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2013-133: Phase Ib Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330), Gemcitabine and nab-Paclitaxel and Phase II Study of Gemcitabine and Selinexor in Patients with Metastatic Pancreatic Cancer

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INVESTIGATORS' AGREEMENT

I have read and understand the contents of this clinical protocol for Study No <insert study number> dated <DD Month YYYY> 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 FDA regulatory requirements.

Principal Investigator's Signature: _____

Principal Investigator's Name:

Institution:

Date:

Co-Investigator's Signature: _____

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Date:

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Institution:

Date:

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Co-Investigator's Name:

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Title: Phase Ib Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330), Gemcitabine and nab-Paclitaxel and Phase II Study of Gemcitabine and Selinexor in Patients with Metastatic Pancreatic Cancer

STUDY SYNOPSIS

Study Title:

Phase Ib Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330), Gemcitabine and nab-Paclitaxel and Phase II Study of Gemcitabine and Selinexor in Patients with Metastatic Pancreatic Cancer

Primary Objectives:

1. Phase I: To determine the recommended phase 2 dose (RP2D) of gemcitabine, nab-paclitaxel and selinexor for untreated metastatic pancreatic cancer [COMPLETED]
2. Phase I: To determine the safety profile of gemcitabine, nab-paclitaxel and selinexor [COMPLETED]
3. Phase II: To test whether the combination of gemcitabine and selinexor improves the median overall survival of patients with metastatic pancreatic cancer who have failed frontline non-gemcitabine containing regimens beyond 5.6 months (median overall survival of patient receiving gemcitabine only based on historical data; J Clin Oncol. 1997 jun;15(6):2403-13)

Secondary Objectives:

1. To determine objective response rate to combination of gemcitabine, nab-paclitaxel and selinexor using RECIST criteria
2. To assess safety of selinexor in combination with gemcitabine in phase II portion of the study
3. To determine progression free survival (PFS) in patients treated with gemcitabine and selinexor
4. To explore the influence of selinexor and gemcitabine on the nuclear expression and localization of tumor suppressor gene proteins

Sample Size:

Phase I: Up to 12 patients with metastatic pancreatic cancer [COMPLETED]
Phase II: up to 44 patients.

Study Design:

This is a multicenter phase Ib study to investigate selinexor when combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic cancer and phase II study of selinexor plus gemcitabine in patients with pancreatic cancer in second line setting. Objectives include the determination of the safety profile of selinexor in combination with gemcitabine and selinexor and the overall survival of patients who receive the gemcitabine-selinexor combination.

The study was a phase Ib study that was designed according to a standard 3+3 design and is now completed. The Maximum Tolerated Dose (MTD) was the lowest dose for which less than a third of patients experienced a Dose Limiting Toxicity (DLT). To ensure sufficient

toxicity data at the MTD, a minimum of 6 patients were to be enrolled at the MTD. We anticipated that the RP2D would be the same as the MTD.

Phase Ib had three cohorts as shown in table 1. Only initial cohort was completed because of DLT.

At this time, up to 44 patients with metastatic pancreatic adenocarcinoma that were previously treated with a non-gemcitabine based regimen will be enrolled onto the phase II part of the study. The first fourteen patients with liver metastases that are accessible for image guided percutaneous core biopsies will be randomized into two post-treatment biopsy groups, group 1 and 2. The remaining 30 patients enrolled in this trial will be placed in group 3 (no biopsy group).The post-treatment biopsy will be done only on C1D3 and the tissue obtained will be studied for changes in expression of tumor suppressor proteins (TSPs) caused by the combination of drugs compared to either biopsy sample obtained at screening or archival tissue obtained at time of diagnosis.

- **Group 1** will receive gemcitabine without selinexor on cycle 1 day 1. This will be followed by a biopsy of metastatic liver lesion approximately 48 hours after administration of the gemcitabine. Following the biopsy (C1D3), patients in group 1 will receive the first dose of selinexor. Then on C1D8 and C1D15, selinexor will be given with gemcitabine. In the subsequent cycles, Selinexor will be given concurrently with Gemcitabine on days 1, 8, and 15 of each 4-week cycle.
- **Group 2** will receive gemcitabine concurrently with selinexor starting on C1D1. A biopsy of the liver will be performed approximately 48 hours after administration of gemcitabine and selinexor. In Group 2, gemcitabine /selinexor combination will be administered once every week for three weeks on days 1, 8 and 15 of each 4-week cycle.
- **Group 3** will receive gemcitabine concurrently with selinexor starting on C1D1 and then weekly for three weeks (days 1, 8 and 15) of each 4-week cycle.

It should be noted that the goal of randomization is to obtain tissue for pharmacodynamics assessment and determine the impact of the treatment on target molecules. If any of the first 14 patients with liver metastates consented to enroll in the study but refused to consider the C1D3 biopsy then those patients will be allocated to Group 3 (no biopsy group).

Table 1: Cohorts in phase I [COMPLETED]

Cohort	Gemcitabine (mg/m^2) Days 1, 8, 15	Nab-paclitaxel (mg/m^2) Days 1, 8, 15	Selinexor (mg) Days 1, 8, 15*
Level 2	1000	125	80
Level 1 (starting)	1000	125	60
Level -1	1000	125	40

Table 2: Phase 2 dose adjustment

	Gemcitabine (mg/m^2) Days 1, 8, 15	Selinexor (mg) Days 1, 8, 15*
Level 1 (starting)	1000	80
Level -1	750	60
Level -2	500	

*Except for C1 of phase II in Group 1 where selinexor will be given on C1D3.

Dose Schedule and Definition of a Treatment Cycle:
Phase 1b [COMPLETED]: A treatment cycle will be 4 weeks (+/- 3 days). In each cycle, patients will have 3 doses of gemcitabine/ nab-paclitaxel and 3 doses of selinexor. Gemcitabine/ nab-paclitaxel combination will be administered IV weekly for 3 weeks with one week off. Selinexor will be administered orally once a week on Weeks 1, 2 and 3 of each 4-week cycle. Once a MTD is determined, it will be the recommended dose of selinexor for Phase II and patients will be treated with it until disease progression or undue toxicities.

Phase II: A treatment cycle will be 4 weeks (+/- 3 days). Group 1 will receive IV gemcitabine without selinexor on day 1 of cycle 1. A liver biopsy will be performed on day 3 of cycle 1 followed by oral administration of the C1 Week1 dose of selinexor. Then, gemcitabine/selinexor will be administered on day 8 and 15 of week 2 and 3. Gemcitabine and selinexor will not be administered on week 4. In the subsequent cycles, both drugs will be given on days 1, 8, and 15 of 4-week cycle. Group 2 will receive gemcitabine/selinexor on day 1, 8, 15 of week 1, 2, 3 of a 4-week cycle. A biopsy of the liver will be performed approximately 48 hours after administration of gemcitabine and selinexor on C1 D1. Gemcitabine/selinexor will not be administered in week 4. Group 3 will receive gemcitabine/selinexor on day 1, 8, 15 of week 1, 2, 3 of a 4-week cycle. No biopsy is planned for this group. Gemcitabine/selinexor will not be administered in week 4

Definition of Dose Limiting Toxicity (DLT):
DLT is defined as any of the following occurring in the first 28 days (first cycle) of study participation that is considered **at least possibly related to selinexor administration**:

- > 1 missed doses in 28 days due to a toxicity that is possibly selinexor-related
- Discontinuation of a patient due to a toxicity that is at least possibly selinexor-related prior to completing Day 28 of the first cycle

Non-Hematologic:

- Grade ≥ 3 fatigue, nausea, vomiting or diarrhea despite receiving optimal supportive medications
- Any other Grade ≥3 non-hematological toxicity [except for electrolyte abnormalities that are reversible and asymptomatic]
- Grade ≥3 AST or ALT elevation lasting longer than 7 days or Grade ≥3 AST or ALT elevation in the setting of bilirubin elevation > 2x ULN

Hematologic:

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm3] lasting ≥7 days
- Febrile neutropenia (ANC<1000/mm3 with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour)
- Thrombocytopenia (platelet count <25,000/mm3) that persists for ≥7 days
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding

Discontinuation Criteria:

The investigator may remove a patient from the study for the following reasons:

- Subjective and/or objective disease progression
- Noncompliance with study procedures
- Need of treatment with medications not permitted by the study protocol
- Patient withdrawing consent to participate in the study
- Intercurrent illness that interferes with study assessments or safe administration of study drugs
- Frequency and/or severity of Adverse Events (AEs) in this study that indicate an unacceptable health hazard to study participants
- For the third occurrence of the same Grade≥3 non-hematological toxicity
- Investigator discretion

Duration of the Study:

The enrollment period for the study is expected to be approximately 28-32 months with an additional 12 months for follow up after the last patient enrolled in the phase II cohort. The treatment period for an individual patient is expected to be greater than 2 months and without mandated maximum treatment duration or number of cycles.

Study Eligibility Criteria:

Inclusion Criteria:

1. Written informed consent in accordance with federal, local, and institutional guidelines
2. Age >18 years
3. Patients with metastatic pancreatic adenocarcinoma who have failed one non-gemcitabine based regimen for metastatic disease.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 1)
5. Adequate hematopoietic function: absolute neutrophil count (ANC) ≥1500/mm^3 and platelet count ≥100,000/mm^3
6. Adequate hepatic function: bilirubin <2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 times ULN) and ALT or AST ≤2.5 times ULN
7. Adequate renal function: serum creatinine ≤ 1.5 mg/dL
8. Serum albumin ≥ 3.0 g/dL
9. Effective contraception: Female patients of childbearing potential must agree to use highly effective methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if

sexually active with a female of childbearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, highly effective methods of contraception must be used throughout the study and for three months following the last dose.

10. Patients with history of previously treated other malignancies who do not have any evidence of recurrent disease for the last three years are allowed

Exclusion Criteria:

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

1. Patients who are pregnant or breast feeding
2. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤3 weeks prior to cycle 1 day 1. Treatment with mitomycin C or radio-immunotherapy must be completed within 6 weeks prior to cycle 1 day 1.
3. Major surgery within 3 weeks of cycle 1 day 1
4. Prior therapy with gemcitabine based regimen for metastatic disease or gemcitabine based adjuvant therapy completed less than twelve months from enrollment
5. Unstable cardiovascular function that includes and may not be limited to:
    - symptomatic myocardial ischemia, or
    - uncontrolled clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), or
    - congestive heart failure (CHF) of NYHA Class ≥3, or
    - myocardial infarction (MI) within 3 months of cycle 1 day 1
6. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose
7. Known to be HIV seropositive who are on anti-HIV drugs because of the unknown interactions between these drugs and the study agents
8. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen)
9. Patients with active CNS malignancy. Asymptomatic small lesions are not considered active. Treated lesions may be considered inactive if they are stable for at least 3 months.
10. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea
11. History of seizures, movement disorders, or cerebrovascular accident within the past 5 years prior to cycle 1 day 1
12. Patients with macular degeneration, uncontrolled glaucoma, or markedly decreased visual acuity based on physician's assessment
13. Serious psychiatric illness (e.g., depression, psychosis) or medical conditions that could interfere with treatment
14. Participation in an investigational anti-cancer study within 3 weeks prior to cycle 1 day 1

15. Concurrent therapy with approved or investigational anticancer therapeutics other that what is stipulated by the protocol
16. Clinically significant ascites

Pharmacodynamic Assessments:
The assay is comprised of immunohistochemistry on paraffin embedded tumor samples to determine nuclear localization of p27, IκB, FOXO, and PAR4 tumor suppressor proteins.

Efficacy Assessment:
Objective disease response assessment will be made according to standard, international RECIST 1.1 criteria for solid tumors[1]. Anti-tumor activity will be described in terms of best overall objective tumor response, duration of response (DOR), progression free survival (PFS), and duration of stable disease and overall survival (primary endpoint). The reasons for going off study treatment will be described for all patients.

Safety Variables & Analysis:
The safety and tolerability of selinexor in combination with gemcitabine will be evaluated by means of DLTs, AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used for grading of AEs. Investigators will provide their assessment of attribution as 1) unrelated, 2) possible,3) probable, or 4) definite for all AEs.

All patients who receive at least one dose of selinexor will be included in the safety population. Interim safety data will be examined on an ongoing basis to ensure patient safety and to comply with the clinical trial dose change rules.

Futility monitoring
A concern with this regimen is that selinexor may impede the activity of gemcitabine, due to possible increased toxicity and decreased exposure to gemcitabine, resulting in worse survival outcomes. While our final analysis will be able to quantify this hypothesis (as it is a two-sided test), it is necessary to continually monitor the patients on trial for futility of treatment. As our final sample size is small for our 1-arm study, utilizing a survival endpoint for futility monitoring is not feasible. Therefore, we will monitor the proportion of patients who survive less than the reported median survival under the null hypothesis (5.6 months). We would recommend reconsidering the phase II portion of the study for futility reasons if there were greater than half of the registered patients at any time who did not survive longer than 5.6 months once at least 10 patients have either had an event or survived longer than 5.6 months. Thus, we will compute the [number of patients who survived less than 5.6 months]/([number of patients who survived less than 5.6 months] + [number of patients will have survived longer than 5.6 months]) and monitor if that proportion ever becomes greater than one half once 10 patients had either outcome in the denominator.

