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Cover Page

Title: An investigator-sponsored, phase 1/2 trial of the oral XPO1 inhibitor selinexor (KPT-330) monotherapy and in combination with docetaxel for previously treated, advanced *KRAS* mutant non-small cell lung cancer (NSCLC)

NCT: NCT03095612

Document Date: August 05, 2022

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An investigator-sponsored, phase 1/2 trial of the oral XPO1 inhibitor selinexor (KPT-330) monotherapy and in combination with docetaxel for previously treated, advanced *KRAS* mutant non-small cell lung cancer (NSCLC)

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Study Drug/Treatment: Selinexor (KPT-330), Docetaxel

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # 5 dated 05 August 2022

IST-USA-000000116600

An investigator-sponsored, phase 1/2 trial of the oral XPO1 inhibitor selinexor (KPT-330) monotherapy and in combination with docetaxel for previously treated, advanced *KRAS* mutant non-small cell lung cancer (NSCLC)

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
ALK	anaplastic lymphoma kinase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase (SGOT)
AV	Atrio-ventricular
BIW	twice weekly

Abbreviation	Definition
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Celsius
CBC	complete blood count
CHF	congestive heart failure
CLL	chronic lymphocytic leukemia
cm	centimeter
CNS	central nervous system
CR	complete remission
CrCl	creatinine clearance
CRF	case report form
CRM1	chromosomal region maintenance protein 1
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCR	disease control rate (CR, PR, SD ≥ 4 weeks)
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
EC	Ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EU	European Union
°F	degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
GSH	glutathione
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen

Abbreviation	Definition
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr	hour
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IMWG	International Myeloma Working Group
INR	international normalization ratio
IR	intermediate risk
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LAFB	left anterior fascicular block
LDH	lactic dehydrogenase
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minute
mL	Milliliter
MM	Multiple Myeloma
mm	Millimeter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	minor response
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NHL	non-Hodgkin’s lymphoma
NK1R	neurokinin 1 receptor
NPM1	Nucleophosmin
NSCLC	Non-small cell lung cancer

Abbreviation	Definition
NYHA	New York Heart Association
ORR	overall response rate (sCR + CR + VGPR + PR)
OS	overall survival
PD	progressive disease
PDn	pharmacodynamic
PE	physical examination
PFS	progression free survival
PK	pharmacokinetic
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
QW	once weekly
RBBB	right bundle branch block
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	relapsed/refractory
SAE	serious adverse event
SAM	S-adenosylmethionine
SC	subcutaneous
sCR	stringent complete response
SD	stable disease; standard deviation
SINE	selective inhibitor of nuclear export
SOC	standard of care; system organ class
T_{max}	time to maximum serum concentration
TSP	tumor suppressor protein
ULN	upper limit of normal
US	United States
VGPR	very good partial response
WBC	white blood cell
wt	wild type
XPO1	exportin 1

Study Design and Schema:

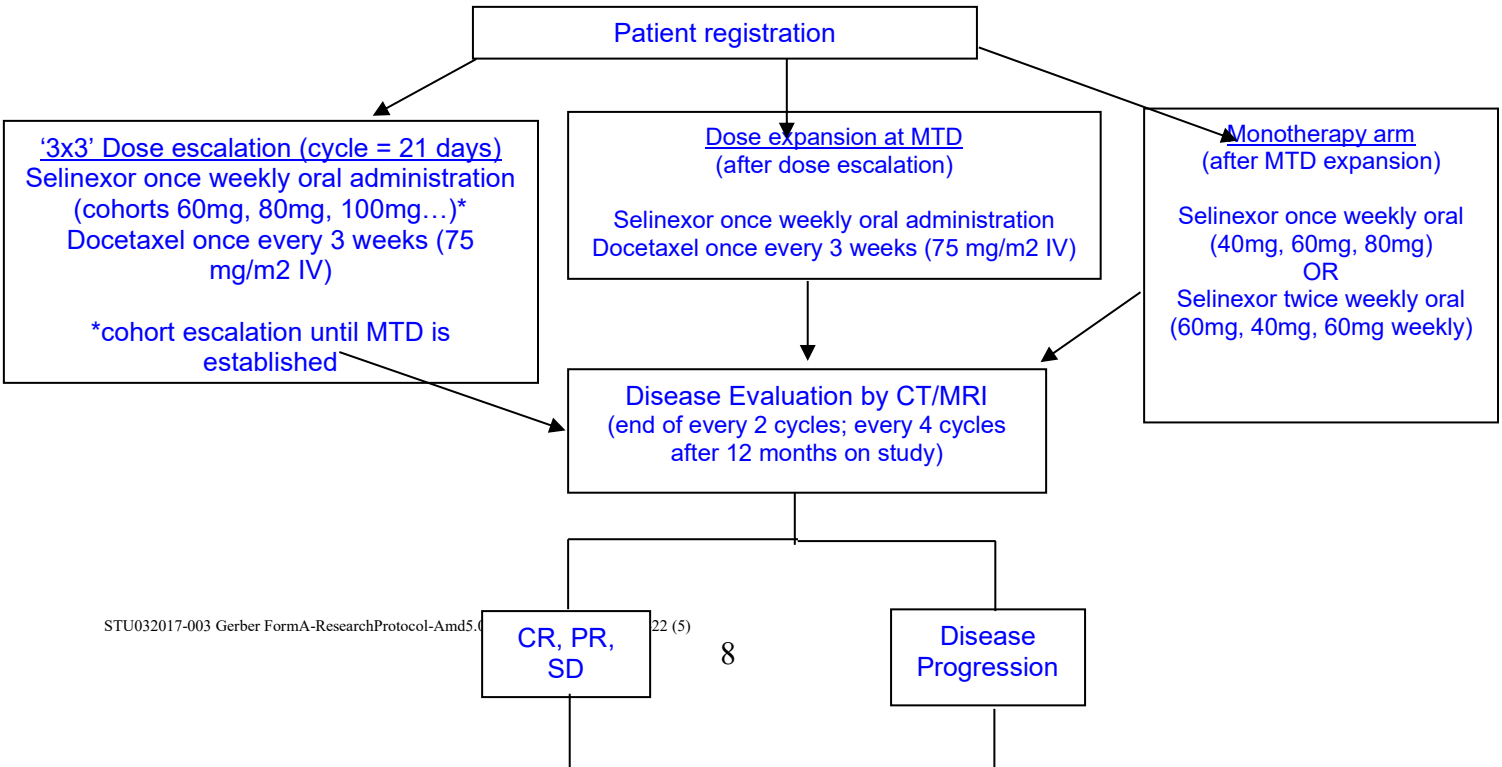
This is a phase 1/2 single-arm, non-blinded, multi-institutional study. In the combination cohorts, selinexor will be administered once weekly starting one week before chemotherapy initiation (to permit pharmacodynamic assessment of selinexor alone and in combination with chemotherapy),

