatments assessed by observation of such treatments in follow-up stage.

13.6 Safety Analysis

13.6.1 Adverse Events

The safety profile of the experimental treatment will be analyzed through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 5.0.

Adverse Events (AEs) will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered to be treatment emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study treatment through 30 days following last dose 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.

AEs will be summarized by patient incidence rates. In all tabulations, a patient may contribute only once to the count for a given AE preferred term.

The number and percentage of patients with TEAEs will be summarized, as well as the number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same TEAE, the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations.

Serious AEs (SAEs) will also be tabulated.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment emergent and post-treatment) will be listed in patient data listings.

Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

13.6.2 Laboratory Data

The actual value and change from baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, by arm, and for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (i.e. those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

13.6.3 Vital Signs and Physical Examinations

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data will be recorded. All examination findings will be presented in a data listing.

14 ADMINISTRATIVE MATTERS

14.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP). Applicable local regulations, including European Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC, and the ethical principles outlined in the Declaration of Helsinki will be followed.

14.2 Ethics Committees

The protocol, the proposed ICF, and any amendment must be reviewed and approved by a properly constituted ethics committee (e.g. IRB/IEC/REB) before proceeding to use these documents.

This study will be performed according to the Ethic Principles originated in The Declaration of Helsinki adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, China, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, clarification note of paragraph 29, added by WMA, Washington 2002, Clarification note of paragraph 30, added by WMA General Assembly, Tokyo 2004, 59th General Assembly, Seoul, Korea, October 2008 (Annex XII), 64th General Assembly, Fortaleza, Brazil, (October 2013) and the Good Clinical Practice issued by the work group of Efficacy of Medicinal Substances of the European Community (1990) (CPMP/ICH/135/95) and all legal requirements and laws of each country participating in the Clinical Trial.

14.3 Regulatory Authority Approval

Before implementing this study, the protocol must be approved by relevant, competent regulatory authorities.

14.4 Protocol Adherence

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 the instructions and procedures found in this protocol and to give access to all relevant data and records to the drug supplier, Quality Assurance representatives, designated agents of the Sponsor-Investigator, ethics committees, and regulatory authorities as required. Investigators attest they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report (CSR). A significant protocol deviation is defined as any change to the execution of the protocol that affects the scientific integrity or design of the study, or the rights, safety or welfare of study patients.

14.5 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be provided by the Sponsor-Investigator, reviewed/approved by the drug supplier, and

approved by Health Authorities where required, and the ethics committee (e.g. IRB). Only amendments that are required for patient safety may be implemented prior to ethics committee (e.g. IRB) 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, the Sponsor-Investigator should be notified of this action and the ethics committee (e.g. IRB) at the study site should be informed according to local regulations but not later than 10 working days.

14.6 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law, ethics committee [e.g. IRB], or regulation), ethics committee (e.g. IRB)-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures. Note age on date consent is signed. 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 (i.e. procedures that are not specific to the conduct of the study).

Informed consent must also be obtained for patients before conducting any study-specific procedures for treatment.

The process of obtaining informed consent should be documented in the patient source documents. 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 the date when the study ICF was signed in the medical records of the patient. The name and role of the witness, if required, should also be documented.

The Sponsor-Investigator will provide to the drug supplier, in a separate document, a proposed ICF that is appropriate for this study and complies with the ICH GCP guideline and regulatory requirements.

14.7 Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of all patients; patients must not be identified by names in any documents submitted to the drug supplier or its designee. Signed ICFs and patient enrollment logs must be kept strictly confidential.

14.8 Collection, Auditing Study Documentation, and Data Storage

14.8.1 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 ICH E6 GCP, and according to the regulatory and institutional requirements.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The study database is the primary data collection instrument for the study. The Investigator is responsible for the accuracy, completeness, and timeliness of the

data reported in the database and all other required reports. Data reported in the database, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the source documents must be recorded. Any missing data must be explained. If electronic records are used, an audit trail will be maintained by the system, in compliance with 21 CFR Part 11.

The Investigator/institution should maintain 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 15 years from the completion of the clinical study unless the Sponsor 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.