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LIST OF ABBREVIATIONS

Acronym	Definition
AE	adverse event
APC	adenomatous polyposis coli gene/protein
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BSA	body surface area
BUN	blood urea nitrogen
CBR	clinical benefit rate
Cmax	maximum plasma concentration
CR	complete response
CRM1	chromosomal maintenance region 1 gene/protein (XPO1)
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
Cys	cysteine
Del	deletion
DOR	duration of response
DLT	dose-limiting toxicity
ECG	electrocardiogram
G-CSF	granulocyte-colony stimulation factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GRP	growth regulatory proteins (e.g., p21CIP, p27KIP)
hERG	human ether-à-go-go-related gene
HNSTD	highest non-severely toxic dose
IC50	50% inhibitory concentration
ICH	International Conference on Harmonization
IND	Investigational New Drug [Application]
IFN	interferon
IκB	Inhibitor of NF-κB
IL	interleukin
IV	intravenous
kD	kilodalton (molecular weight)
LMB	leptomycin B
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MTD	maximum tolerated dose
NDA	New Drug Application
NEI	nuclear export inhibitor / inhibition
NES	nuclear export sequence
NF-κB	nuclear factor kappa B
NOAEL	no observed adverse effect level
NPC	nuclear pore complex
NPM	nucleophosmin gene/protein
NS	not specified

Acronym	Definition
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
p21	cyclin dependent kinase (CDK4) inhibitor protein of 21K molecular weight
p27	cyclin dependent kinase (CDK2) inhibitor protein of 27K molecular weight
P2RD	phase 2 recommended dose
p53	tumor suppressor gene/protein of 53K molecular weight, TP53
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PDn	pharmacodynamics
PI3K	phosphoinositol triphosphate kinase
PK	pharmacokinetics
PO	per os (oral)
PR	partial response
pRB	retinoblastoma gene/protein
PTEN	phosphatase and tensin homolog
RP2D	Recommended phase 2 dose
QOD	every other day dosing
QODx3	every other day dosing for 3 doses (over 5 days)
QT interval	the interval between Q and T waves of the electrocardiogram
QTc interval	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SINE	selective inhibitor/inhibition of nuclear export
STD10	severely toxic dose to 10% of animals
t1/2	half-life
TEAE	treatment emergent adverse events
TIW	three times weekly
TK	toxicokinetics
TSP	tumor suppressor proteins
topo2	topoisomerase 2
TTP	time to progression
ULN	upper limit of normal
Vss	volume of distribution at steady state
XPO1	exportin 1 gene/protein (CRM1)

1 INTRODUCTION

1. 1 Overview

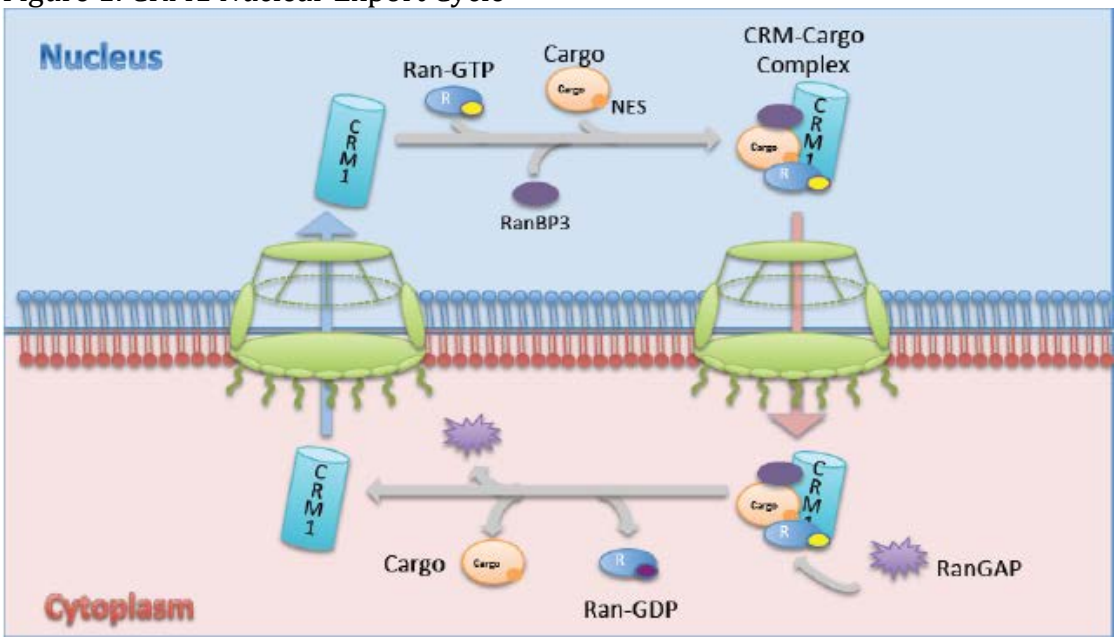
Over 10 major tumor suppressor pathways have evolved to prevent the development and progression of cancer. The majority of the tumor suppressor (TSP) and growth regulatory proteins (GRPs) mediating these pathways act in the cell nucleus downstream of signaling pathways. Accumulating data suggest that in order to maintain their malignant behavior, neoplastic cells must inactivate most or all of the known TSP and GRP pathways [2]. Active nuclear *export* of TSP/GRP is a very efficient and rapid means of overcoming the normal cell cycle and genomic instability checkpoints mediated by these proteins. Essentially, all known TSP/GRP utilize a single non-redundant nuclear export protein complex in order to exit the nucleus. Exportin 1 (XPO1), more commonly called chromosomal region maintenance protein 1 (CRM1), is the primary component of this export complex, and is overexpressed in many types of cancer [3].

Selinexor is a *S*elective *I*nhibitor of *N*uclear *E*xport (SINE) that binds in a reversible manner and inactivates CRM1, thereby forcing the nuclear retention of key TSPs/GRPs, such as FOXO, p21, p27, PAR4, p53. Transient retention of TSPs/GRPs in the nucleus at high levels via CRM1 blockade re-activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released.

1.1.1 Nuclear Export

The majority of proteins (>40kD) and many RNAs require specific transporters in order to enter and exit the nucleus through the nuclear pore complex (NPC), and these transporters are known as importins or exportins, depending on their specific activity.
CRM1, also called exportin 1 (XPO1), is the major nuclear export protein in the cell [4]. CRM1/XPO1 controls the nuclear export of key TSPs and GRPs in the cell through the NPC. CRM1 forms trimeric transport complexes with RanGTP and a cargo molecule, a process that is promoted by the Ran-binding protein RanBP3 (Figure 1). Approximately 200 different mammalian CRM1 cargo proteins are known [5], including the vast majority of known TSPs and GRPs. CRM1 "recognizes" most of these cargo proteins for nuclear export through canonical Nuclear Export Sequences (NES), typically leucine-rich repeats in the cargo protein. These NES are often buried in the protein cargoes, and only unmasked when cells receive specific signals from their environments. CRM1 itself has a very specific cargo-binding groove that allows it to accommodate NES-bearing proteins from very diverse families without undergoing significant conformational changes [5]. In some cases, cargoes require adaptor proteins such as 14-3-3 in order to bind to CRM1 [6]; this binding is also usually under post-translational control. In addition, CRM1 mediates the export of a small number of RNAs [7]such as COX2 [8], though most RNAs are exported by NXF1/TAP [7].

Figure 1: CRM1 Nuclear Export Cycle



1.1.2 Inactivation of TSP/GRP by Nuclear Export

The regulation of TSPs and GRPs is normally tightly regulated by the cell in response to environmental signals. In order for cells to divide efficiently, ordered activation and inactivation of cell cycle control proteins is required. One of the most efficient means of altering a protein's functions is simply to change the protein's location within the cell. Because TSPs and GRPs mediate most of their control functions in the nucleus, the nuclear export of these molecules is an effective means of inactivating them. Emerging data suggest that tumor cells take advantage of this by increasing CRM1 levels [9, 10]. Most TSPs/GRPs are not good substrates for CRM1-mediated export unless they undergo post-translational modification. A diverse set of cargo modifications have been linked to nuclear export and only a few are mentioned here with specific TSPs.

The tumor suppressor protein p53 is normally activated by stress and damage signals from the environment, including chemotherapy and radiation, and is rapidly synthesized and imported into the nucleus. It activates a diverse set of downstream proteins leading to cell cycle arrest, initiation of a 'genome survey', and apoptotic cell death when cell damage is severe [11]. Mono-ubiquitination of p53 by MDM2 (hDM2), a protein that is often overexpressed in neoplastic cells, renders it an excellent substrate for CRM1, and it is exported from the nucleus to be degraded in the cytoplasm by the proteasome [11]. Most tumors harboring wild type p53 (p53wt) show overexpression of MDM2, indicating that p53 inactivation is probably necessary for the neoplastic phenotype. In cells that are defective (deleted or mutant on both p53 alleles), the related TSP p73 can be engaged [12]. CRM1 blockade forces p53 and p73 nuclear retention and even in cells with a single p53wt allele there will be activation of downstream cell cycle regulatory and apoptotic functions [3].

A commonly activated pathway across human cancers is the PI3K/AKT/mTOR pathway [6, 13]. Activation is accomplished by a number of mechanisms including loss of the TSP PTEN (phosphatase and tensin homolog) or activating mutations in *PI3K* or *AKT*. One of the major downstream effects of activation of this pathway is the phosphorylation and subsequent nuclear export of TSPs known as forkhead-box (FKH) proteins. The O-subfamily of FKH proteins, called FOXO, particularly FOXO3, are potent cell cycle regulators with clear TSP function [13, 14]**.** CRM1 blockade forces FOXO and p53 nuclear retention and counteracts an activated PI3K/AKT pathway that is independent of the upstream aberration in the pathway.

The IκB kinase that is activated in inflammation, stress, and in several metastatic cancers, phosphorylates the inhibitor (I-κB) of nuclear factor κB (NF-κB)[15, 16]. IKK also phosphorylates FOXO, leading to its nuclear export[17]**.** Phosphorylated I-κB is a good substrate for CRM1, and is rapidly exported from the nucleus and degraded in the cytoplasm. Blockade of CRM1 prevents export of I-κB from the nucleus, neutralizes NF-κB activity, and reduces inflammation and NF-κB mediated metastasis [16].

CRM1 also regulates the nuclear export of nucleosphosmin (NPM1) which is mutated in up to 35% of AML [18]. The mutant forms of NPM1, called NPM1c, create a novel CRM1-binding site (NES) and lead to the inappropriate nuclear export of NPM1 and localization to the cytoplasm. Cytoplasmic localization of NPM1 appears to be sufficient to convert it from a tumor suppressor to an oncogene [19]. Blockade of CRM1 leads to nuclear accumulation of NPM1 – even in NPM1 mutant AML (YM Chuk, Personal Communication) – and induces rapid apoptosis in these cells (DP Lane, Personal Communication, R Garzon, Unpublished Data).

CRM1 inhibition upregulates a number of TSPs/GRPs in addition to those discussed here. CRM1 appears to stimulate at least one counteracting pathway for major growth and tumor stimulating pathways across different cancers. This may explain the broad activity of CRM1 inhibitors *in vitro* and in animal *in vivo* models. By activating a genome survey, TSPs/GRPs can 'distinguish' between cancerous and normal cells, inducing apoptosis in the former and maintaining cell cycle arrest (until the CRM1 export block is released) in the latter (Figure 2):

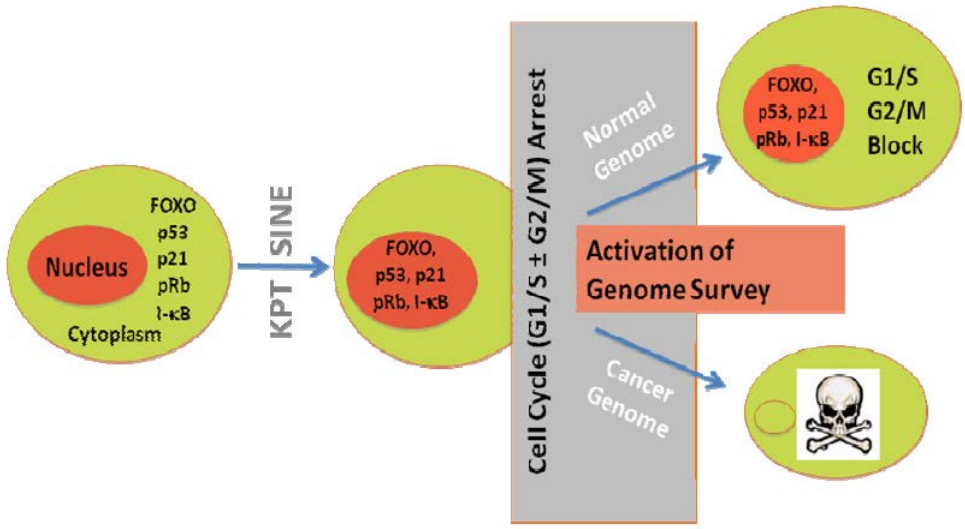


Figure 2: KPT-SINE (CRM1 Inhibitors) Induce Distinct Outcomes in Normal and Malignant Cells.

1.1.3 CRM1 in Human Cancer

As mentioned earlier, human cancers frequently overexpress CRM1 and/or show inappropriate cytoplasmic expression of TSPs/GRPs, suggesting a major dysfunctional nucleocytoplasmic transport system. Overexpression of CRM1 has been reported in ovarian, pancreatic, hepatocellular, neuroblastoma, cervical, and other tumors, and often correlated with poorer prognosis [3]. Studies have similarly demonstrated increased CRM1 levels in various hematologic malignancies compared with their normal cell counterparts. Overexpression of CRM1 will drive TSPs/GRPs out of the nucleus and extinguish their growth and survival regulatory properties. Inhibition of CRM1 forces the nuclear expression of TSPs/GRPs and induces cell cycle arrest through activation of multiple pathways. Normal cells recover from the arrest, but neoplastic cells initiate apoptosis (or necrosis), likely because TSP/GRP induce a genome survey [11, 20, 21].

1.1.4 Selinexor

Selinexor is an oral, first in class, slowly reversible, potent and Selective Inhibitor of Nuclear Export (SINE) that specifically blocks chromosomal regional maintenance 1 (CRM1). Selinexor restores many of the tumor suppressor (TSP) and growth regulatory (GRP) proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage seen in tumor cells, both *in vitro* and *in vivo*. All cell types exposed to SINE *in vitro* undergo G1/S±G2/M cell cycle arrest, followed by a 'genomic fidelity' review, and cells with damaged genomes are induced to undergo apoptosis. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by CRM1 inhibition; normal hematopoietic cells and their functions are largely spared.

Selinexor is supplied as 20 mg tablets in blister packs for oral administration. Each blister pack will contain 12 tablets. All packages will be shipped as open-label stock (i.e., it will not be labeled for a specific subject/patient).

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, including multiply resistant cancers, with the majority of IC50s for cytotoxicity <800 nM and most hematologic tumor lines having IC_{50}s of 20-400 nM for selinexor. In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC_{50}s were typically >5 μM. As noted above, selinexor had little effect on normal (nonmalignant) lymphocytes or other non-transformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis, and other gastrointestinal dysfunction.

Selinexor, as well as other SINE compounds, has been tested for efficacy studies in mice and dogs and for toxicology in rats and monkeys. The dosing regimen was every other day x 3 each week (QoDx3/wk); anti-tumor activity has also been shown with twice weekly dosing. Efficacy was demonstrated at doses of 15-60 mg/m^2 (5-20 mg/kg) in mouse models of myeloma, mantle cell lymphoma (MCL), and T-cell acute lymphocytic leukemia (T-ALL) xenografts. Moreover, efficacy including significant survival advantages was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)] and chronic lymphocytic leukemia (CLL) (TCL-1) leukemografts. Efficacy was also demonstrated in solid tumor xenografts including prostate, breast, liver, glioblastoma, and kidney and colon cancers. In an attempt to predict activity and tolerability in larger animals with spontaneous tumors, KPT-276 and KPT-335 that are closely related to selinexor, have been given orally to several dogs with various cancers in pilot studies. Preliminary evidence of antitumor activity with acceptable tolerability has been obtained (e.g., in a De Novo CHOP-resistant diffuse large B cell non-Hodgkin's lymphoma (DLBCL-NHL) in dogs). Reduced food intake accompanied by weight loss was observed; food supplementation can largely overcome this and dosing has been maintained for up to 6 months in dogs with cancer.

Projected antitumor doses are in the 15-45 mg/m^2 range based on studies in mice and dogs; this corresponds to a minimal area under the curve (AUC) value of ~5,000 ng•hr/mL in mice and lower levels in dogs. Based on pharmacokinetic studies in multiple nonclinical species (mice, rats, dogs, monkeys), it is anticipated that an AUC value of >5,000 ng•hr/mL will also be achieved at doses of 15-45 mg/m^2 in humans. These doses were generally well tolerated in rats and monkeys, with the primary adverse effects observed being reduced food intake and consequent weight loss. At projected antitumor doses of SINE compounds (=45 mg/m^2), vomiting is very uncommon in monkeys or dogs, and diarrhea quite rare in any species. Thus, the etiology of the reduced food intake and weight loss is under further investigation.