chemotherapy),in combination with docetaxel. Docetaxel will be given once every 3 weeks. Treatment will be administered in 21-day cycles. Dose limiting toxicities (DLTs) will be assessed based on the first cycle (7-day lead-in plus 21-day cycle = 28 days) toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03. A standard 3 + 3 dose escalation paradigm will be used.

In the **docetaxel plus selinexor cohort**, depending on cohort expansion requirements, a total of 9-24 patients will be accrued to the dose-escalation phase 1 pilot trial, with a minimum of 6 patients treated at the MTD. A total of 35 patients will be enrolled to this expansion cohort, for a total of 31-46 patients. For the **selinexor monotherapy** cohort, 6 patients each will be treated in two dosing cohorts (weekly and biweekly). Based on the totality of clinical data, one regimen will be selected for the expansion cohort, enrolling an additional 22 patients for a total of 28 patients. Thus, the total enrollment to the selinexor monotherapy cohort will be 6 + 6 + 22 = 34 patients. The expected total enrollment for the overall study is 31-46 + 34 = 65-80 patients. Because the trial population will be drawn from a multi-institution base, it is anticipated that accrual will be completed over 36 months.

In the docetaxel plus selinexor expansion cohort, enrollment of 35 patients will provide 90% power to detect an improvement in the primary endpoint of radiographic response rate from 10% (historical control) to 35%, with a two-sided alpha of 0.05. The sample size estimate is based on the exact one-sample binomial test for proportions.

Subjects will be enrolled into the study after informed consent is signed and all inclusion/exclusion criteria have been verified. At that time, the dose level and subject identification number will be assigned, followed by randomization to any of the available treatment arms for which the subject is eligible.



STUDY SUMMARY

Title	An investigator-sponsored, phase 1/2 trial of the oral XPO1 inhibitor selinexor (KPT-330) monotherapy and in combination with docetaxel for previously treated, advanced *KRAS* mutant non-small cell lung cancer (NSCLC)
Short Title	Phase 1/2 Trial of Selinexor (KPT-330) Monotherapy and With Docetaxel for *KRAS* mutant NSCLC)
Protocol Number	IST-USA-000000116600
Phase	1/2
Methodology	. Open label
Study Duration	48 months
Study Center(s)	Multi-Center clinical trial with UT Southwestern Medical Center as lead center and 4 sub-sites
Objectives	Primary Objective: To determine the safety and the MTD and RP2D of selinexor administered with the standard dose of docetaxel in patients with advanced *KRAS* mutant NSCLC (docetaxel + selinexor cohort). Secondary Objective: To evaluate the efficacy of selinexor monotherapy and in combination with docetaxel in patients with advanced *KRAS* mutant NSCLC
Number of Subjects	65-80
Diagnosis and Main Inclusion Criteria	Mutant Non-small cell lung cancer (NSCLC)
Study Product(s), Dose, Route, Regimen	Selinexor monotherapy and in combination with docetaxel
Reference therapy	Docetaxel

Statistical Methodology	General considerations: UT Southwestern will be the coordinating center for this study and will be responsible for registering patients and for maintaining a complete database of the study information. Analysis of Clinical Endpoints: The design of this Phase 1-2 trial is described earlier, as is the definition of MTD and the rules for dose escalation. Safety and efficacy will be assessed using the CTCAE and RECIST criteria as above. Estimated accrual time: Review of patient accrual onto recent studies suggests that the study should be completed in 48 months. Justification for sample size: *Combination—docetaxel plus selinexor:* We anticipate enrolling 9-24 patients in the dose escalation component as follows: number dose levels=3-4; number patients per dose level=3-6. In the expansion cohort, enrollment of 35 patients will provide 90% power to detect an improvement in the primary endpoint of radiographic response rate from 10% (historical control) to 35%, with a two-sided alpha of 0.05. The sample size estimate is based on the exact one-sample binomial test for proportions. *Single-agent selinexor:* Initially two separate dose/schedule regimens will be evaluated: 60 mg PO twice weekly (N=6) and 80 mg PO once weekly (N=6). Based on the totality of clinical data from these 12 patients, one of these regimens will be selected to complete an expansion cohort of 28 total patients. The 6 patients from the selected regimen will be included in the expansion cohort, so 22 additional patients will be required, for a total 6 + 6 + 22 = 34 patients.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

KRAS mutant lung cancer remains a challenging and resistant disease. In non-small cell lung cancer (NSCLC), *KRAS* mutations convey a poor prognosis, insensitivity to adjuvant chemotherapy, and resistance to epidermal growth factor receptor (EGFR) inhibitors. Representing approximately 30% of adenocarcinomas, *KRAS* mutant NSCLC, in contrast to tumors harboring *EGFR* mutations or anaplastic lymphoma kinase (*ALK*) rearrangements, lacks a specific therapy. Development of RAS inhibitors has been hindered by the strong affinity of the GTP substrate to RAS, which prevents effective binding of pharmacologic agents. There has been some suggestion that targeting downstream mediators of *KRAS* signal transduction might be an effective alternative to direct targeting. In the Biomarker-Integrated Approaches of Targeted Therapy for Lung cancer Elimination (BATTLE) trial, the RAF inhibitor sorafenib demonstrated >50% disease control rate in *KRAS* mutant NSCLC.[2] However, despite promising results in a phase 2 trial, the strategy of MEK targeting in *KRAS* mutant NSCLC did not demonstrate efficacy in a confirmatory phase 3 trial. Specifically, the combination of docetaxel and selumetinib did not improve progression-free survival compared to docetaxel alone.