14.8.2 Auditing Procedure

Institution could be audited by GEIS and health authorities.

GEIS will give notice with 3 weeks in advance to the site the auditing date and the planned agenda.

14.9 Termination of the Study

It is agreed that, for reasonable cause, either the Sponsor-Investigator or drug provider, may terminate the Investigator's participation in this study after submission of a written notice. The drug provider may terminate the study at any time upon immediate notice for any reason including the drug provider's belief that discontinuation of the study is necessary for patient safety.

15 DATA MANAGEMENT

15.1 Electronic case report form (eCRF)

In this protocol the term electronic case report form (e-CRF) refers to a web-based electronic data record in which the patient data will be collected.

An e-CRF is required to be completed by each participating site for each recruited patient. Only duly authorized and trained staff of each center will be granted access to enter and modify data in the e-CRF. Staff in charge of e-CRF usage will be given a unique user name and password.

The completed original electronic CRF files are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or regulatory authorities, without written permission from the Sponsor.

The investigators have the ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the e-CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic, attributable, complete, consistent, legible, timely, enduring and available when requested. The e-CRF must be signed electronically by the investigator or by an authorized staff member to attest that the data contained in the e-CRF is true. Any changes to entries made in the e-CRF will be tracked by an audit trail system that will identify the old and new values of the data fields, the person who made the change and the reason of modification (if necessary), thus not obscuring the original entry.

The data will be recorded in the e-CRF GCP-compliantly at the study center. The e-CRF application is designed to be entirely server-based. All stages in the processing, with the exception of the actual data entry and display, are performed centrally on a web/database server. All the data will be stored in the central server. The server will be securely housed at a professional hosting provider hired by the study CRO in Spain, guaranteeing effective security and backup mechanisms.

For data entry and print-outs, the e-CRF system is based fully on a web interface. Entry forms and reports are displayed on the client computer as HTML pages via any Web browser (Firefox 57+ and Chrome 75+). No additional software is necessary to operate the e-CRF on the investigator's client computer (no plugin installations or software/hardware adaptations needed). The e-CRF is operating system independent (Win/Mac).

The data will be checked for correctness by validity and consistency checks. Implausible or missing data can be corrected or supplemented following discussion with the investigator. All corrections will be tracked and stored by the audit trail system.

Other than the investigator, only expressly authorized persons trained for the study may complete the e-CRF. Access control will be implemented by an auditable registry of user logins and logouts. Automatic session logouts will be implemented after predefined periods of inactivity for security reasons. The e-CRF will not show patient personal identification data (each subject will be identified by a unique trial number only).

A comprehensive Data Management Plan will be developed by the study CRO specifying e-CRF/Database design and data-related procedures and policies.

15.2 Record keeping

To permit evaluations, audits and/or inspections from regulatory authorities or the Sponsor, investigators agree to keep records, including the identity of all participating patients (e.g. enough information to link records), all original signed informed consent documents, safety reporting forms, source documents and appropriate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be kept by the investigator according to International Conference on Harmonisation (ICH) and local regulations. In case an investigator becomes unable for any reason to continue the retention of study records for the required period, the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor. Investigators must receive the Sponsor's written permission before disposing of any records.

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Appendix 1 Eastern Cooperative Oncology Group Performance Status Criteria

ECOG Performance Status Scale[39]	
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 (e.g. 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.

Appendix 2 Nausea management recommendations

Primary prophylaxis

- **Ondansetron 8mg** (or another inhibitor, according to standard of care): Its administration is recommended 30-60 minutes before each selinexor dose. Then, it is recommended to take it every 8 hours during the following 2-3 days (extend or shorten the interval according to patient's tolerance).
- **Olanzapine 2.5 mg:** Its administration is recommended once per day (preferably at night). It is permitted to take it the day before selinexor administration. Maintain daily or intermittent dose according to patient's tolerance. If nausea are under control only with ondansetron, olanzapine can be interrupted.

Optional

- Metoclopramide: 10 mg every 6-8 hours can be added.
- Dexamethasone: It can be added on day 1 and 8 with gemcitabine administration according to standard of care. It is not mandatory and to limit administration days is recommended.