Selinexor has been studied at 10 μM in an in vitro selectivity assay including receptors, kinases, and cysteine proteases (including caspases and matrix metalloproteinases), with none of the targets significantly affected by selinexor except for Monoamine Oxidase B

(MAO-B; binding IC50 of >5 μM and minimal functional activity). Minimal inhibition of human Ether-à-go-go Related Gene (hERG) tail current density was displayed by selinexor (IC50 >25 μM in the absence of serum protein), which is substantially below the expected circulating levels of selinexor. In the pivotal, GLP, 4-week monkey study, ECGs were recorded on all animals during the pretest period, and on all animals assigned to the study during the final dosing cycle (1-2 hours post dose on Day 21) and during the last week of the recovery period on Day 39. There was no ECG evidence of a direct or indirect effect of selinexor on the morphology and intervals of the ECG at up to 36 mg/m^2 (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for selinexor. A GLP, rat neurofunctional study (Irwin test) has also been performed at dose levels of 12, 60, or 300 mg/m2 (2, 10, and 50 mg/kg). No behavioral changes were observed at all doses tested. In addition, no central nervous system (CNS)-related adverse side effects were observed in the GLP, rat and monkey 4-cycle toxicity studies.

Preclinical PK parameters were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). While PK studies were limited to male animals for all three species, TK evaluations were conducted in both sexes for rats and monkeys as part of the selinexor toxicology studies, and no consistent sex-related differences were observed in either species. No accumulation was observed in any of the multi-dose toxicology studies with an every other day dosing regimen for selinexor. Overall, systemic exposure was generally dose-proportional in all TK studies that involved multiple dose levels. Higher Cmax and earlier Tmax values were observed in monkeys that were fasted versus fed prior to dosing. Systemic exposure (AUClast) was not affected by the feeding status in monkeys. PO dosing of selinexor drug product in gelatin capsules was also investigated in monkeys and rats. Systemic exposure to selinexor achieved with capsules was comparable to that achieved with oral suspension dosing, with lower Cmax and later Tmax values observed with capsules. Oral bioavailability (F%) of selinexor was remarkably consistent among the three species, with average values of 66.5%, 61.2%, and 67.5% in mice, rats, and monkeys, respectively.

Selinexor underwent minimal metabolism *in vitro* by liver microsomes from humans, mice, rats, dogs, or monkeys, as well as minimal metabolism by the human liver S9 fraction. In protein binding studies, selinexor demonstrated high protein binding to mouse, rat, monkey, and human plasma proteins with 95%, 96.3%, 96.2%, and 94.1% binding, respectively and only moderate binding (54.2%) to dog plasma proteins. KPT330 showed no significant in vitro interactions with any of the cytochrome P450 (CYP450) enzymes (i.e., IC_{50} >10 μM), except for one substrate of CYP3A4 (testosterone) which displayed an IC_{50} of 4.7 μM (the IC_{50} for midazolam, the other CYP3A4 substrate, was >10 μM). Conjugation of glutathione (GSH) to selinexor is the major product of metabolism both in vitro and in vivo, and led to inactive metabolites including N-acetylcysteinyl- and cysteinyl-derivatives which were found in the urine of monkeys. No induction of CYP450 activity was observed for CYP1A2 or CYP3A4.

Sprague-Dawley rats and cynomolgus monkeys were chosen as the toxicology species for the selinexor nonclinical safety program. In both species, the primary effects of KPT-330

were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs given selinexor and related SINE compounds. Increases in amylase and/or lipase, ALT (with less effects on AST), CK, and LDH were observed, but generally were not indicative of organ failure across species. Dose-dependent lymphocyte depletion in lymphoid organs was observed, with alterations in blood hematology parameters generally considered to be clinically insignificant. At high repeated doses of selinexor associated with marked weight loss, there were changes in cerebellar granular layer of neurons in both rats (=300 mg/m^2) and monkeys (=72 mg/m^2), but only monkeys showed any CNS symptoms. In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

In rats, DLT was related to subacute progressive weight loss and GI tract atrophy across all of the studies. There have been no adverse CNS clinical signs observed in any of the rat studies. Acute single PO gavage doses of selinexor at up to 3,000 mg/m^2 (500 mg/kg) showed no mortality at up to 24 hours post-dose. There were dose-dependent reductions in food and water intake and body weight, and non-bloody diarrhea was observed. Clinically significant changes in serum chemistry (LFTs, CK, LDH) were observed at the highest dose tested, with no clinically significant changes in hematological or coagulation parameters. Gross necropsy showed thinning of the gastrointestinal wall. In a non-GLP, 2-week study, selinexor was administered on Days 1, 3, 5, 8, 10, and 12 by PO gavage, similar to the proposed clinical regimen. Mortality was observed at the highest dose, 300 mg/m^2 (50 mg/kg), after 3-4 doses, and was characterized by a marked reduction in food intake with ~30% weight loss; death was attributed to atrophy, ulceration, and erosion in the GI tract (with essentially no diarrhea).

Alterations in clinical pathology included moderate LFT, CK, and LDH increases, with moderate reductions in most hematological parameters. Necrosis in the granular layer of the cerebellum was observed only at the high dose, 300 mg/m^2 (50 mg/kg), and there were no clinical signs attributable to this finding; no recovery group was planned in this study so reversibility was not assessable. The 60 mg/m^2 (10 mg/kg) dose level showed ~10% body weight loss after two weeks, reduced food consumption, and modest adverse effects with mucosal atrophy in the colon and crypt hyperplasia in the duodenum; this was considered the MTD. In general, selinexor at 12 mg/m^2 (2 mg/kg) was relatively well tolerated over 2 weeks.

The rat GLP, 4-cycle study (dosing QoDx3 each week; 12 doses in 28 days) confirmed that the DLT in rats was a reduction in food intake and a corresponding reduction in body weight gain, as compared to control animals. Mortality was observed in 8 males (1 at 8.5 mg/kg, 7 at 15 mg/kg) and 4 females (15 mg/kg) with tests with bone marrow, gastrointestinal, and lymphoid findings contributing to death. Gastrointestinal, lymphoid, and bone marrow microscopic changes were considered adverse in the 5 and 15 mg/kg group males and 15 mg/kg group females and contributed to body weight loss and debilitation. Intestinal, pancreatic, gland (salivary, lacrimal, Harderian), bone, and bone

marrow lesions were not observed at the recovery necropsy. Single cell necrosis was observed mainly in the 5 and 15 mg/kg groups in multiple organs (glands, pancreas, intestine, urinary bladder, and ureters) and was accompanied by crypt hyperplasia in the intestine of males and females and transitional cell hyperplasia in the urinary bladder of males. Hyperplasia was considered reactive indicating that normal cells can recover under treatment. Minimal to mild cardiomyocyte necrosis and degeneration with interstitial cell hypertrophy was found only at the high dose in primary necropsy. Lower testes and epididymis weight reductions were noted in males at all dose groups in primary and recovery necropsy. Seminiferous tubule degeneration and/or atrophy and epididymal hypospermia also occurred during treatment and recovery periods. Lower ovary/oviduct and uterus/cervix weight parameters were noted in females at all dose groups at primary and recovery necropsy and were associated with decreased ovarian follicles. Based on these findings the STD10, was considered to be ≥30 mg/m^2.

Monkeys showed similar DLTs as observed in rats, namely dose-dependent weight loss associated with reduced food intake that were both rapidly reversible. A pilot non-GLP study included two male monkeys administered selinexor at 90 mg/m^2 (7.5 mg/kg) on Days 1, 3, 5, and 8. Adverse clinical signs were observed in both animals starting on Day 2 and included non-bloody loose feces and occasional vomiting. There was a marked decrease in body weight and food consumption during the treatment period. Starting on Day 7, both animals displayed involuntary swinging along with uncoordinated movements. One animal was found dead on Day 11 and the cause of death was attributed to marked weight loss. In a non-GLP, 2-week study, selinexor was given at doses up to 72 mg/m^2 (6 mg/kg) on Days 1, 3, and 5 each week, with a 2-week recovery period. On Days 9-11, 3 of 4 males and 3 of 4 females in the high dose (72 mg/m^2) group were sacrificed moribund. At 72 mg/m^2, adverse clinical signs included soft feces (without diarrhea), decreased defecation, impaired muscle coordination, and intermittent to continuous convulsions without loss of consciousness, with weight loss of ~8.5% by Day 7. For the surviving high-dose animals (1 male/1 female), effects on body weights were fully reversible by the end of the 2-week recovery period and there were no abnormal muscle symptoms. In moribund animals, clinically significant laboratory changes were not present. In the 72 mg/m^2 (6 mg/kg) group only, test-article related microscopic findings (mild to moderate) were observed in the granular cell layer of the cerebellum, the inner nuclear layer of the eye (similar morphology to cerebellar granular cells), the pancreatic parenchymal cells, gastric and duodenal atrophy and gastric ulceration, bone marrow, mesenteric lymph node, salivary glands and thymus, with severity ranging from minimal to moderate. Diffuse atrophy throughout the gastrointestinal tract was noted. Death was attributed to reduced food intake and weight loss, possibly related to the GI and to a lesser extent, the pancreatic findings. At 30 mg/m^2 (2.5 mg/kg) after two weeks of dosing, there were no clinically significant laboratory changes. Small thyroid glands and male sex organs were noted on gross pathology. Mild changes were observed on histopathology and, except for thymic atrophy, all were completely reversible. Body weight losses were =5% at 12 mg/m^2 (1 mg/kg) and there were no major pathological findings; reduced sex organ weights were completely reversible after 2 weeks. Based on this study, 30 mg/m^2 was considered the MTD for selinexor administered QoDx3 weekly to monkeys for 2 consecutive weeks.

In the monkey GLP 4-week study (dosing QoDx3 each week; 12 doses in 28 days), dose levels of 9, 18 or 36 mg/m^2 (0.75, 1.5, and 3 mg/kg) were tested. One female died at Day 15 due to acute thoracic cavity inflammation, likely secondary to gavage-related injury, unrelated to the test article. One female was euthanized on Day 26, apparently related to rapid weight loss. The DLT in monkeys, as in rats, included body weight loss accompanied by reduced food intake. There were no adverse CNS clinical signs in this study at any dose level. Minimal diarrhea or vomiting was observed. Animals that had >7.5% body weight loss were given Ensure® and additional food supplements during the study. The body weights of the recovery group animals returned to approximately baseline levels by the end of the recovery period (two weeks) and substantial recovery had already occurred by 4-5 days after dosing. Macroscopic findings following early or scheduled sacrifice and recovery necropsy were minimal and included discolored and distended GI tract for both sexes, decreased size of spleen, thyroid gland and thymus, adhesion of lungs and decreased size of seminal vesicle for males, mainly in the 36 mg/m^2 group animals. There were no significant alterations in clinical pathology except for lipase elevations (with minimal (<2 fold) changes in amylase levels) in animals in the high dose group. Selinexor related microscopic findings included: thymic atrophy at = 9 mg/m^2 (0.75 mg/kg); minimal to mild single cell pancreatic necrosis, bone marrow depletion and salivary gland atrophy at = 1.5 mg/kg/day; and, mild pancreatic acinar atrophy, minimal kidney nephrosis (without creatinine increases; not adverse), minimal single cell necrosis of the testes (males), and minimal to moderate lymphoid depletion of lymph nodes, spleen, and Peyer's patches at 3 mg/kg/day. Thymus atrophy persisted in a dose-related manner following the 2-week recovery period, but kidney nephrosis, testicular necrosis, bone marrow depletion, pancreatic acinar atrophy, and lymphoid depletion of the spleen, lymph nodes, and Peyer's patches showed complete recovery. In the 36 mg/m^2 (3 mg/kg) group, pancreatic necrosis and salivary gland atrophy showed partial recovery, being minimal and present in 1 female each at the recovery necropsy. Based on these data, the highest non-severely toxic dose (HNSTD) in monkeys was 18 mg/m^2 (1.5 mg/kg) and the NOAEL was 9 mg/m^2.

ICH guidance for starting dose of oncology drugs in humans uses the rat STD10÷10 or the monkey (if it is the more appropriate species) HNSTD÷6. In the selinexor GLP studies, the rat STD10÷10 is 30mg/m^2 ÷10 = 3mg/m2, and the monkey HNSTD÷6 is 18mg/m2 ÷6 = 3mg/m^2. Therefore, human clinical trials were started with 3 mg/m^2.

Selinexor is currently under clinical investigation for the treatment of patients with advanced hematologic and advanced solid malignancies. Three Phase 1 studies (KCP-330-001, KCP-330-002, and KCP-330-003 with NCT numbers of NCT01607905, NCT01607892, NCT01896505) and six Phase 2 studies (KCP-330-004, KCP-330-005, KCP-330-007 and KCP-330-008) are currently ongoing or in process of being initiated. In these trials, a dose range of 3-85 mg/m^2 was explored and 65 mg/m^2 was determined to be the recommended phase II dose for single agent selinexor. Weekly selinexor dosing were designed based on pharmacodynamic markers showing that the biological effects of selinexor have prolonged durations. Multiple clinical trials have employed weekly dosing regimens in hematological and solid malignancies and have demonstrated both efficacy and tolerability. Maximum selinexor serum levels of 1-2 μM can typically be achieved in cancer patients following selinexor oral doses of 40-100 mg (~25-60 mg/m2). An analysis of existing PK data from

phase 1 studies KCP-330-001 and KCP-330-002 supports the use of fixed, rather than body surface area (BSA) based dosing. In the combination setting, selinexor is typically recommended at a starting dose of 40-60 mg weekly across multiple indications and responses were observed in combination setting with selinexor doses as low as 20 mg flat. Preliminary safety information available for 1175 patients indicated that selinexor is generally well tolerated with the most frequent selinexor-related treatment-emergent adverse events including low-grade nausea, fatigue, anorexia, thrombocytopenia, and vomiting that were manageable with standard supportive care.

1.2 Rationale for the Study

Pre-clinical *in vitro* and *in vivo* data have shown that both hematologic and solid tumor cells are susceptible to single-agent cytotoxicity by selinexor, consistent with its restoration of multiple tumor suppressor and growth regulatory pathways leading to the death of cancer cells. The major adverse event across all tested species to date (mice, rats, dogs, monkeys) is reversible weight reduction accompanied by reduced food intake without significant vomiting or diarrhea. Based on these observations, selinexor is currently being developed in both hematologic and solid tumor indications. Given the novel mechanism of action, the risk benefit assessment favors further development of selinexor. Further information about the preclinical pharmacology and toxicology of selinexor is presented in the Investigator's Brochure.