More recently, direct $KRAS^{G12C}$ inhibitors (eg, AMG 510) have demonstrated efficacy in this subset, which represents approximately one-third of KRAS mutations in NSCLC. As of May 2020, these agents remain in clinical development.

Lung cancer remains the leading cause of cancer-related deaths worldwide with an estimated incidence of 1.6 million cases resulting in 1.4 million deaths annually. Non-small-cell lung cancer (NSCLC) represents 80-85% of cases, and adenocarcinoma is the most common histology. The majority of NSCLC patients present with advanced or metastatic disease that is not amenable to surgical resection. For these patients, platinum-based combination chemotherapy has reached a therapeutic plateau with a median overall survival (OS) of 7.4 to 9.9 months. *KRAS* mutations are the most commonly identified driver mutation in NSCLC, occurring in 25 percent of adenocarcinomas. The presence of oncogenic *KRAS* alterations has been proposed to portend poor response to conventional treatment and poor clinical outcomes.

To date, pharmacologic attempts at inhibiting *KRAS* directly have proven unsuccessful, with the exception of direct KRAS G12C inhibitors limited to that subset of cases. Further, the mechanistic networks active in *KRAS* mutant lung cancers are subject to substantial diversity, proving the identification of an appropriate therapeutic surrogate target challenging. Therefore, novel concepts are needed to improve treatment and outcomes in *KRAS* mutant NSCLC.

Pre-clinical studies performed at UT Southwestern have demonstrated sensitivity of *KRAS* mutant NSCLC cell lines to the novel group of selective inhibitor of nuclear export (SINE) compounds. In a multi-genomic, data-driven approach obtained by analysis of 106 cell lines, nuclear transport machinery was identified as an obligatory function required for cell survival. By application of selinexor (KPT-330), tumor cell growth was halted and apoptotic cell death was induced at bioavailable concentrations (0.5 – 10 μM). Specificity to nuclear export machinery (XPO1 cargo transport) was identified via temporary modification of target expression. Accumulation of IκB

in the nucleus and resulting dysregulation of crucial survival pathways via NFκB as the responsible mechanism of cell death induction was identified. Resistance mechanisms through over-activation of FSTL5/Hippo pathway by co-occurring mutations in *FSTL5* were elucidated. Compared to *KRAS* mutant cell lines, treatment of *KRAS* wild-type cell lines resulted in significantly lower induction of cancer cell death.

As of March 2020, Selinexor had been received by over 3,720 patients in over 12 Karyopharm-sponsored trials, over 30 investigator-sponsored clinical studies, and through an expanded access program. Preliminary findings from ongoing studies show that selinexor induces durable anti-tumor responses across a broad range of hematologic and solid malignancies. Preliminary safety information available for 1,175 patients indicated that selinexor is generally well tolerated with the most frequent selinexor-related treatment-emergent adverse events including low-grade nausea (62%), fatigue (55%), anorexia (50%), thrombocytopenia (43%), and vomiting (38%) that were manageable with standard supportive care.

The combination of selinexor with docetaxel is proposed for the following reasons: (1) among the two FDA approved cytotoxic agents for advanced NSCLC progressing after platinum doublet therapy (docetaxel, pemetrexed), it is the most feasible in this indication, as pemetrexed is increasingly used as a component of first-line and/or maintenance therapy; (2) the activity of docetaxel monotherapy has been extensively characterized in advanced NSCLC, including *KRAS* mutant cases; (3) preclinical data combining selinexor with taxane-based therapy suggests strong synergy (combinations with paclitaxel in breast and ovarian cancer mouse models); (4) the widespread use of docetaxel as a backbone for combination therapy in NSCLC (including *KRAS* mutant cases) offers a straightforward developmental path to subsequent clinical development Although selinexor has not previously been combined with docetaxel in human clinical trials, it has been administered with the related drug paclitaxel. Specifically, the safety and efficacy of paclitaxel 80 mg/m2 IV Days 1 and 8 every 3 weeks combined with selinexor 60 mg PO twice weekly was explored in an investigator-sponsored trial. It was found to be safe and well tolerated in the 9 patients who have been dosed to date, and the cohort is currently being expanded.

Selinexor monotherapy is being studied in a cohort of patients for the following reasons: (1) preclinical data demonstrate single-agent activity of selinexor in *KRAS* mutant lung adenocarcinoma models; (2) some patients with *KRAS* mutant NSCLC treated with docetaxel plus selinexor appear to have experienced clinical benefit (eg, improved pain, diminished size of cutaneous metastasis, decreased LDH and alkaline phosphatase) during the 7-day lead-in period of selinexor monotherapy.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), thereby forcing the nuclear retention of key tumor suppressor proteins (TSPs). Transient retention of TSPs in the nucleus at high levels via XPO1 blockade 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. The reactivation of multiple tumor suppressor pathways and inhibition of translation of key pro-survival proteins through inhibition of a non-redundant, single protein represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms. More information about the mechanism of action,

pharmacology, and pre-clinical studies of selinexor is available in the *Selinexor/KPT-330 Investigator's Brochure (IB)*.

In July 2019, the FDA granted accelerated approval to selinexor (Xpovio) for use in combination with dexamethasone for the treatment of adult patients with relapsed/refractory multiple myeloma who have received ≥4 prior therapies and whose disease is refractory to ≥2 proteasome inhibitors, ≥2 immunomodulatory agents, and a CD38-targeted monoclonal antibody. The approval was based on a 25% response rate in a subgroup of patients in the pivotal phase IIb STORM study.

Beyond multiple myeloma, selinexor has been studied in several hematologic malignancies and solid tumors. Phase 1 studies with oral selinexor have been being conducted in advanced hematological malignancies including non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and acute myeloid leukemia (AML) (KCP-330-001), in solid tumors and in soft tissue and bone sarcomas (KCP-330-002 and -003). In addition, Phase 2 studies have been conducted in glioblastoma, gynecological malignancies, squamous cell carcinoma, prostate cancer, acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL), and Richter's transformation. More than 1,900 patients with objectively progressing tumors at study entry have received selinexor as of 01 November 2016 (refer to latest IB for more details).