Pancreatic cancer is one of the most fatal malignancies. Gemcitabine alone has been the standard of treatment for pancreatic cancer until recently and has been associated with a median survival of approximately six months. The addition of nab-paclitaxel to gemcitabine improved the survival outcome to 8.5 months as presented in the annual meeting of ASCO 2013[22]. FOLFIRINOX has prolonged the median overall survival to approximately 11 months [23], and is the standard first line therapy for patients who are able to tolerate this chemotherapy. Significant number of patients who progress on FOLFIRINOX will not tolerate the combination of gemcitabine and nab-paclitaxel as a next line of treatment and they go on to receive gemcitabine as single agent. This is especially a setback for patients with good performance status who do not qualify for the use of nab-paclitaxel due to baseline neuropathy or acquired neuropathy post FOLFIRINOX regimen. Gemcitabine as single agent in the second line setting would lead to a survival of around 5.6 months[24-26]. New treatments aiming to improve the effectiveness of treatment in second or third line is therefore needed. Our preliminary data show that pancreatic cancer cell lines *in vitro* are susceptible to the cytotoxicity of selinexor. Our collaborators in association with Karyopharm Therapeutics have demonstrated synergy between selinexor and gemcitabine in pancreatic cancer cell lines and animal xenograft models as well[27]. Mechanistically, these studies demonstrated that KPT-330 (selinexor) and gemcitabine promoted apoptosis, induced p27, depleted survivin, and inhibited accumulation of DNA repair proteins. The Clonogenic assay results from our laboratory demonstrate long term colony suppressing effects of selinexor-gemcitabine combination compared to single agent treatment (Fig 3A&B). Additionally, in agreement with the published findings, we also observe superior inhibition of tumor growth in the combination treatment of selinexor (used at sub-optimal doses) and gemcitabine (Fig3C)

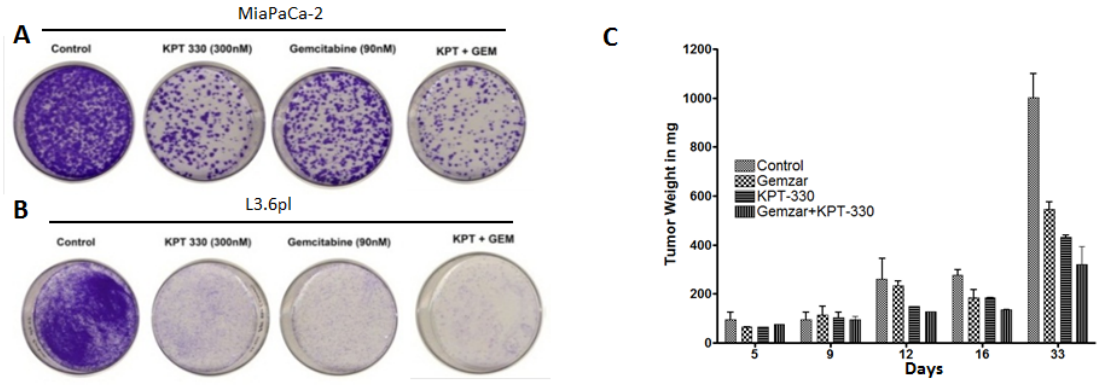


Figure 3. Nuclear export inhibitor KPT-330 (selinexor) enhances the activity of gemcitabine in pancreatic ductal adenocarcinoma cellular and xenograft model. Detailed synergy analysis between selinexor and gemcitabine in pancreatic cancer models in vitro and in vivo has been published by Karyopharm and our collaborator Dr. Amit Mahipal (PMCID: PMC4577050 DOI: 10.1158/1535-7163.MCT-15-0104) [A&B] MiaPaCa-2 and L3.6pl cells were grown at a density of 50,000 cells per well in six well plates and exposed for 72hrs to either vehicle, KPT-330 (300 nM); gemcitabine (90 nM) or the combination of KPT-330 (300 nM)+Gemcitabine (90 nM). At the end of the treatment period, the cells were trypsinized and 1000 cells were re-plated in 100 mm petri dishes for additional three weeks. At the end of the 3-week period, the plates were stained with Comassie Blue. The stained colonies were photographed under an inverted light microscope. Colonies were counted manually under inverted light microscope. [C] AsPC1 PDAC cell line was grown to form tumors at the subcutaneous site in ICR-SCID mice. The mice were administered selinexor (KPT-330) three times a week for three weeks at 7.5 mg/kg (sub maximum tolerated dose) in the absence or presence of gemcitabine (Gemzar) 50 mg/kg twice a week for two weeks.

1.2.1 Rationale for Starting Dose and Dosing Schedule

From the ongoing human studies, selinexor as single agent at the dose of 65 mg/m^2 by mouth twice a week has been found to be safe and well tolerated. The common adverse events at this dose level have been reversible weight loss, anorexia and thrombocytopenia. At dose level 1, we kept gemcitabine and nab-paclitaxel at standard doses. For the safety of patients, we started selinexor at dose as low as 60 mg flat dose on Mondays and Wednesdays every week in combination with weekly standard dose of gemcitabine and nab-paclitaxel. Because of the possible selinexor-related toxicity of mood changes that required hospitalization of two patients in cohort 1, we decided to stay at the same dose level but give the selinexor on Day 1 only and eliminated the Day 3 dose. We confirmed that there was no DLT in this cohort..

Based on review of toxicity profile of the phase I cohort of selinexor, gemcitabine and nabpaclitaxel we came to the conclusion that the regimen's side effects were related to the gemcitabine and nab-paclitaxel **rather than the selinexor per se**. We also had the experience of one patient who had an outstanding response to therapy that was prolonged to close to three times the expected time to disease progression and who was treated on

lower dose of gemcitabine plus selinexor and without nab-paclitaxel for the most of his treatment course. Based also on the safety data provided by Karyopharm regarding the 80 mg dose of selinexor we felt it is appropriate to move forward in the phase II to do single agent gemcitabine and selinexor at dose level of 80 mg flat dose given weekly.

1.3 Study Population and Sample Size

Phase Ib: Up to 12 patients with untreated metastatic pancreatic cancer will be enrolled [COMPLETED].

Phase II: In this portion of the study, 44 patients will be enrolled. The first 14 patients with liver metastases accessible for core biopsies will be randomized into two groups, group 1 and group 2. The remaining 30 patients will be allocated to group 3 (no biopsy group). If any of the first 14 patients with liver metastates consented to enroll in the study but refused to refused to consider the C1D3 biopsy then those subjects will be allocated to Group 3 (no biopsy group). Altogether, 44 patients will be enrolled in phase II. The study will be conducted at multiple sites across the US, including Karmanos Cancer Institute, Stony Brook University Cancer Center (Long Island, NY), Froedtert and the Medical College of Wisconsin (Milwaukee, WI) and The University of Kansas Medical Center (Westwood, KS).

1.4 Pharmacodynamic (PDn) Biomarkers

Exposure of mixed white blood cells ex vivo from humans and other species to selinexor leads to 2-5 fold induction of CRM1 mRNA using quantitative reverse transcription polymerase chain reaction (qRT-PCR). This induction of CRM1 is the expected cellular response to increase CRM1 synthesis following inhibition of CRM1 protein function. In addition, p53 mRNA and mRNA from the p53-dependent gene monocyte inhibitory cytokine 1 (MIC1) also increase following selinexor exposure. In the phase II part of the study, patients will have a biopsy of liver lesions pre- (fixed paraffin embedded archival tissue) and post treatments. We will study the expression of p27, FOXO, PAR4 and IκB on liver tissues before and after treatment.

2 OBJECTIVES

2.1 Primary Objectives

1. Phase I: To determine the recommended phase 2 dose (RP2D) of gemcitabine, nab-paclitaxel and selinexor for untreated metastatic pancreatic cancer [COMPLETED].
2. Phase I: To determine the safety profile of gemcitabine, nab-paclitaxel, and selinexor [COMPLETED].
3. Phase II: To test whether the combination of gemcitabine and selinexor improves the median overall survival of patients with metastatic pancreatic cancer who have failed frontline non-gemcitabine containing regimens, beyond 5.6 months (median overall survival of patients receiving gemcitabine only based on historical data; J Clin Oncol. 1997 Jun;15(6):2403-13)

2.2 Secondary Objectives

1. To determine objective response rate to the combination of gemcitabine and selinexor using RECIST criteria

2. To assess safety of selinexor in combination with gemcitabinein phase II portion of the study
3. To determine progression free survival (PFS) in patients treated with gemcitabine and selinexor
4. To determine the influence of selinexor and gemcitabine on the nuclear expression and localization of tumor suppressor gene proteins

3 PATIENT SELECTION

This trial will be conducted in compliance with the protocol, GCP, and applicable regulations. Any questions about eligibility criteria must be addressed prior to patient registration.

3.1 Inclusion Criteria

Patients must meet **all** of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent in accordance with federal, local, and institutional guidelines
2. Age >18 years
3. Patients with metastatic pancreatic adenocarcinoma who have failed one non-gemcitabine based regimen for metastatic disease.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 1)
5. Adequate hematopoietic function: absolute neutrophil count (ANC) ≥1500/mm^3 and platelet count ≥100,000/mm^3
6. Adequate hepatic function: bilirubin <2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 times ULN) and ALT or AST ≤2.5 times ULN
7. Adequate renal function: serum creatinine ≤ 1.5 mg/dL
8. Serum albumin ≥ 3.0 g/dL
9. Effective contraception: Female patients of childbearing potential must agree to use highly effective methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, highly effective methods of contraception must be used throughout the study and for three months following the last dose.
10. Patients with history of previously treated other malignancies who do not have any evidence of recurrent disease for the last three years are allowed

3.2 Exclusion Criteria

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

1. Patients who are pregnant or breast feeding

2. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤3 weeks prior to cycle 1 day 1. Treatment with mitomycin C or radio-immunotherapy must be completed within 6 weeks prior to cycle 1 day 1.
3. Major surgery within 3 weeks of cycle 1 day 1
4. Prior therapy with gemcitabine based regimen for metastatic disease or gemcitabine based adjuvant therapy completed less than twelve months from enrollment
5. Unstable cardiovascular function that includes and may not be limited to:
    - symptomatic myocardial ischemia, or
    - uncontrolled clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), or
    - congestive heart failure (CHF) of NYHA Class ≥3, or
    - myocardial infarction (MI) within 3 months of cycle 1 day 1
6. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose
7. Known to be HIV seropositive who are on anti-HIV drugs because of the unknown interactions between these drugs and the study agents
8. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen)
9. Patients with active CNS malignancy. Asymptomatic small lesions are not considered active. Treated lesions may be considered inactive if they are stable for at least 3 months.
10. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea
11. History of seizures, movement disorders, or cerebrovascular accident within the past 5 years prior to cycle 1 day 1
12. Patients with macular degeneration, uncontrolled glaucoma, or markedly decreased visual acuity based on physician's assessment
13. Serious psychiatric illness (e.g., depression, psychosis) or medical conditions that could interfere with treatment
14. Participation in an investigational anti-cancer study within 3 weeks prior to cycle 1 day 1
15. Concurrent therapy with approved or investigational anticancer therapeutics other that what is stipulated by the protocol
16. Clinically significant ascites
17. Major surgery within 3 weeks of C1D1

3.3 Patient Registration

All patients will be screened by the principal investigator or co-investigators prior to entry into this study. An explanation of the study, discussion of the expected side effects, alternative treatment options, benefits versus risks, and full disclosure of the "informed consent" document will take place. Consented and eligible patients will be registered into the study.

The contact information for registrations is indicated below:

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Email: wolgasta@karmanos.org

Registration will be done through Karmanos Cancer Institute, Clinical Trial Office utilizing OnCore, and the Clinical Trial Management System. A unique set of patient ID numbers will be assigned to each patient, which should be used on all documentation and correspondence. Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to Karmanos Cancer Institute and received a Local Activation Letter. Teleconferences will be held with all participating sites on monthly basis during the Phase II part of the study to verify potential patients at each site, accrual status, and toxicity reports. Available slots will be announced through email by Karmanos Cancer Institute.

No patient can receive protocol treatment until registration has taken place. Registration of a patient can only occur if confirmation of a slot has been provided in writing by Karmanos Cancer Institute. All eligibility criteria must be met at the time of registration. There will be no exceptions or waivers from eligibility. Any questions should be addressed with Karmanos Cancer Institute prior to registration. The eligibility checklist must be completed, and signed by the investigator, who must be listed on the FDA 1572, prior to registration. Sites will email the signed, completed eligibility checklist and pertinent registration documents to Karmanos Cancer Institute's Study Coordinator, Allison Wolgast at wolgasta@karmanos.org. If email is not possible, the signed, completed eligibility documents should be faxed to 313-576-8368 with a follow up phone call to the Study Coordinator, Allison Wolgast; 313-576-8994 to alert the Study Coordinator of a registration submission. Karmanos Cancer Institute will then review the checklist and confirm eligibility. The site will receive the Confirmation of Registration form indicating the unique patient ID number and confirmation of registration into the trial. Only after this faxed or emailed Confirmation of Registration sheet has been received from Karmanos Cancer Institute can the patient receive study drug(s). Protocol treatment should begin within 7 days of patient registration.

4 STUDY CALENDARS

The calendar of events for phase Ib and phase II part of the study is illustrated in table 1 and 2 below.

Table 1: Calendar of Events for Phase Ib [COMPLETED]

		Cycle 1							Cycle 2 and beyond				
Phase Ib Calendar	Screening	Week 1			Week 2-3		Week 4		Week 1-3		Week 4		Off Treatment Visit
	D-28 to D-1	D1	D2		D8, 15		D22		D1, 8,15		D22		
Written Informed Consent	x												
Inclusion/Exclusion Criteria	x												
Medical History and prior cancer treatments	x												
Complete Physical Examination	x	x			x		x		x		x		x
Visual acuity and full eye exam	x												
ECOG	x	x			x		x		x		x		x
Weight	x	x			x		x		x		x		x
Vitals	x	x			x		x		x		x		x
12 lead EKG	x				x								
CBC with differentials	x	x			x		x		x		x		x
Complete Serum Chemistry	x	x			x		x		x		x		x
Serum CA19-9	x								x				
PT, INR, PTT	x												
Serum pregnancy test	x												
Complete Urinalysis	x				x								
Imaging with tumor measurement (CT or MRI)[1]	x[1]								x[1]				
Selinexor in clinic[2]		x			x				x				
Gemcitabine infusion		x			x				x				
nab-Paclitaxel infusion		x			x				x				
Archival Tumor tissue	x												
Adverse Events	x	x			x		x		x		x		x
Concomitant medications	x	x			x		x		x		x		x

1: CT or MRI of chest, abdomen with and without contrast or PET/CT are allowed. The imaging study needs to be repeated every 8 weeks for response assessment (+ / – 5 days). MRI of brain is required if intracranial metastasis is suspected.

2: Selinexor given in clinic

Table 2: Calendar of Events for Phase II

		Cycle 1				Cycle 2 and beyond			
Phase II Calendar	Screening	Week 1		Week 2-3	Week 4	Week 1-3	Week 4	Off Treatment Visit	Follow up
	D -28 to D -1	D1	D3	D8, 15		D1, 8, 15			
Written Informed Consent	x								
Inclusion/Exclusion Criteria	x								
Medical History and prior cancer treatments	x								
Complete Physical Examination	x	x		x		x		x	
Visual acuity and full eye exam	x								
ECOG	x	x		x		x		x	
Weight	x	x		x		x		x	
Vitals	x	x		x		x		x	
12 lead EKG	x								
CBC with differentials	x	x		x		x		x	
Complete Serum Chemistry	x	x		x		x		x	
Serum CA 19-9	x					x			
Serum pregnancy test	x								
Imaging with tumor measurement (CT or MRI)	x [1]						x [1]		
Selinexor in clinic		x [3,4]	x [2]	x		x			
Gemcitabine infusion		x		x		x			
Tumor biopsy	x		x [5]						
Blood for pharmacodynamics markers[5]	x [6]		x [6]						
Adverse Events	x	x		x		x		x	
Concomitant medications	x	x		x		x		x	
Survival									x [7]

1: CT or MRI of chest, abdomen with and without contrast is allowed. The imaging study needs to be repeated every 8 weeks for response assessment (+/or – 5 days). Imaging modality must be consistent in serial studies. MRI of brain is required only if intracranial metastasis is clinically suspected.
2: Group 1, selinexor after liver biopsy
3: Group 2
4: Group 3
5: Tumor biopsy or archival tissue at screening. Group 1 liver biopsy on C1, D3 approximately 48 hours after administration of gemcitabine and **before** taking selinexor. Group 2 will have a liver biopsy C1, D3 approximately 48 hours after administration of gemcitabine and selinexor.
6: Blood for pharmacodynamics markers at baseline (or prior to C1 D1 treatment) and D3
7: Follow up every 2 months for one year (12 months)

5 TREATMENT PLAN

5.1 Study Design

This is a multicenter phase Ib study to investigate selinexor when combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic cancer and phase II study of selinexor plus gemcitabine in patients with pancreatic cancer in second line setting. Objectives include the determination of the safety profile of selinexor in combination with gemcitabine and selinexor and the overall survival of patients who receive the gemcitabine-selinexor combination.

The study was a phase Ib study that was designed according to a standard 3+3 design and is now completed. The Maximum Tolerated Dose (MTD) was the lowest dose for which less than a third of patients experienced a Dose Limiting Toxicity (DLT). To ensure sufficient toxicity data at the MTD, a minimum of 6 patients were to be enrolled at the MTD. We anticipated that the RP2D would be the same as the MTD

Phase Ib had three cohorts as shown in table 3. Only initial cohort was completed because of DLT.

At this time, up to 44 patients with metastatic pancreatic adenocarcinoma that were previously treated with a non-gemcitabine based regimen will be enrolled onto the phase II part of the study. The first fourteen patients with liver metastases that are accessible for image guided percutaneous core biopsies will be randomized into two post-treatment biopsy groups, group 1 and 2. The remaining 30 patients enrolled in this trial will be placed in group 3 (no biopsy group).The post-treatment biopsy will done only on C1D3 and the tissue obtained will be studied for changes in expression of tumor suppressor proteins (TSPs) caused by the combination of drugs compared to either biopsy sample obtained at screening or archival tissue obtained at time of diagnosis.

- **Group 1** will receive gemcitabine without selinexor on cycle 1 day 1. This will be followed by a biopsy of metastatic liver lesion approximately 48 hours after administration of the gemcitabine. Following the biopsy (C1D3), patients in group 1 will receive the first dose of selinexor. Then on C1D8 and C1D15, selinexor will be given with gemcitabine. In the subsequent cycles, Selinexor will be given concurrently with Gemcitabine on days 1, 8, and 15 of each 4-week cycle.
- **Group 2** will receive gemcitabine concurrent with selinexor starting on C1D1. A biopsy of the liver will be performed approximately 48 hours after administration of gemcitabine and selinexor. In Group 2, the gemcitabine/selinexor combination will be administered once every week for three weeks on days 1, 8 and 15 of each 4-week cycle.
- **Group 3** will receive gemcitabine concurrently with selinexor starting on C1D1 and then weekly for three weeks (days 1, 8 and 15) of each 4-week cycle.

It should be noted that the goal of randomization is to obtain tissue for pharmacodynamics assessment and determine the impact of selinexor on target molecules. If any of the first 14 patients with liver metastates consented to enroll in the study but refused to consider the C1D3 biopsy then those patients will be allocated to Group 3 (no biopsy group).

Table 3: Cohorts in phase I [COMPLETED]

Cohort	Gemcitabine (mg/m^2) Days 1, 8, 15	Nab-paclitaxel (mg/m^2) Days 1, 8, 15	Selinexor (mg) Days 1, 8, 15*
Level 2	1000	125	80
Level 1 (starting)	1000	125	60
Level -1	1000	125	40

Table 4: Phase 2 dose adjustment

	Gemcitabine (mg/m^2) Days 1, 8, 15	Selinexor (mg) Days 1, 8, 15*
Level 1 (starting)	1000	80
Level -1	750	60
Level -2	500	

*Except for C1 of phase II in Group 1 where selinexor will be given on C1D3.

5.2 Dose Schedule

Phase 1b [COMPLETED]: A treatment cycle will be 4 weeks (+/- 3 days). In each cycle, patients will have 3 doses of gemcitabine/ nab-paclitaxel and 3 doses of selinexor. Gemcitabine/ nab-paclitaxel combination will be administered IV weekly for 3 weeks with one week off. Selinexor will be administered orally once a week on Weeks 1, 2 and 3 of each 4-week cycle. Once a MTD is determined, it will be the recommended dose of selinexor for Phase II and patients will be treated with it until disease progression or undue toxicities.

Phase II: A treatment cycle will be 4 weeks (+/- 3 days). Group 1 will receive IV gemcitabine **without** selinexor on day 1 of cycle 1. A liver biopsy will be performed on day 3 of cycle 1 followed by oral administration of the C1 Week1 dose of selinexor. Then, gemcitabine/selinexor will be administered on day 8 and 15 of week 2 and 3. Gemcitabine and selinexor will not be administered on week 4. In the subsequent cycles, both drugs will be given on days 1, 8, and 15 of 4-week cycle. Group 2 will receive gemcitabine/selinexor on day 1, 8, 15 of week 1, 2, 3 of a 4-week cycle. A biopsy of the liver will be performed approximately 48 hours after administration of gemcitabine and selinexor on C1 D1. Gemcitabine/selinexor will not be administered in week 4. Group 3 will receive gemcitabine/selinexor on day 1, 8, 15 of week 1, 2, 3 of a 4-week cycle. No biopsy is planned for this group. Gemcitabine/selinexor will not be administered in week 4

5.3 Suggested Supportive Care/Pre-medication

Required 5-HT3 Antagonists

In order to minimize nausea, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (8 mg or equivalent) unless contraindicated, starting on C1D1 before the first dose of study treatment and continued 2 to 3 times daily thereafter, as needed. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists.

5.3.1 Supportive Care Recommendations for Selinexor-Related Adverse Events

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 5.3.1), supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) should be used as clinically indicated at the discretion of the Investigator. Supportive care guidelines for managing AEs are provided in the table 5 in 5.9.1.

5.4 Criteria for Initiation of Next Cycle

In order to be eligible to start the next cycle of treatment, patients will be required to have adequate hematologic parameters:

- ANC $\geq$ 1.0 x 10^9/L
- Platelets $\geq$ 100 x 10^9/L

Adequate resolution of non-hematological toxicities (excluding alopecia) from the previous cycle to grade 2 or lower is required.

5.5 Definition of RP2D

MTD is defined as the next lower dose level below the one in which ≥ 2 of 6 patients experience DLT. In general, we anticipate that the MTD will be the RP2D. However, based on evaluation with participating investigators, sponsor and how patients tolerate long-term treatment with selinexor, the RP2D dose may be less than the MTD. The RP2D will be further evaluated in the Phase II Cohort.

5.6 Phase II cohort

Approximately 44 patients will be included in the phase II part of the trial. The first 14 patients with liver metastases who consent to a second liver biopsy will be randomized into two groups, group 1 and group 2. The dose schedule for this cohort will be the same as that for the phase I part, except the omission of selinexor on day 1 of cycle 1 in patients randomized to group 1 as described in section 5.1. There is no maximum duration of participation for any patient enrolled in this study and will be based on tolerance of study drugs and the clinical judgment of the treating physician and patient wishes.

5.7 Definition of Dose Limiting Toxicity (DLT)

DLT is defined as any of the following occurring in the first 28 days (first cycle) of study participation that is considered **at least possibly related to selinexor administration:**

- > 1 missed doses in 28 days due to a toxicity that is possibly selinexor-related
- Discontinuation of a patient due to a toxicity that is at least possibly selinexor-related prior to completing Day 28 of the first cycle

Non-Hematologic:

- Grade ≥ 3 fatigue, nausea, vomiting, or diarrhea despite receiving optimal supportive medications
- Any other Grade ≥3 non-hematological toxicity (except for electrolytes abnormalities that are reversible and asymptomatic)
- Grade ≥3 AST or ALT elevation lasting longer than 7 days OR Grade ≥3 AST or ALT elevation in the setting of bilirubin elevation > 2x ULN

Hematologic:

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm^3] lasting ≥7 days
- Febrile neutropenia (ANC<1000/mm3 with a single temperature ≥ 38.3^{o}C or sustained temperature of >38°C for over 1 hour)
- Thrombocytopenia (platelet count <25,000/mm^3) that persists for ≥7 days
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding

Note the following: patients who missed ≥2 doses during cycle 1 for reasons unrelated to study drug are not evaluable for DLT and will be replaced.

An event may not be considered a DLT if it is not clinically meaningful or significant even if it falls within the definition of a DLT as defined above. If this occurs, a discussion among all investigators, PI, and the Sponsor must take place after thoroughly reviewing the event, supporting data and the reasons for not considering the event a DLT. This must also be

clearly documented by the study coordinators. Conversely, certain adverse events may occur that do not meet the definition of a DLT but are clinically concerning and may therefore be considered DLTs after an agreement between investigators, PI, and the Sponsor.

5.8 Safety Cohort Review

The following sections of the Cycle 1 and Cycle 2 Day 1 case report form (CRF) and source documentation for laboratory results data will be reviewed.

- Study Drug Administration
- Adverse Events Log
- Hematology and Biochemistry.
- Laboratory normal ranges page, if applicable
- Concomitant Medications

It is imperative that the CRF data listed above are entered promptly and as soon as a patient is removed from the study, if prior to completion of cycle 1, to assess safety at the opened dose level and to determine the feasibility of proceeding to a new dose level.

An "Accrual on Hold" notice will be sent out to investigators by electronic mail once the study has recruited the required number of patients per cohort. A safety cohort review meeting may take place with the PI, investigators, and Karyopharm. After a decision is made by the sponsor based on the data submitted for a cohort regarding whether the study will be re-opened, a cohort will be expanded, or if there will be escalation, etc., all applicable parties will be notified. This process for toxicity review and cohort review will continue to be repeated and followed regularly until the RP2D is reached.

5.9 Dosing Adjustments

5.9.1 Dose Modifications for Selinexor

All dose modifications will be captured in the in the site's internal database.
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 5 for pre-specified dose modifications for AEs related to study treatment.

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. 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.

The CTCAE v 4.03 is used for grading the severity of AEs; the therapy modifications described in Table 5 are applied according to this severity grading. Toxicity will be documented as described in Section 9.1.1. 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 5: Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

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

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[a,b]
Grade 1 weight loss Grade 2 anorexia	• Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 2 weight loss Grade 3 anorexia	• Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. • Reduce selinexor by 1 dose level. • Rule out other causes. Consider nutritional consultation and use nutritional supplements (e.g, Ensure®, Boost®) • Initiate appetite stimulants as above
Nausea, Acute	
Grade 1 or 2	• Maintain dose. Rule out other causes. Use standard additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. • If persistent, use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	• Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia. • Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level. • Patients with significant nausea/vomiting after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	• Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. • Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). • Treat hyponatremia per institutional guidelines including dietary review. Provide supplemental oral and/or intravenous fluids if dehydration is present. Consider addition of salt tablets to patient's diet.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[a,b]
Grade 3 with sodium levels <130-120 mmol/L without symptoms	• Rule out other causes including drug (e.g., diuretic) effects. • Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). • If (corrected) sodium is Grade ≤3 and continues to be asymptomatic, then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. • If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	• Rule out other causes including drug (e.g., diuretic) effects. • Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). • Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	• Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.
Grade 2	• Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. • For first occurrence, restart selinexor at current dose. • For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3 or 4	• Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.
Thrombocytopenia	
Grade 1 or 2	• Maintain dose. Rule out other causes including drug effects.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[a,b]
Grade 3 without bleeding	• Rule out other causes including drug effects. • For first occurrence: skip 1 dose and reduce selinexor by 1 dose level. • If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents such as romiplostim 5 to 10 μg/kg SC weekly (preferred) or eltrombopag 100 to 150 mg QD. • In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor-Investigator may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored. Thrombopoietin stimulating agents are recommended.
Grade 4 without bleeding	• Rule out other causes including drug effects. • Interrupt selinexor until patient recovers to Grade 2 or baseline. Selinexor dosing may be reduced by 1 dose level (it is recommended to have only 1 dose modification per cycle) • If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above. • In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor-Investigator may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.
Grade ≥3 with bleeding	• Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[a,b]
	• If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above.
Neutropenia	
Grade 3 or 4 neutropenia (afebrile) OR Febrile neutropenia	• If afebrile: Continue Selinexor, may consider using colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. • If febrile: Interrupt Selinexor and check neutrophils at least weekly until recover to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reinitiate selinexor therapy at the same dose level and may use colony stimulating factors per institutional guidelines. • If recurrent, may continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤2 or baseline levels, and reduce the dose of Selinexor at reinitiation by 1 dose level.
Anemia	
• Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Sponsor-Investigator.	
Other selinexor-related adverse events	
Grade 1 or 2	• Rule out other causes. Maintain dose. Start treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	• Rule out other causes. Interrupt selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. • Isolated values of Grade ≥3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.
IV: intravenous; NCCN: National Comprehensive Cancer Network; QD: once daily; PO: oral; SC: subcutaneous	

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

5.9.1.1 Conditions not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the above guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolytes abnormalities that are reversible with standard interventions (see special consideration or Grade 3-4 Hyponatremia in table 5)
- 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.

5.9.1.2 Dose Adjustments with Changes in BSA

Dose adjustments do not need to be made for weight gains/losses of ≤20%. If weight changed by >20% from baseline recorded at the beginning of the study then Gemcitabine dose maybe adjusted based on the body surface area (BSA) per investigator discretion. No dose adjustment for Selinexor is required based on weight changes.

5.9.1.3 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. Missed doses will not be replaced. Patients may continue antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

5.9.1.4 Missed or Vomited Doses

Missed doses should be managed as follows:

- If a dose was missed, the schedule of that week should be altered to accommodate 1 dose in that week with at least 5 days between 2 consecutive doses.

- If a dose must be skipped (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. 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 will be reported. The schedule however, will be followed as before. As an example, if patient missed Cycle 2 Day 8 and Cycle 2 Day 15, schedule will be resumed at Cycle 3 Day1 after the break.

Vomited doses should be managed as follows:

- 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.

5.9.1.5 Delays, Modifications, and Reintroduction

All delays, modifications, and reintroductions of selinexor dosing will be made in consultation with the PI and the Sponsor.

5.9.2 Dose Adjustment for Gemcitabine

- If toxicity is attributed to gemcitabine and it necessitates dose modification in the opinion of investigators, following general guidelines are recommended.
- If toxicity is attributed to gemcitabine alone, modifications should be made to gemcitabine dose.
- Gemcitabine will be permanently discontinued for any of the following:
    - Unexplained dyspnea or other evidence of severe pulmonary toxicity
    - Severe hepatic toxicity
    - Hemolytic-Uremic Syndrome
    - Capillary Leak Syndrome
    - Posterior reversible encephalopathy syndrome
- If the patient tolerates a reduced dose for two cycles, patient may be dose escalated to the dose they received prior to the reduction only after authorization from the study PI and sponsor.
- No dose modifications are recommended for alopecia, nausea, or vomiting.