Overall, in clinical studies selinexor has been relatively well tolerated, with the most frequently reported selinexor-related treatment-emergent adverse events (TEAEs) being generally low-grade nausea (62%), fatigue (55%), anorexia (50%), thrombocytopenia (43%), and vomiting (38%), that were manageable with standard supportive care.

Selinexor treatment is not associated with significant major organ toxicity. Moreover, clinically-relevant cumulative toxicities have not been observed during long-term treatment, with more than 28 patients receiving single-agent selinexor for over 1 year and 6 patients for over 2 years. These results suggest that selinexor may be administered long term with acceptable tolerability, and offer promise when used in combination with a wide range of other anti-cancer therapies.

Selinexor has shown single-agent, durable, anti-cancer activity in patients with multiple RR hematologic and solid tumor malignancies. Additional information about clinical studies of selinexor is available in the Selinexor/KPT-330 IB.

Over 3,100 patients have received selinexor in clinical studies (including Karyopharm sponsored trials and ISTs), most with single-agent selinexor. Based on this experience, selinexor has been relatively well tolerated, with the most frequently reported treatment-emergent adverse events (TEAEs) in Karyopharm-sponsored trials being nausea (65%), fatigue (58%), thrombocytopenia (52%), anorexia (51%), anemia (42%), and vomiting (38%). These events are generally low-grade, reversible, and manageable with standard supportive care and dose modification (Section 5.4, and Section 6.4 "Clinical Safety Results," IB v9.0).

Karyopharm plans to continue the development of selinexor to treat a wide variety of malignancies, including diseases that are not currently mentioned in the IB.

Preliminary findings from ongoing clinical studies have shown that selinexor induces durable anti-tumor responses across a broad range of relapsed/refractory (RR) hematologic and solid tumor cancers, which is consistent with its proposed mechanism of action, namely, induction of TSPs and reduction in oncoprotein levels in malignant cells. In general, these effects appear to be

independent of tumor type or prior treatment(s). More information about preliminary results from ongoing clinical studies is available in the current Selinexor/KPT-330 IB.

Selinexor is currently US FDA approved for the treatment of multiple myeloma and remains in clinical development for multiple other indications. Clinical experience with Selinexor has been evaluated to date in >2,000 and >1,000 patients enrolled in Company-sponsored and investigator-sponsored trials (IST), respectively, with the longest duration of >2 years without clinically significant toxicities. Use of Selinexor has been generally safe and well tolerated, and no major organ and/or systemic toxicities were observed to date.

A brief summary of preclinical data is provided below. More detailed information is available in the *Selinexor/KPT-330 IB*.

Pre-clinical studies with SINE compounds (not limited to KPT-330) on MM *in vivo* predict favorable efficacy and safety responses in the treatment of hematological malignancies and other types of cancer in humans. Selinexor and dexamethasone in combination were found to have a synergistic effect on MM1.S human MM cell viability relative to either drug alone. Enhanced activity of selinexor plus dexamethasone was also observed in two MM1.S xenograft models of human MM, which may predict enhanced efficacy of selinexor with dexamethasone in MM patients who are refractory to dexamethasone alone.

In animal models, the combination of selinexor and dexamethasone is synergistic for *in vitro* and *in vivo* MM cell cytotoxicity. Selinexor has also shown additive or synergistic activity when combined with other MM drugs, including proteasome inhibitors,[3-5], topoisomerase II inhibitors,[4] and lenalidomide (unpublished data). These studies suggest that selinexor has anti-MM activity that can cause decreased cancer cell viability, increased apoptosis, and increased cell cycle arrest *in vitro* and lead to potent inhibition of MM tumor growth *in vivo*, and that the addition of dexamethasone can augment these effects.

More information is provided in the *Selinexor/KPT-330 IB*.

Preclinical Data in *KRAS* mutant NSCLC is described in “Study Rationale” (Section 1.4) below.

1.3 Clinical Experience

1.3.1 Pharmacokinetics and Pharmacodynamics

Oral selinexor pharmacokinetics (PK) are predictable, approximately dose-proportional, and exhibit moderate- to moderately-high inter-patient variability across a wide dose range of doses in male and female patients with advanced hematological malignancies or solid tumors. Additional details are available in the Selinexor/KPT-330 Investigator’s Brochure.

Clinical pharmacodynamics (PDn) of selinexor have been studied in patients with advanced neoplasms. Following selinexor treatment, XPO1 mRNA was induced in peripheral white blood cells (WBC) from patients following XPO1 inhibition. Peak XPO1 mRNA induction was observed at 4-8 hours post dose and levels remained elevated for 24 48 hours; there was no difference in extent or kinetics of XPO1 induction in peripheral WBC when evaluated by cancer subtype. XPO1 MRNA induction was maximal during Cycle 1 and waned in later cycles due in large part to persistent elevation of XPO1 mRNA expression at baseline. The half-life for decline

of XPO1 mRNA exceeded that of selinexor half-life suggesting a prolonged PDn effect likely due to the covalent inhibition of XPO1 and the relatively long half-life of the XPO1 protein.

1.4 Efficacy

Preliminary findings from ongoing clinical studies, notably studies KCP-330-001 and -002, have shown that selinexor induces durable anti-tumor responses across a broad range of relapsed/refractory (RR) hematologic and solid-tumor cancers, which is consistent with its proposed mechanism of action, namely, induction of TSPs and reduction in oncoprotein levels in malignant cells. Broad anti-tumor activity has also been preliminarily observed in additional ongoing clinical studies with selinexor in patients with hematologic or solid tumors (clinical studies KCP-330-003 to -010 and -013). In general, these effects appear to be independent of tumor type or prior treatment(s). Responses across a variety of hematologic malignancies have generally been more rapid, deeper, and more durable compared to those in solid tumors. Please refer to the *Selinexor/KPT-330 IB* for more information.

1.5 Safety

Over 3,100 patients have received selinexor in clinical studies (including Karyopharm sponsored trials and ISTs), most with single-agent selinexor. Based on this experience, selinexor has been relatively well tolerated, with the most frequently reported treatment-emergent adverse events (TEAEs) in Karyopharm-sponsored trials being nausea (65%), fatigue (58%), thrombocytopenia (52%), anorexia (51%), anemia (42%), and vomiting (38%). These events are generally low-grade, reversible, and manageable with standard supportive care and dose modification (Section 5.4, and Section 6.4 “Clinical Safety Results,” IB v9.0).