5.9.2.1 Dose Adjustment Guidelines for Non-hematologic Toxicities

	Recommended action
≥Grade 3 Non-hematologic Gemcitabine related toxicities	*Hold gemcitabine until toxicity resolves to ≤ Grade 1 or baseline (maximum 14 days). *If the toxicity resolves to ≤Grade 1 or baseline within 14 days, restart at 75% of starting dose (dose reduction by 25%) *If toxicity recurs, a 2nd dose reduction to dose level 50% of starting dose may be permitted (dose reduction by 50%).

5.9.2.2 Dose Adjustment Guidelines for Hematologic Toxicities

Both gemcitabine is myelosuppressive. If ≥grade 3 hematologic toxicities are noted, following paradigm will be used.

	Recommended action
≥ Grade 3 hematologic toxicities	*Hold gemcitabine first until toxicity resolves to ≤ Grade 1 or baseline (maximum 14 days). *If the toxicity resolves to ≤Grade 1 or baseline within 14 days, restart gemcitabine at 75% of starting dose (dose reduction by 25%) *If grade 3-4 toxicity recurs despite a 25% dose reduction in gemcitabine it should be permanently discontinued.

5.10 Patient Compliance and Replacement

To the extent possible, patients must strictly follow the standard dosing schedule. Patients will be requested to complete a pill diary or calendar. Patients who miss more than 2 doses or more of selinexor in a cycle in the absence of study drug related toxicity will be discontinued unless these are consecutively missed doses due to a required medical procedure that is unrelated to study drug or an anticipated personal emergency.

Compliance to study medication will be ascertained by use of patient diaries for the days where patient receives the study drug. Compliance to study medication will be determined by the investigator or a delegate and recorded in source documents. The date, time and number of tablets consumed will be recorded as per study drug schedule. The principal investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification with the reasons. The investigator / designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

Patients who miss 1 or more doses of gemcitabine in a cycle in the absence of drug related toxicity will be discontinued unless these are consecutively missed doses due to a required medical procedure that is unrelated to the study regimen or an anticipated personal emergency.

Patients withdrawn in cycle 1 because of non-compliance not related to study drug related toxicity will be replaced.

5.11 Premature Withdrawal/ Discontinuation Criteria

Patients may withdraw from the study at any time. Patients who discontinue from the study will be encouraged to return to the study site to undergo the evaluations listed for the Off Treatment Visit.

At the discretion of the Investigator, the investigator may remove a patient from the study for the following reasons:

- Disease progression based on clinical and/or radiological grounds.

- Noncompliance with study procedures
- Need of treatment with medications not allowed by the study protocol
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments and outcome
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- For the third occurrence of the same Grade ≥3 non-hematological toxicity
- Investigator discretion
- Other treatments become available

If the reason for withdrawal is the occurrence of an AE or drug related DLT, the patient will be followed up by the investigator until such events resolve, stabilize, and according to the Investigator's judgment there is no need of further follow-up. The reason for withdrawal from the study will be documented in the case report form.

Sponsor and Karyopharm must be notified within 24 hours of a patient's discontinuation from the study.

6 Concomitant Medications

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications must be recorded on the source documents and case report form beginning 14 days prior to Day 1 and through the end of the patient's study participation.

6.1 Permitted Concomitant Medications

Prevention of Pregnancy

Female patients of childbearing potential must agree to use highly effective methods of contraception and must have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, highly effective methods of contraception must be used throughout the study and for three months following the last dose of study drugs.

Use of Blood Products

During the administration of study regimen, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated and per institutional guidelines.

Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted. Treatment with selinexor shall not be discontinued solely due to palliative radiation. However, gemcitabine will be discontinued while getting palliative radiation.

Glucocorticoid Therapy
As part of supportive care (e.g. for nausea or anorexia), oral dexamethasone, up to 40 mg/week, can be given to patients based on the investigator discretion.

Supportive Care Guidelines
Supportive measures for optimal medical care shall be provided during participation in this clinical trial.

- Appropriate anti-coagulation is allowed during the study (e.g.: LMW heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided that patients are monitored for INR twice a week in cycles 1 and 2 and anytime the dose is adjusted. If the INR is stable after the first two cycles, then monitoring may revert to the local practice.
- Erythropoietin and growth factors are not permitted to be used prophylactically in cycle 1 but are allowed if needed in cycle 2 and onwards. However, these can be used therapeutically to treat hematologic toxicities throughout the study including in cycle 1.
- Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.
- Standard appetite stimulants are allowed.
- Use of any immunosuppressive agents during the study must be confirmed by the sponsor.

6.2 Prohibited Concomitant Medications

Erythropoietin and growth factors are not permitted to be used prophylactically in cycle 1 but allowed if needed in cycle 2 and onwards. However, these can be used therapeutically to treat hematologic toxicities throughout the study.

Anticancer Therapy
Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids and gemcitabine as specified herein, are not allowed.

Investigational Agents
Other investigational agents should not be used during the study.

Drugs undergoing Glutathione conjugation
The primary metabolism of selinexor in vitro and in vivo appears to be inactivated by glutathione conjugation. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. In vitro studies using human liver microsomes confirm in vivo findings that selinexor undergoes minimal CYP450 metabolism. Therefore, administration of selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen. It should be noted that no studies of selinexor in combination with acetaminophen have been performed to date and that these recommendations are empirical. It should also be noted that ethanol ingestion is associated with glutathione

depletion; therefore, use of products containing ethanol should be minimized or avoided on selinexor dosing days.

7 Drugs

7.1 Selinexor

7.1.1 Drug Preparation and Administration

Selinexor is an investigational product and will be provided by Karyopharm.

Selinexor will be supplied 20 mg blister packs for oral administration. Each blister pack will contain 12 tablets.

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 (4 ounces) of water at approximately the same time each dosing 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.

Each dose will consist of selinexor for oral administration on a flat dose basis starting at 80 mg once a week for 3 weeks of each 4-week cycle. Selinexor will not be taken during week 4 (total three doses per cycle).

All drugs will be prepared, stored and administered as approved by FDA and according to the institutional standards.

7.1.2 Drug Storage

Selinexor tablets will be stored at or_below_86°F_(30°C) in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

7.1.3 Accountability and Destruction of Investigational Medicinal Product

The Principal Investigator (or an authorized designee) at each participating institution must maintain a careful record of the inventory of the Investigational medicinal product received using the Drug Accountability Form. The study drug will be destroyed as per site's destruction policies and documentation of study drug destruction will be provided to Karyopharm. Both used and unused study drug may be returned to Karyopharm if requested by Karyopharm.

7.1.4 Drug Administration

Study drug is provided by Karyopharm Therapeutics Inc. and will be labeled as per the applicable regulations. Sites must request selinexor through Karyopharm's automated drug ordering system (Endpoint DRIVE).The sponsor's research pharmacists are required to attend a DRIVE training and to train their respective sites afterwards. Karyoharm's

Addditional Site Forms must be completed and sent to Karyopharm prior to additional sites' being able to order drug. The sponsor is required to keep track of all onsite drug supply and expiry for all study sites. Drug should be ordered 2-3 weeks in advance of need, therefore pre-planning for estimated supply requirements needs to be done regularly. This requires regular communication between the sponsor's clinical team and the research pharmacists.

Study drug accountability records will be maintained at the site pharmacy and will be available for monitoring and submission to Karyopharm upon request.

Study drug must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

The Investigational Product should not be used for any purpose outside the scope of this protocol, nor can the Investigational Product be transferred or licensed to any party not participating in the clinical study. Karyopharm's data for Investigational Products are confidential and proprietary and shall be maintained as such by the Investigators.

7.2 Gemcitabine hydrochloride (Gemzar®)

For full prescribing information on gemcitabine, please refer to FDA website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Information regarding warning, recommendations for dose reduction and discontinuation, precautions for preparation and administration, preparation for iv administration, stability of gemcitabine, clinical trial experience, post-marketing experience, drug interactions, use in specific patient population (geriatric patient, patients with renal or hepatic impairment, pregnancy, nursing mother etc.), overdose, clinical pharmacology and toxicology are available on the above webpage.

Briefly, gemcitabine is available from commercial providers. It is provided in single use vial containing 200mg/vial or 1 gram/vial of gemcitabine. The vial with 200 mg gemcitabine can be reconstituted with 5 ml 0.9% sterile normal saline solution and 1 gram vial with 25 ml, each reconstitution yielding gemcitabine concentration of 38 mg/ml. Before administration to the patient, gemcitabine needs to be diluted with injection of appropriate amount of normal saline. The final concentration can be as low as 0.1 mg/ml. Reconstituted gemcitabine solution is stable for 24 hours at room temperature 20-25 °C (68-77 °F) and it should not be refrigerated to avoid crystallization.

Gemcitabine is approved for treatment of pancreatic cancer. Patients participating in this study will treated with 1000 mg/m^2 of gemcitabine on day 1, 8, 15 of a 4-week cycle.

Treatment will be continued until disease progression, prohibitive toxicity or start of alternative treatment. Patiens with prohibitive toxicitywho have no disease progression (achieved PR or SD), necessitating treatment discontinuation, at the discretion of the investigator, may continue with weekly selinexor upon recovery to ≤ grade 1 of the toxicity.

8 MEASUREMENT OF DRUG EFFECTS

8.1 Safety Assessment

The safety and tolerability of selinexor in combination with gemcitabine will be evaluated by means of drug related DLT, AE reports, physical examinations, and clinically significant changes in the laboratory safety evaluations. A teleconference will be held every week to discuss the safety of all patients enrolled in phase Ib. All the investigators, drug provider or their designee must participate in the weekly teleconference. In the case when a participating investigator cannot participate in the teleconference discussion, he/she will be asked to update the sponsor/principal investigator about safety of the patients via email.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03.

8.2 Efficacy Assessments

All patients who received at least one dose of selinexor in combination with gemcitabine shall be included in the efficacy analysis. The clinical activity will be evaluated for its effects on disease response criteria in terms of best response, duration of response, progression free survival (PFS), duration of stable disease and overall survival.
Objective disease response assessment will be made according to standard, international RECIST 1.1 criteria for solid tumors. Patients who discontinue treatment for safety related reasons and and NOT for progressive disease will continue being followed up with scheduled disease assessment until disease progression or start of of alternative therapy.

8.3 Pharmacodynamics

As noted earlier, the first fourteen patients participating in the phase II part will be randomized to group 1 and 2. Each group will have liver biopsies on day three . The expression of p27, FOXO, PAR4 and IκB on liver tissues before and after treatment will be determined by immunohistochemistry.

For immunohistochemistry**,** the hematoxylin and eosin-stained slides will be reviewed for grading and the selection of representative tissue block(s) for immunohistochemical analysis. Immunohistochemistry will be performed on liver biopsies from the study patients for antibodies against p27, FOXO, PAR-4 and IκB. After deparaffinizing and hydrating to phosphate-buffered saline (PBS) buffer (pH 7.4), the sections will be pretreated with hydrogen peroxide (3%) for 10 minutes to remove endogenous peroxidase, followed by antigen retrieval via stem bath for 20 minutes in EDTA. A primary antibody will be applied, followed by washing and incubation with the biotinylated secondary antibody for 30 minutes at room temperature. Detection will be performed with diaminobenzidine (DAB) and counterstaining with Mayer hematoxylin followed by dehydration and mounting.

Immunostaining will be scored semiquantitatively by assessing the localization and intensity in tumor cells nucleus. The staining will be then categorized into: 0, none; 1, up to 10% staining; 2, 11% to 50% staining; and 3, >50% staining. Intensity will be scores as 1 for low and 2 for high. Final score will be obtained by multiplying the 2 scores.

Biopsies will be performed at the participating sites for phase 2 portion of the protocol. When available, baseline archival tissue in the Phase 1 portion of the study will be submitted. Tissues and blood obtained for pharmacodynamics will be shipped to Karmanos Cancer Center for processing.

Dr. Ramzi Mohammad/Dr. Asfar Azmi
Karmanos Cancer Institute
HWCRC 732
4100 John R
Detroit, MI
48201
Tel # 3135768328
Fax # 3135778389
Email: mohammad@karmanos.org

9 SAFETY AND REPORTING REQUIREMENTS

9.1 Adverse Events

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.
- *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.

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 recorded (e.g., anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to normal 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 (severity per the current version of NCI CTCAE) does not automatically indicate an SAE unless it meets the definition of serious as defined under the definitions above and/or as per the Investigator's discretion. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE.

9.1.1 Adverse Event Documentation

The severity* of the AE should be graded by the Investigator according to the NCI CTCAE Grading Scale, utilizing a current version of NCI CTCAE. NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If NCI CTCAE grading does not exist for an AE, the severity should be characterized as 'mild,' 'moderate,' 'severe,' 'life-threatening', or 'fatal' (corresponding to Grades 1 to 5) according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.
- Life-threatening
- Fatal event.

*Severity ≠ Seriousness: 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. Grades do not define seriousness.

9.1.1.1 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 treatment. AE monitoring 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 AEs occur during the study. AEs may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

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

9.1.1.2 Adverse Event Reporting:

The Investigator 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)

See the excel spreadsheet template in Appendix 3.

9.1.1.3 Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in the following table.

Classification of Adverse Events by Causality

Not related	The lack of a temporal relationship of the event to the study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation.
Related	The temporal relationship of the event to the study treatment makes 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

An AE that meets the criteria of any untoward medical occurrence that, at any dose,

- results in death
- is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.
- 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

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).

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 (ie, 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 (eg, 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 Karyopharm's SAE Report Form in addition to being recorded in the sponsor's database. 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.

9.3 Reporting of Serious Adverse Events

9.3.1 Reporting Serious Adverse Events to the Principal Investigator and Clinical Trials Office (CTO) at Karmanos

All serious adverse events (SAE) as defined must be reported immediately.

SAEs that are unexpected and/or related to protocol therapy will have a written report (the MedWatch form may be used) sent to the following within 24 hours:

1. Study Principal Investigator - Mohammed Najeeb Al Hallak, MD,MS
(alhallakm@karmanos.org)

2. Clinical Trials Office:
Allison Wolgast
Karmanos Cancer Institute
4100 John R-MM03CT
Detroit, MI 48201
Office: (313) 576-8994
Fax: (313) 576-8368
Email: wolgasta@karmanos.org

or
Taylor Brewer
Study Coordinator
brewert@karmanos.org
Tel # 313-576-8526
Fax # 313-576-8368

The Clinical Trials Office will coordinate the reporting process between the Investigator and the IRB, as well as other applicable reporting agencies (FDA). Investigators, with the help of clinical trials office staff, will inform the FDA of any unexpected possibly related SAEs that occur in the course of the study within 15 calendar days of when he or she becomes aware of the occurrence. Fatal or life threatening SAEs must be reported to the FDA no later than 7 calendar days from the time that he or she becomes aware of them.