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1.5.1 Reproductive Risks

No mutagenic potential was observed in nonclinical studies that included a GLP bacterial reverse mutation assay (Ames Test), in a chromosomal abnormality screen, or in a micronucleus assay.

There have been no adequate and well-controlled studies of selinexor in pregnant women. In non-clinical toxicology studies, macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies, most of which partially or fully resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. It is unknown whether similar effect may occur in humans. Please refer to the Selinexor/KPT-330 IB for additional information. As it is unknown whether selinexor might have reproductive toxicity in humans, patients must agree to use effective contraception (see Section 5.3.3.3) during the study and for 3 months after the end of treatment.

1.6 Rationale

Lung cancer remains the leading cause of cancer-related deaths worldwide with an estimated incidence of 1.6 million cases resulting in 1.4 million deaths in annually. Non-small-cell lung cancer (NSCLC) represents 80-85% of cases, and adenocarcinoma is the most common histology.[6] The majority of NSCLC patients present with advanced or metastatic disease that is not amenable to surgical resection. *KRAS* mutations are the most commonly identified driver mutation in non-small cell lung cancer, occurring in 25 percent of adenocarcinomas.[7] The presence of oncogenic *KRAS* alterations has been proposed to portend poor response to conventional treatment and poor clinical outcomes. Platinum-based combination chemotherapy has reached a therapeutic plateau with a median overall survival (OS) of 7.4 to 9.9 months.

To date, pharmacologic attempts at inhibiting KRAS directly have proven unsuccessful. Further, the mechanistic networks active in *KRAS* mutant lung cancers are subject to significant diversity, proving the identification of an appropriate therapeutic surrogate target challenging. Therefore, novel concepts are needed to improve treatment in *KRAS* mutant non-small cell lung cancer.

Recently, pre-clinical data derived in the laboratory of Dr. Michael White at UT Southwestern have demonstrated sensitivity of *KRAS* mutant NSCLC cell lines to the novel group of selective inhibitors of nuclear export (SINE) (**Figures 1-3**). In a multi-genomic, data-driven approach obtained by analysis of 106 cell lines, we identified the nuclear transport machinery as an obligatory function required for cell survival. By application of selinexor (KPT-330), tumor cell growth was halted and apoptotic cell death was induced at bioavailable concentrations (0.5 – 10 μM). Specificity to the nuclear export machinery (XPO1 cargo transport) was identified via temporary modification of target expression, identify accumulation of IκB in the nucleus and resulting dysregulation of crucial survival pathways via NFκB as the responsible mechanism of cell death induction and were also able to identify resistance mechanisms through over-activation of FSTL5/Hippo pathway by co-occuring mutations in FSTL5. Treatment of *KRAS* wild-type cell lines resulted in significantly lower induction of cancer cell death.

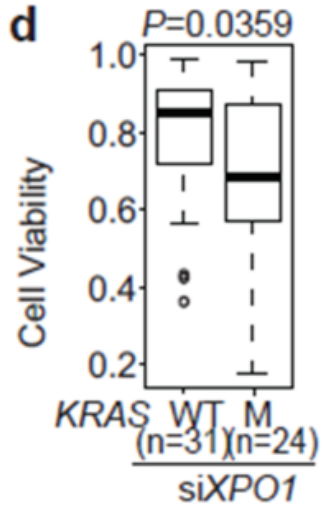

Figure 1. Differential cell viability following XPO1 depletion in *KRAS* mutant versus *KRAS* wt cell lines.[8]

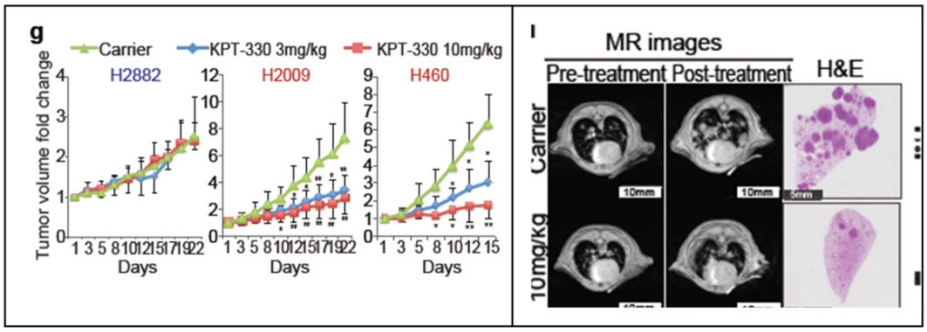

Figure 2. *In vivo* selective sensitivity of *KRAS* mutant NSCLC cells (red, *KRAS* mutant; blue, *KRAS* wt) to chemical inhibition of the nuclear transport receptor XPO1. (a) Tumor volume fold change of *KRAS* mutant and *KRAS* wt xenografts upon XPO1 inhibition. **P*<0.05; ***P*<0.01. (b) Representative lung MR image of *KRAS* G12D mutant mouse shown before and after treatment for each cohort. Post-treatment H&E-stained left lung lobe is shown.[8]

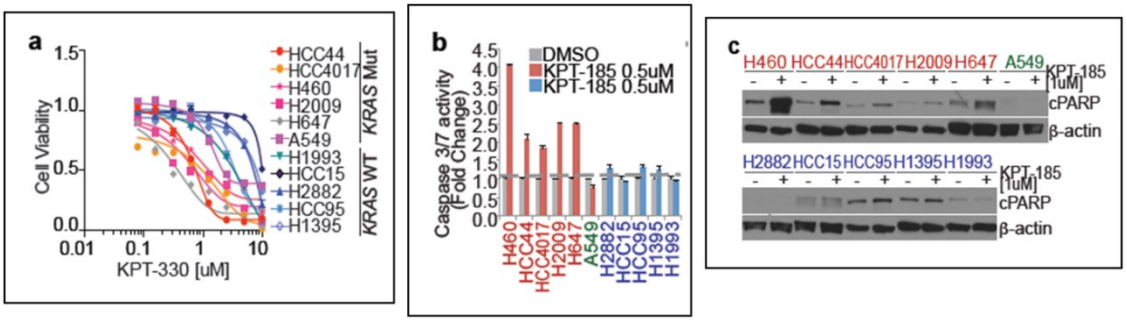

Figure 3. *In vitro* selective sensitivity of *KRAS* mutant NSCLC cells (red, *KRAS* mutant; blue, *KRAS* wt) to chemical inhibition of the nuclear transport receptor XPO1. (a) dose response curves following 72-hr exposure to KPT-330; (b) Induction of caspase 3/7 activity in KRAS mutant lines by KPT-185; (c) accumulation of cleaved PARP in *KRAS* mutant lines following exposure to KPT-185.[8]