9.3.2 Reporting SAEs to Karyopharm

The Clinical Trials Office will coordinate the process of reporting the SAEs to Karyopharm. Every SAE, regardless of the causal relationship to the Karyopharm study drug, occurring after the patient has signed informed consent until at least 30 days after the patient has stopped the Karyopharm study drug must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department (Appendix 4).

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

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
E mail: pharmacovigilance@karyopharm.com

Fax: +1-617-334-7617 (USA)
+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has causal relationship to the Karyopharm study drug. 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.

9.3.3 Reporting Serious Adverse Events to Local Ethics Boards

The sponsor will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in US. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Institutional Research Board (IRB) or Research Ethics Boards (REBs) or Independent Ethics Committee (IEC) in accordance with local regulations and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to IRBs/REBs/IEC must be forwarded to the sponsor and Karyopharm for filing.
Documentation can be any of the following:

- Letter from the IRB/REB/IEC acknowledging receipt
- Stamp from the IRB/REB/IEC, signed and dated by IRB/REB/IEC chair, acknowledging receipt
- Letter demonstrating the SAE was sent to the board

All expedited local serious adverse events occurring within a center should also be reported to local IRBs/REBs/IEC as per the ethics board's or committee's guidelines.

9.3.4 Reporting Period for Adverse Events and Serious Adverse Events

The CRF should capture all AEs occurring from cycle 1 day 1 till the date of scheduled 4 weeks (+ 1 week) follow-up visit or 30 days after discontinuation of the study drug, whichever is later.

In addition, any known untoward event of any severity that occurs subsequent to the AE reporting period that the Investigator assesses as at least possibly related to the study therapy (i.e., the relationship cannot be ruled out) should also be reported as an AE.
For the SAEs that have been deemed by the investigator as unrelated to protocol treatment, the SAE reporting period begins after patient signs informed consent and ends on the date of scheduled 4 weeks (+ 1 week) follow-up visit or 30 days after discontinuation of the study drug, whichever is later. For the SAEs that have been deemed by the investigator as at least possibly related to protocol treatment, the SAE must be reported even if this occurs after the date of scheduled 4 weeks (+ 1 week) follow-up visit or 30 days after discontinuation of the study drug.

SAEs that occur prior to dosing will not be reported in an expedited fashion to any health authority, and will be summarized and described in the clinical study report. The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the patient is lost to follow up. Resolution status of such an event should be documented on the CRF.

9.3.5 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 Karyopharm study drug administered. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" (FDA 2012) or as per national regulatory requirements in participating countries.

Selinexor SUSARs originating from Karyopharm's CSTs in specific countries do not need to be cross-reported to the Competent Authorities. Please see memo in Appendix 5, for more information (list of countries).

9.4 Procedures for Handling Special Situations

9.4.1 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 (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.
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-Investigator of this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm Pharmacovigilance.
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 Karyopharm, regardless of whether the patient received the Karyopharm study drug 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 (eg, 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 9.3).

A pregnancy in a female partner of a male patient must be reported to Karyopharm Pharmacovigilance 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.

9.4.2 Overdose, Abuse, Misuse, Medication Errors, and Occupational Exposure

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

9.4.2.1 Overdose

An overdose is a deliberate or accidental administration of any Karyopharm study drug to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, Karyopharm Pharmacovigilance 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 Karyopharm's SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

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

9.4.2.2. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the Karyopharm study drug 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 Karyopharm study drug are to be recorded on Karyopharm's SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

9.4.2.3 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 Karyopharm study drug are to be recorded on Karyopharm's SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the occupational exposure.

If the occupational exposure is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

9.5 Relationship to Study Drug

All laboratory findings as defined in the CTCAE v4.03 that have been deemed by the Investigator as clinically significant should be recorded as AEs.

For all AEs, relationship to study drug will be reported on the appropriate AE CRF page. The investigator must judge whether the study drug caused or contributed to the AE or SAE and whether or not the SAE is reportable to regulatory authorities.

The Principal Investigator may delegate duties such as the assessment of causality of the AEs/SAEs to Sub-Investigators but must assure that these Sub-Investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the Form FDA 1572.

Causality will be assessed as 1) unrelated 2) possibly related, or 3) probably or definitely related for all AEs. In addition, each AE will be categorized as clinically significant (CS) and non-clinically significant (NCS).

10 STATISTICAL ANALYSES

10.1 Study Design/Endpoints

The objectives of this combined phase Ib/II clinical trial are to identify the maximum tolerated dose of selinexor and gemcitabine combination (phase I component), determine the toxicity profile of the drug combination and test whether the combination improves overall survival (OS) as compared to an historical standard (phase II component). Secondary endpoints are to determine the pharmacodynamics (PDn) of selinexor in combination with gemcitabine, to determine response rate of the 2 drug combination, to confirm safety of RP2D of selinexor in combination with gemcitabine in phase II portion of

the study, to determine progression free survival (PFS) in phase II cohort treated with the 2 drug combination, and correlative studies.

To facilitate investigation of correlative objectives; the administration of selinexor will be delayed in half of the 14 patients who consent to a second biopsy during the Phase II trial until after a second biopsy has occurred (48 hours post first treatment). This design will allow for two separate but clinically relevant comparisons to be made: pre and post treatment differences in the molecular profile of combination of gemcitabine and selinexor, and the difference in the molecular profile of gemcitabine and selinexor versus gemcitabine only. We denote the group initially receiving the 2-drug combination treatment (gemcitabine only) as group 1 and the group initially receiving the 2 drug combination treatment as group 2. As the selinexor treatment is only delayed 48 hours for group 1, the effect on the survival endpoints for patients in group 1 should be negligible, although we will test for it to be certain.

Our purpose in creating two different treatment regimens is to obtain biomarker data on a group of patients receiving gemcitabine to compare to patients receiving the 2 drug combination initially. These patients will still receive the experimental drug, but in a delayed fashion to allow us to measure our correlative objective. Since there are 2 groups in the treatment schedule (in case there is a survival difference between the groups), a permuted block design of random block size will be used to assign patients to groups. The Biostatistics Core will produce the randomization and monitor the compliance of the treatment assignments. This will help eliminate the impact of known or unknown confounding variables.

10.2 Sample Size

The phase I portion of this trial will employ a modified 3+3 design as detailed in section 5.1. At the conclusion of the phase I study there will be 6 patients enrolled at the MTD for the 2 drug combination. We will include those 6 patients in the phase II efficacy and toxicity studies. A previous study indicated that the median survival of advanced/metastatic pancreatic cancer patients taking gemcitabine as second line is 5.6 months[24]. The hypothesis in this trial is that the addition of selinexor to this treatment regimen will increase the median overall survival to 8.4 months (a 50% increase). A sample size of 44 yields 80% power to detect an increase in median survival of 2.8 months assuming exponentially distributed death times, 24 months of accrual and 12 months minimum follow up with a two-sided Type I error of 0.10[28].

10.3 Analysis

Descriptive statistics (point and exact 90% confidence interval estimates from the resultant Kaplan-Meier curve) will be generated for the primary endpoint as well for the PFS endpoint in the tertiary objectives. If the lower bound of the 90% confidence interval does not include 5.6 months, then the study will be deemed a success. The median OS and PFS will be estimated on an intention-to-treat basis (using all registered patients), and on a response-evaluable basis (using all patients who completed at least one 4-week treatment cycle) using the Kaplan-Meier method. Toxicity rates will be estimated using all treated patients from the phase II portion of the trial. Point and 90% Wilson's confidence intervals

will be estimated to describe binary endpoints including toxicity rate and response rate. Patients who did not have an event 24 months after the last patient was enrolled will be censored for the survival endpoints (date of last contact for OS and date of last evaluation for progression for PFS). Exploratory Cox regression analyses will be undertaken to determine if any of the clinical covariates measured at the beginning of the trial (e.g., age, race, group assignment) are associated with OS and/or PFS.

The pilot correlative studies that will be undertaken include the validation of CRM1 measured through H & E staining and nuclear TSP alterations measured using IHC (including FOXO, IkB, p27, Par4 and pSTAT3) as the target of selinexor. We will utilize the first 14 patients from the phase II portion of the trial who consent to the required 2 biopsies. Our study design will ensure that half of these 14 will be group 1 patients and half will be group 2 patients. As our sample size is small, at most these correlative studies will be able to estimate mean change in gene expression in the 7 patients in each group. Seven patients in each group will yield a two-sided 90% confidence interval with a distance from the mean change to the limits of 0.75 standard deviation units. A two-sided alpha of 0.10 will be used for all analyses.

10.4 Evaluation of Toxicity

All registered patients will be evaluated for toxicity probably related to the treatment. It is anticipated that one-third of the patients will experience a grade 3 or higher toxicity probably or definitely due to the treatment (using the toxicity rates reported from prior studies of selinexor, Section 1.1.4). Toxicity data will be collected at least weekly during the course of treatment.

10.5 Specific Toxic Outcomes

We will closely monitor the following outcomes: weight loss, loss of appetite, liver function tests, including AST, ALT and bilirubin, complete blood count. If 4 or more patients out of the first 10 (or fewer) treated in the phase II portion of the study develop a grade III (using the CTCAE guidelines) or higher toxicity in any of these categories that are probably or definitely related to the treatment received within the 6 months after the completion of treatment, we would recommend revisiting the study for safety reasons. We will continue to monitor these specific toxic outcomes throughout the course of the trial, in a sliding window fashion.

10.6 Other Toxic Outcomes

Data on other toxic side effects (excluding those detailed in the previous paragraph) that patients may experience will also be collected. We have chosen a safety threshold of 0.25 to monitor other toxic side effects. We would recommend reconsidering the phase II portion of the study for safety reasons if there were **X** many occurrences of grade 3 or higher toxicity (using the CTCAE guidelines) among the first **N** (or fewer) patients treated, as it would result in an upper confidence limit greater than 0.25:

N	X	p	UCL
8	1	0.125	0.255

13	2	0.154	0.256
18	3	0.167	0.253
22	4	0.181	0.261
27	5	0.185	0.256
32	6	0.188	0.252

In the above table, **N** = the number of patients treated; **X** = the cumulative number of patients with a grade 3 or higher toxicity currently observed; **p** = the observed toxicity rate; and **UCL** = the exact 1-sided upper 80% confidence limit for **p**, using Wilson's method without a continuity correction. After treating 32 patients, the potential toxicity risk of this regimen should be well defined, and thereafter the possible need for termination of the study based on toxicity should be minimal.

10.7 Futility monitoring

A concern with this regimen is that selinexor may impede the activity of gemcitabine, due to possible increased toxicity and decreased exposure to gemcitabine, resulting in worse survival outcomes. While our final analysis will be able to quantify this hypothesis (as it is a two-sided test), it is necessary to continually monitor the patients on trial for futility of treatment. As our final sample size is small for our 1-arm study, utilizing a survival endpoint for futility monitoring is not feasible. Therefore, we will monitor the proportion of patients who survive less than the reported median survival under the null hypothesis (5.6 months). We would recommend reconsidering the phase II portion of the study for futility reasons if there were greater than half of the registered patients at any time who did not survive longer than 5.6 months once at least 10 patients have either had an event or survived longer than 5.6 months. Thus, we will compute the [number of patients who survived less than 5.6 months]/([number of patients who survived less than 5.6 months] + [number of patients will survived longer than 5.6 months]) and monitor if that proportion ever becomes greater than one half once 10 patients had either outcome in the denominator.

10.8 Expected Accrual Rate, Accrual Duration, and Study Duration

Our anticipated accrual rate is 16-20 patients per year, including collaborative centers. We anticipate the accrual of ~12 patients per year at Karmanos and ~6 patients per year at other participating sites. Thus, it should take approximately 30 months to accrue the maximum 44 patients needed for the phase II portion of the trial. Allowing for 12 months of follow-up to obtain the primary endpoint on the last patient enrolled and 4 months to assemble, analyze and interpret the data the total study duration is projected to be at most 4 years.

11 ETHICS

11.1 Patient Protection

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines. The local principal investigators are responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical

principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical practice (GCP) and applicable local regulatory requirements.

11.2 Patient Information

Before entry into the trial all eligible patients will receive written patient, information describing the aim of the study, as well as probable and possible side effects and risks. Oral information from one of the investigators or a delegated person at the institution will also be given, and the patient must have the opportunity to ask questions, and to consider participation together with his/her family members if applicable. It will be emphasized that the participation is voluntary and that it is the right of the patient to refuse further participation in the study whenever he/she wants and that this will not influence his/her subsequent care.

11.3 Informed Consent

Patient / Legally acceptable representative (LAR) (as applicable) written consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements and must conform to the ICH guidelines for Good Clinical Practice, prior to any study-specific screening procedures and trial entry. The written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Investigator at the institution and available for inspection regulatory authority at any time.

The sponsor will provide the Investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the sponsor for approval, prior to submission to the IRB/REB/IEC. The IRB/REB/IEC will review the consent form for approval. A copy of the approved form must be submitted to the sponsor prior to initiation of the study.

11.4 Ethics Board Approval

Each site is responsible for submission of this study to the appropriate ethics board for approval, i.e. Institutional Review Board (IRB).

Serious Adverse Events, Safety Updates and Investigator Brochure Updates during the course of the study may be sent to you for reporting to your IRB/REB/IEC. The investigator is responsible for notifying their IRB/REB/IEC of any such updates and documentation of ethics submission of this information must be forwarded to the sponsor.

Initial approval: All study sites are required to obtain full board local ethics approval of the protocol and consent form by the appropriate REB/IRB/IEC prior to commencement of the clinical trial at each site.

Continuing approval: Annual (or as required by the REB/IRB/IEC) re-approval may be required until a closeout visit has been completed. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor, who will inform sites in writing of any substantive changes to this protocol as a protocol amendment. Sites are responsible for submitting all protocol amendments with a revised informed consent form, if applicable, for review by their REB/IRB/IEC. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by REB/IRB/IEC prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial patients or when the change(s) involves only logistical or administrative aspects of the trial. The Investigator should not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial patient or when the change(s) involves only logistical or administrative aspects of the trial.

REB/IRB/IEC Refusals: If an REB/IRB/IEC refuses to approve this protocol (or an amendment/revision to this protocol), the sponsor must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to the regulatory authorities.

Upon completion of the trial, the Investigator must provide the IRB/REB/IEC with a summary of the trial's outcome.

Annual Report: The sponsor will submit annual reports to the FDA and may request information from the sites to support the completion of this annual report.

12 DOCUMENTATION, RECORD ACCESS, AND MAINTENANCE OF STUDY RECORDS

12.1 Documentation of Patient's Participation

A statement acknowledging the participation of a patient in this clinical trial must be documented in the patient's medical records along with the signed ICF.

Source Documentation

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs).

12.2 Regulatory Requirements

As this study will be submitted under an IND, the following documents are required for all sites:

- All Investigators must complete and sign an FDA Form 1572.

- All Investigators must complete and submit a Financial Disclosure Statement.