The combination of selinexor with docetaxel is proposed for the following reasons: (1) among the two FDA approved cytotoxic agents for second-line treatment of advanced NSCLC (docetaxel, pemetrexed), it is the most feasible in this indication, as pemetrexed is increasingly used as a

component of first-line or maintenance therapy; (2) the activity of docetaxel monotherapy has been extensively characterized in advanced NSCLC, including KRAS mutant cases; (3) preclinical data combining selinexor with taxane-based therapy suggests strong synergy (combinations with paclitaxel in breast and ovarian cancer); (4) the widespread use of docetaxel as a backbone for combination therapy in NSCLC (including *KRAS* mutant cases) offers a straightforward developmental path to regulatory approval. Although selinexor has not previously been combined with docetaxel in human clinical trials, it has been administered with the related drug paclitaxel. Specifically, the safety and efficacy of paclitaxel 80 mg/m^2 IV Days 1 and 8 every 3 weeks combined with selinexor 60 mg PO twice weekly was explored in an investigator-sponsored trial. It was found to be safe and well tolerated in the 9 patients who have been dosed to date, and the cohort is currently being expanded.

1.7 Correlative Studies

Inhibition of XPO1 results in nuclear retention of cargo proteins. Biopsies from various tumors collected from patients before and during the first cycle of selinexor treatment and evaluated histologically by hematoloxylin and eosin (H&E) and immunostaining of XPO1 cargos shows evidence of PDn effects of selinexor. H&E staining showed reduction in tumor burden based upon reduction in the number of tumor cells in the biopsies. Selinexor-induced nuclear localization of TSPs was evident, including p53, p27, FOXO-3A, and IkB. Reduction in the proliferation marker Ki67 with increases in apoptotic markers were also observed.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To determine the dose limiting toxicity (DLT) and maximum tolerated dose for KPT safety and the MTD and RP2D of selinexor administered with the standard dose of docetaxel in patients with advanced *KRAS* mutant NSCLC (docetaxel + selinexor cohort).

2.2 Secondary Objectives

To evaluate the efficacy of selinexor monotherapy and in combination with docetaxel in patients with advanced *KRAS* mutant NSCLC

2.3 Exploratory Objectives

To identify predictive and pharmacodynamic biomarkers of selinexor monotherapy and in combination with docetaxel.

2.4 Endpoints

- Dose Limiting toxicity as defined in section 4.2 during the first cycle of study treatment and assessed per CTCAE v4.03.
- Radiographic response per RECIST.

3.0 Subject Eligibility

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

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. The patient must provide informed consent prior to the first screening procedure. However, the Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF.
2. Age ≥ 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Histologically or cytologically confirmed advanced (stage 4, according to the American Joint Committee on Cancer [AJCC] version 7.0 Staging manual) NSCLC
5. Molecular identification of a *KRAS* mutation (codons 12, 13, or 61 mutations detected by sequencing) by a CLIA-certified assay (source documentation required).
6. Tissue available for analysis at time of enrollment for biomarker analysis: 10 unstained slides plus 1 H+E slide. If archival tumor tissue is not available in select cases, subjects may be permitted to enroll on the study with prior approval of the study PI.
7. At least one and up to two previous lines of systemic cytotoxic therapy for advanced NSCLC, of which one must have been a platinum-based doublet therapy. Up to four total previous lines of systemic therapy (including immunotherapy and molecularly targeted therapy) for advanced NSCLC.
8. Radiographic or clinical disease recurrence or progression during or after the last line of systemic therapy
9. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1500 cells/µL; hemoglobin ≥ 9 g/dL; platelets ≥ 100,000/µL. Patients may be transfused with PRBCs up to 7 days prior to when enrollment labs are drawn to achieve Hgb ≥9.0 mg/dL.
10. Adequate renal function (calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation)
11. Adequate hepatic function (total bilirubin ≤ upper limit of normal [ULN], alanine aminotransferase [ALT] ≤ 2 × ULN and aspartate aminotransferase [AST] ≤ 2 × ULN). ALT and/or AST may be ≤ 5 × ULN if due to liver metastases. If ALT or AST is > 2 and ≤ 5 × ULN in patients with liver metastases, alkaline phosphatase must be ≤ 2.5 × ULN (unless elevated alkaline phosphatase clearly due to skeletal—rather than hepatic—process; eg, normal GGT, presence of multiple bone metastases, absence of bulky and/or central liver metastases). Patients with Gilbert's syndrome are allowed if total bilirubin ≤ 2 × ULN and direct bilirubin is ≤ ULN.
12. Female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method 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. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose of study treatment. Female patients of child-

bearing potential must have a negative serum pregnancy test at screening and agree to use 2 reliable methods of contraception throughout the study and for 3 months after their last dose of medication. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility (including hysterectomy and/or bilateral oophorectomy, but not tubal ligation alone) or evidence of post-menopausal status defined as any of the following:

- Natural menopause with last menses >1 year ago
- Radiation-induced oophorectomy with last menses >1 year ago
- Chemotherapy-induced menopause with last menses >1 year ago.

Male patients and their partners must use 2 reliable methods of contraception, at least one of them a barrier method (if sexually active with a female of child-bearing potential).

13. Measurable disease according to RECIST v1.1
14. Previously treated (surgery and/or radiation therapy) or untreated brain metastases are eligible, provided that patients are asymptomatic and not requiring escalating doses of corticosteroids.
15. Previous treatment-associated clinically significant toxicities resolved to CTCAE grade ≤2 (except alopecia) or to their baseline. NOTE: Prior immunotherapy-related endocrinopathy controlled with ongoing medical management (eg, hypothyroidism, adrenal insufficiency, diabetes) is permitted
16. At least 3 weeks or 5 half-lives, whichever is shorter, since receiving systemic anticancer therapy, including investigational agents, prior to starting study therapy. At least 2 weeks since receiving radiation therapy prior to starting study therapy

3.2 Exclusion Criteria

Exclusion Criteria:

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

1. Patients who are pregnant or lactating
2. Major surgery (excluding skin biopsies and procedures for insertion of central venous access devices) within 2 weeks of first dose of study drug
3. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety
4. Concurrent active malignancy that would interfere with treatment administration or assessment in the opinion of the treating investigator
5. Unstable cardiovascular function:

- Symptomatic ischemia, or
- Uncontrolled clinically significant conduction abnormalities (i.e., ventricular tachycardia on anti-arrhythmics is excluded; 1st degree AV block or asymptomatic LAFB/RBBB are not excluded; asymptomatic rate controlled atrial fibrillation is not excluded), or
- Congestive heart failure (CHF) of NYHA Class ≥3, or
- Myocardial infarction (MI) within 3 months

6. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose; however, prophylactic use of these agents is acceptable even if parenteral
7. Pre-existing grade 3 or 4 neuropathy
8. Active Hepatitis A, B or C infection

9. Known human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this study)
10. Patients unable to swallow tablets, patients with malabsorption syndrome, or any other GI disease or GI dysfunction that could interfere with absorption of study treatment
11. Prior exposure to docetaxel, selinexor, or another selective inhibitor of nuclear transport (SINE) compound (NOTE: prior docetaxel exposure permitted in selinexor monotherapy cohort)
12. Patients unwilling to comply with study protocol.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Dosing Rational-combination therapy:

Weekly selinexor dosing regimens were designed based on pharmacodynamic observations that the biological effects of oral selinexor have prolonged durations. Multiple clinical trials have employed weekly dosing regimens and have demonstrated both efficacy and tolerability. Maximum selinexor serum levels of 1-2 μM are typically achieved in cancer patients following selinexor oral doses of 40-100 mg (~25-60 mg/m^2). 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 60 mg weekly across multiple indications, which is proposed as the starting dose in our study. Selinexor will be administered once weekly in combination with docetaxel starting one week before chemotherapy initiation. 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.

4.1.2 Dosing Rationale—selinexor monotherapy:

Initially two separate dose/schedule regimens will be evaluated: 60 mg PO twice weekly (N=6) and 80 mg PO once weekly (N=6). Both of these regimens have demonstrated efficacy and tolerability in earlier trials. Based on the totality of clinical data from these 12 patients, one of these regimens will be selected to complete an expansion cohort of 28 total patients.

4.2 Concomitant Medications:

Commercially available docetaxel will be used for this study. It will be supplied in accordance with applicable local laws and regulations. Docetaxel 60 or 75 mg/m^2 depending on the dose level will be administered as a 1-hour IV infusion. The amount of docetaxel administered will be determined on Day 1 of each cycle by calculating the patient's BSA. When calculating the dose of docetaxel, rounding the BSA according to institutional practice is permitted. The dose of docetaxel may be capped at the dose corresponding to a BSA of 2 m^2 if necessary to comply with institutional practices. Premedication for docetaxel will follow the local institutional standard of care guidelines.

Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor- Investigator.

Patients may continue their baseline medication(s). Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as part of standard care. Medications to treat concomitant diseases such as diabetes, hypertension, etc., are allowed. All prescription, non-prescription, or over-the-counter medications, including herbal remedies, taken by the patient at entry and during the study must be clearly documented in the CRF. The patients must be instructed that no additional medication will be allowed without the prior consent of the Investigator. In general, concomitant medications to control side effects of therapy may be given during treatment, with specific guidelines provided throughout the protocol.

Table 3: Pre-specified dosing levels of selinexor and docetaxel[†]

Dose Level	Dose of Selinexor (mg oral)	Dose of Docetaxel (mg/m^2 IV), every 3 weeks
1[a]	60 once weekly	75
2[a]	80 once weekly	75
3	100 once weekly	75
-1	40 once weekly	75
-2	40 once weekly	60

[a]If the maximum tolerated dose (MTD) is exceeded in Dose Levels 1, 2, or 3, docetaxel dose may be reduced to 60 mg/m^2 and additional cohorts enrolled starting with the corresponding selinexor dose level and subsequent selinexor dose escalation (for Levels 1 and 2) as appropriate according to 3+3 dose escalation guidelines. If these cohorts are enrolled without exceeding the MTD, a subsequent cohort with docetaxel dose re-escalated to 75 mg/m^2 every 21 days with concurrent myeloid growth factor support every cycle may be enrolled

Table 4A. Selinexor monotherapy cohort dose levels—weekly dosing

Dose Level	Dose of Selinexor (mg oral)
1	80 once weekly
-1	60 once weekly
-2	40 once weekly

Table 4B. Selinexor monotherapy cohort dose levels—twice weekly dosing

Dose Level	Dose of Selinexor (mg oral)
1	60 twice weekly
-1	40 mg twice weekly
-2	60 mg once weekly

4.3 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.4 Dose Adjustments

Patients who are experiencing low-grade tolerability symptoms and are deriving clinical benefit from the treatment, may receive a dose schedule reduction at the discretion of the PI. Patients whose dose or schedule is reduced may subsequently have their previous dose schedule adjusted upwards, according to the above guidelines, at the discretion of the PI. PI may consult with Karyopharm Therapeutics Inc. as necessary. If one of the therapeutic agents is withheld or discontinued for toxicity, the other agent may be continued.