Before the start of the study, the following documents must be forwarded to the sponsor

- An original U.S. Form FDA 1572 for the site, signed by the Principal Investigator.
- Current (within 2 years of study start) Curriculum Vitae (CV) for the Principal
- Investigator and all Sub Investigators
- Original financial disclosure forms for the Principal Investigator and all Sub
- Investigators listed on the U.S. Form FDA 1572
- Current IRB membership list and/or Department of Health and Human Services number
- Copies of all appropriate laboratory certifications and laboratory normal ranges
- IRB approval of the protocol: the approval letter must identify the protocol
- Number, title and date of protocol
- IRB approved informed consent: the approval letter must identify the protocol number, title of protocol and date of the informed consent.
- IRB approval of any advertising materials to be used for study recruitment, if applicable
- IRB approval of any other study materials (e.g. patient diary)
- HIPAA Forms (if applicable)
- Original signed Investigator agreement
- Original signed and dated Investigator Protocol Signature page
- Site delegation list

Study Completion

The following documents/data must be received by the sponsor before a study site may be closed:

- All completed CRFs and corresponding data clarifications
- All laboratory samples (received by sponsor) and data
- Original, final SAE reports and copies of all relevant de-identified supporting documentation (i.e., discharge summaries, laboratory results)
- Original, final Pregnancy Information Forms (PIF) and copies of all relevant de-identified supporting documentation
- Complete and accurate drug accountability records and inventory logs
- Original screening and enrollment log
- Copies of all ethics board correspondence (including, e.g., annual reports, SAE notifications, ethics board submissions) and approvals for the protocol, amendments, informed consent, and advertising materials (if applicable)
- A copy of the ethics board study summary close letter
- All regulatory documents (i.e., current CV's for the Principal Investigator and
- Sub-Investigators, updated FDA Form 1572, current laboratory certifications, normal ranges, completed delegation log)
- Updated financial disclosure forms for the Principal Investigator and all Sub-Investigators listed in the FDA Form 1572. All remaining study materials (i.e.,

unused CRFs, used/unused study drug) must be returned to the sponsor or disposed of following notification and approval by Sponsor.

12.3 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. FDA and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) or Research Ethics Board (REB) or Institutional Ethics Committee (IEC) requirements.

Before the investigational drug is shipped to the Investigator, the Investigator will provide the sponsor with a copy of the IRB or REB approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

12.4 Patient Confidentiality and Access to Source Data/Documents Patient Identification

A sequential unique identification number will be attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. A patient will not be identified by name, only by his/her initials. The patient's name or any identifying information will not appear in any reports published as a result of this study. In order to avoid identification errors, patient's initials and date of birth (as permitted by the ethics board) will also be reported on the study forms. Any research information obtained about the patient in this study will be kept confidential. However, information obtained from individual patient's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The patient's medical records/charts, tests will be made available to the Sponsor, the US FDA and Karyopharm Therapeutics Inc., the REB/IRB/IEC and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have signed a confidentiality agreement. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A patient may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

12.5 Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel and by the IRB/REB/IEC. The Investigator shall permit sponsor and Karyopharm, authorized agents of the sponsor and Karyopharm and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor. Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

12.6 Registration of Clinical Trial

Prior to the first patient being registered/enrolled into this study, Karmanos Cancer Institute will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

12.7 Data Reporting

Clinical trial data will be collected utilizing OnCore's electronic data capture system electronic CRF's.

Appropriate personnel at all participating sites will be trained to utilize the Oncore system by the Karmanos Informatics department.

Trial data entered in Oncore will be verified by source documentation. CRFs should be completed by participating sites within 10 business days of the availability of clinical documentation of a study visit. Data clarification and queries should be completed within 7 working days of notification.

A monitor specialist from KCI CTO will remotely monitor essential clinical trial data. Frequency of monitoring will be based on accrual at a site but will occur at least once every 2 months if a patient has been enrolled.

Monthly screening and enrollment logs are to be sent to the KCI Lead Study Coordinator.

12.8 Data Monitoring:

The investigators who accrue the patients will be responsible for patient assessment and documentation of patient status in the patient records. All adverse events will be duly recorded by investigators. All study personnel have access to data. Our data managers and coordinators are highly experienced in running complex trials.

The GI MDT has a weekly meeting whereby attendings, research nurses, data managers and other staff attend and discuss the studies and monitor patient accrual. Regular communication will be established with collaborating institutions by phone on a 1-2 weekly basis and whenever necessary.

Patient survival will always be known and if death happens is recorded in the electronic chart and all study personnel have access to it.

12.9 Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

According to 21 CFR 312.62(c), the Investigators shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Investigator shall retain these records until two years after the investigation is discontinued and the FDA is notified.

The Investigator must retain protocols, amendments, IRB approvals, copies of the Form FDA 1572, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

13 QUALITY ASSURANCES AND QUALITY CONTROL

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), Karmanos Cancer Institute will be responsible for implementing and maintaining quality assurance and quality control systems.

13.1 Data and Safety Monitoring

Scheduled meetings will be held monthly or more frequently depending on the activity of the protocol. Meetings will include the protocol investigators and study coordinator involved with the conduct of the protocol.

During these meetings, the investigators will discuss matters related to:

- Safety of protocol participants (Adverse Event reporting)
- Validity and integrity of the data
- Enrollment rate relative to expectation of target accrual, characteristics of participants
- Retention of participants, adherence to the protocol (potential or real protocol violations)

- Data completeness on case report forms and complete source Documentation

Following these meetings, the study coordinator will complete a protocol specific Data Safety and Monitoring form that will include summaries of all accrual data, all AE's grade 3+, regardless of attribution, protocol deviations and IRB amendments. These reports will be cumulative and will also include reasons that patients are taken off study.

Completed Data and Safety Monitoring Reports of these regular investigator meetings will be kept on file in the office of the Clinical Trials Office at KCI per SOP #35. These reports will be completed monthly and submitted quarterly according to the quality assurance schedule by the study coordinator and given to the Clinical Trials Quality Assurance Manager for review and processing with the Data and Safety Monitoring Committee (DSMC).

The Barbara Ann Karmanos Cancer Institute DSMC will meet on a monthly basis to review the prior months Serious Adverse Event forms and Data and Safety Monitoring Reports that have been filed.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Deviations and Violations

All violations or deviations are to be reported to the site's IRB/REB/IEC (as per the ethics board's guidelines). All IRB/REB/IEC correspondence is to be forwarded to the sponsor. The site must notify the sponsor immediately of any protocol violations.

14.2 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for patients will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority (ies) will be informed.

The REB/IRB/IEC will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible in the case of a premature discontinuation of study.

15 PUBLICATION POLICY

The results, both positive and negative, will be published in a peer reviewed journal. Authorship will follow the Vancouver Publication rules. Specifically, for the main publication:

- First author will be decided by Dr. Mohammed Najeeb Al Hallak who will be the senior author.
- Subsequent authors in decreasing order of accrual.

16. APPENDICES

16.1 Appendix 1: Eastern Cooperative Oncology Group Performance Status Criteria

Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

16.2 Appendix 2:

Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03
Published: May 28, 2009 (v4.03: June 14, 2010)

16.3 Appendix 3: Template for Line Listing of Adverse Events

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	Unique Patient ID [1]	Malignancy	Malignancy Group [2]	Age [3]	Sex	Patient Dosed with Selinexor (Yes/No)	Cycle 1 Day 1 Selinexor Dose (with units)	Date of First Selinexor Dose	Adverse Event Term [4]	Serious Event? (Yes/No)	Onset Date [5] (complete or partial)	End Date [5,6] (complete or partial)	Action Taken with Selinexor [7]	Causality to Selinexor	Ongoing [6] (Yes/No)	Outcome of Adverse Event [8]	Severity CTCAE Grade (1-5)	Preferred Term [9]	System Organ Class [9]
2																			
3																			
4																			
5																			
6																			
7																			
8																			
9																			
10																			
11																			
12																			
13																			
14																			
15																			
16																			
17																			
18																			
19																			
20																			
21	Notes:																		
22	1. Please match this patient ID with the ID number in the patient tracker.																		
23	2. Possible answers for malignancy group (column C) are "DLBCL excl. RT", "BCL excl. DLBCL&RT", "RT", "TCL" and "Non-Lymphoma". This is optional. Please report them if available. Detailed explaination for the malignancy groups is provided at tab "Malignancy".																		
24	3. Age at the study entry.																		
25	4. Verbatim name of the event would be perferred in column I. Please report the derived code in "Preferred Term" column (column R) if available.																		
26	5. Please provide a partial date to the best of your knowledge if the exact date is unknown.																		
27	6. If the AE was still ongoing at the time of data cut (2018-10-15), please mark the "Ongoing" column (column O) as "Yes" and leave the end date (column L) blank.																		
28	7. Please indicate any change to treatment of selinexor due to AE in column M. Possible answers are "Dose not changed", "Dose reduced", "Drug interrupted" and "Drug withdrawn".																		
	8. Possible answers for outcome of AE (column P) are "Recovered/Resolved", "Recovered/Resolved with sequelae", "Recovering/Resolving", "Not recovered/Not resolved", and "Fatal".																		
29	9. Preferred Term and System Organ Class (Column R and S) are optional. Please report them if available.																		

16.4 Appendix 4: Serious Adverse Event Report Form

Karyopharm Therapeutics	FRM-PV-0001 v. 6.0
Serious Adverse Event Report Form	**Effective:** 30 Nov 2017

Protocol Number:		Initial Report: ☐	Follow-up Report Number:
Investigator:	Site ID#:	Country of Incidence:	
PATIENT INFORMATION			
Patient ID#:		Weight (kg):	Height (cm):
Date of birth *(DD-MMM-YYYY)*:		☐ Male	☐ Female
Baseline Diagnosis:		Date of Baseline Diagnosis *(DD-MMM-YYYY)*:	

MEDICATION ERROR (ONLY) ☐ YES *(If YES, please complete below section)*

Please select the most applicable Medication Error category below:

☐ Abuse ☐ Misuse ☐ Medication Error ☐ Overdose ☐ Occupational Exposure

Associated with Serious Adverse Event?

☐ **NO** (Please proceed to Page 2, and complete applicable sections on Pages 2 and 3)

☐ **YES** (Please complete the remainder of the SAE Report Form, including the below Serious Adverse Event Information section)

ADVERSE EVENT INFORMATION

Event Term(s) (concise medical diagnosis)	Serious Criteria	Severity by CTCAE Grade	SAE Start Date *DD-MMM-YYYY*	SAE End Date *DD-MMM-YYYY*	SAE Outcome	Relationship to Study Drug(s)	Other Possible Cause

Please complete the following sections, as applicable:

☐ ***Subject Hospitalized:***	☐ ***Subject Died:***	***Other Possible Causes for the Event:***
Date of Admission *(DD-MMM-YYYY)*:	Cause of Death:	1 = Pre-existing disease *Specify:*
Date of Discharge *(DD-MMM-YYYY)*:	Date of Death *(DD-MMM-YYYY)*:	2 = Other treatment (concomitant or previous) *Specify:*
	Was autopsy completed? ☐ No ☐ Yes *If yes, please forward report.*	3 = Protocol required procedure *Specify:*
	Is Death Certificate available? ☐ No ☐ Yes *If yes, please forward.*	4 = Other *Specify:*

KEY	***Serious Criteria:***	***Outcome:***	***Relationship to Study Drug(s):***
	1 = Death	1 = Death	1 = Not Related
	2 = Life-threatening	2 = Not Recovered/Not Resolved	2 = Related
	3 = Hospitalization/Prolonged Hospitalization	3 = Recovered with Sequelae	
	4 = Persistent/Significant Disability/ Incapacity	4 = Recovered/Resolved without Sequalae	
	5 = Congenital Anomaly/Birth Defect		
	6 = Important Medical Event		

Protocol Number:	
Patient ID#:	Site ID#:
STUDY DRUG INFORMATION	
Study Drug(s):	
Therapy Dates *(DD-MMM-YYYY)*:	Medication Dosage and Frequency
Date of First Dose:	First dose: mg *or* mg/m^2
Date of Last Dose Prior to Event:	Frequency:
ACTION TAKEN WITH STUDY DRUG	
☐ Dose unchanged	
☐ Dose reduced Date of dose reduction *(DD-MMM-YYYY)*: Dose reduced to: mg *or* mg/m^2	Did event abate or improve after stopping/reducing medication? ☐ Yes ☐ No ☐ N/A
☐ Temporarily interrupted *Date (DD-MMM-YYYY)*:	
☐ Date of re-initiation *(DD-MMM-YYYY)*: Re-initiation dose: mg *or* mg/m^2	Did event reappear after re-administration? ☐ Yes ☐ No ☐ N/A
☐ Permanent withdrawal Date *(DD-MMM-YYYY)*:	
☐ Not Applicable (Please explain):	

RELEVANT PAST MEDICAL HISTORY AND/OR RELEVANT CONCURRENT CONDITIONS

Medical condition(s)	Ongoing Condition?	Start date *(DD-MMM-YYYY)*	End date *(DD-MMM-YYYY)*
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		
	☐ Ongoing		

Protocol Number:			
Patient ID#:		Site ID#:	
RELEVANT CONCOMITANT MEDICATION(S)			
MEDICATION NAME(s) AND INDICATION(s)		DATES *(DD-MMM-YYYY)* AND DOSE / FREQUENCY OF ADMINISTRATION	
1	Product name:	Start date:	Stop date:
	Indication:	Dose / Frequency:	mg/
2	Product name:	Start date:	Stop date:
	Indication:	Dose / Frequency:	mg/
3	Product name:	Start date:	Stop date:
	Indication:	Dose / Frequency:	mg/
4	Product name:	Start date:	Stop date:
	Indication:	Dose / Frequency:	mg/
5	Product name:	Start date:	Stop date:
	Indication:	Dose / Frequency:	mg/
EVENT DESCRIPTION: EVENT DETAILS, TREATMENT(S) RECEIVED, RELEVANT LABORATORY AND DIAGNOSTIC TEST RESULTS			
REPORTER CONTACT DETAILS			
Report Completed By:		Telephone	
		Email	
Investigator/Sub-Investigator Signature:		Date of this Report:	

Send this form within 24 hours by mail to pharmacovigilance@karyopharm.com
***or* by FAX to North America: 1-617-334-7617 *or* Germany: +49-89-9218-5650**

16.5. Appendix 5: Memo Regarding Cross-reported SUSAR form KPT CSTs

Karyopharm Therapeutics, Inc.
85 Wells Ave., 2nd floor
Newton, MA 02459
Phone: 617-658-0600
Fax: 617-244-9420

Date: 25 October 2017

To: Investigator Sponsored Trials that Utilize Selinexor

RE: **Reporting of Selinexor SUSARs Originating from Company Sponsored Trials**

From: Karyopharm Pharmacovigilance

Dear Investigator:

This memo is to clarify that Karyopharm reports all selinexor SUSARs originating from Company Sponsored Trials to all Competent Authorities involved in the review and approval of these Company Sponsored Trials. Your IST may be reviewed and approved by the same Competent Authority as a Karyopharm Company Sponsored Trial. Selinexor SUSARs originating from Company Sponsored Trials therefore do not need to be cross reported to the Competent Authorities of the Countries listed below. Please continue to cross report to your IRB/IEC and other applicable authorities as required by Good Clinical Practice and all national and local regulatory requirements.

United States
Canada
Austria
Belgium
Bulgaria
Czech Republic
Denmark
France
Germany
Greece
Hungary
Israel
Italy
Netherlands
Poland
Russia
Serbia
Spain
United Kingdom
Ukraine

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