4.5 Dose Limiting Toxicity (DLT) definition:

DLT will include the following when considered to be at least possibly related to study drug administration:

- > 1 missed doses (out of 4 doses) of study treatment during cycle 1 due to study treatment related toxicities
- Discontinuation of study therapy before completion of Cycle 1, due to study-drug related toxicity

Non-hematologic toxicity

- Grade ≥ 3 nausea, vomiting, dehydration, diarrhea or fatigue lasting > 3 days despite optimal supportive medications
- Any other Grade ≥3 non-hematological toxicity with the following exceptions:
  - Electrolyte abnormalities that are reversible and asymptomatic
  - Hair loss

- Grade 3 ALT, AST or alkaline phosphatase levels in the setting of baseline ≤ Grade 2 elevations from disease
  - Delay in initiating cycle 2 therapy for > 21 days.
  - Any other Grade 4 non-hematologic toxicity

Hematologic toxicity

- Febrile neutropenia (Grade ≥3, by definition)
- Grade 4 neutropenia lasting > 7 days
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura, or requiring transfusion

To be evaluable for DLT, a patient must receive at least one dose of docetaxel and at least three of four doses of selinexor. To be considered not to have experienced DLT, a patient must complete the first (28-day) cycle of treatment before a dose-escalation evaluation is made. Patients who are not evaluable for toxicity will be replaced.

Although all toxicities at each course will be recorded, only adverse events thought possibly, probably, or definitely attributable to selinexor and docetaxel during the first treatment cycle will be used in the decision to dose escalate, expand, or de-escalate. In the absence of unacceptable toxicity, patients will be allowed to continue receiving selinexor in combination with docetaxel until disease progression.

Exceptions to DLT:

Adverse events that meet the above definitions but that are clearly unrelated to study drug will not be considered to be DLTs.

In rare instances, an event may fall within the definition of a DLT, as defined above, but the event may be considered not to be a DLT (e.g., not be clinically meaningful). If this occurs, the Sponsor-Investigator and the drug supplier will review the event and supporting data, and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale.

In addition, other events may occur which do not meet the definition of a DLT but are of concern to the Sponsor-Investigator and the drug supplier and may be considered to be DLTs.

4.6 Safety Cohort Review

The Investigator, in conjunction with the drug supplier, will determine whether a dose level will be re-opened, a cohort will be expanded, or if there will be a dose modification/escalation, etc. These discussions will occur during planned calls between the Investigators, study team, subsites team members, and Drug supplier and in weekly Phase 1 disease oriented team meetings.

Escalation to the next dose level will occur only after three evaluable patients on the previous dose level have been observed for a complete 28 day cycle. The Safety Assessment: End of Cycle 1 form must be completed and provided to the UT Southwestern phase 1 QA Coordinator either via fax to the attention of Oluwaseyi Sowemimo and Payal Dixit at 214-648-1578 or scanned then emailed to oluwaseyi.sowemimo@utsouthwestern.edu and payal.dixit@utsouthwestern.edu. This form will be reviewed by the Principal Investigator then submitted to the UTSW DSMC for review

and approval for dose escalation. Allow at least 48 hours for the cycle 1 safety assessment review process and once approval to proceed to the next dose level has been received an email notification from the phase 1 manager will be sent. Intra-patient dose escalation will be permitted. After completing one cycle (cycle 1) at the assigned dose, the cohort review committee can allow a patient to be moved to the latest defined safe dose if that patient has at least stable disease on their current dose and did not experience a dose limiting toxicity (DLT) at their assigned dose.

This process will be followed until the RP2D is reached, at which time eligible patients will enter the Expansion Phase.

4.7 Dose Reduction and Supportive Care Guidelines

Selinexor, a specific XPO1 inhibitor, alters a variety of tumor suppressors, cell cycle regulators, oncoproteins, and transcriptional factors. Given this complex mechanism, the relationship between dose and antitumor activity, as well as tolerability, is expected to be highly dependent on both tumoral and patient factors. Consistent with this, based on observations from the ongoing studies in patients with advanced hematological and solid tumors, selinexor shows a wide therapeutic range with antitumor activity from 12 to 120 mg. Therefore, in order to optimize the antitumor activity and tolerability, dose reductions and/or schedule modifications will be allowed as outlined below and in Table 4 and Table 5. For some AEs, dose interruption and/or reduction is recommended. See Table 5 for specific recommendations.

While drug-related major organ toxicities are relatively uncommon, there are a number of constitutional side effects (and thrombocytopenia) that 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 four to six weeks of dosing. Finally, some patients with rapid tumor responses experience significant fatigue, nausea, malaise and/or asthenia after 1 or more doses of selinexor. This effect has not been associated with typical markers of tumor lysis syndrome, but if suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

The CTCAE version 4.03 will be used for grading the severity of AEs; the study treatment modifications described below are applied according to this severity grading. Toxicity will be documented as described. 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 4 and Table 5).

Table 4 summarizes the starting doses (Dose Level 1) and preferred dose modifications (i.e., Dose Levels -1 through -3) for AEs listed in Table 5. General supportive care guidelines are provided in *Section* ***Error! Reference source not found.***.

4.7.1 Selinexor Dose Adjustment and Supportive Care Guidelines for AEs related to Selinexor

Table 5 Selinexor Supportive Care and Dose Adjustment Guidelines[a,b,c]

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Fatigue (common)	
Grade 1 or Grade 2 lasting ≤ 7 days	Maintain dose. Rule out other causes. If found to be anemic, consider transfusing for hemoglobin < 8 g/dL. Patients with significant fatigue after several doses of selinexor may have an ongoing antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting ≤7 days	As per the 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, consider transfusing for hemoglobin < 8 g/dL. 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 ongoing antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. As per the 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 a repeat nutritional consultation and utilize nutritional supplements (e.g., Ensure®, Boost®, etc.) For persistent symptoms, start appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), per NCCN guidelines.
Grade1 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 and weight loss	Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level. Rule out other causes. Consider a repeat nutritional consultation and utilize nutritional supplements (e.g., Ensure®, Boost®, etc.) Start appetite stimulants as above.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Nausea, Acute (common)	
Grade 1 or 2 (If intolerable or persistent Grade 2 not responsive to supportive care, follow guidelines for Grade 3)	Maintain dose. Rule out other causes. Utilize standard additional anti-nausea meds to supplement the protocol-required 5-HT3 antagonists. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Utilize additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, 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 (common)	
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.
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. 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 (common)	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
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.
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, start 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 (i.e., ≥ 50% marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), or if there is baseline thrombocytopenia Grade 2-4, the Principal 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, start treatment with moderate to high doses of thrombopoietin stimulating agents as above. In cases where there is significant disease involvement in the bone marrow (i.e., ≥ 50% marrow involvement) 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. If recurrent, unless contraindicated, start treatment with moderate to high doses of thrombopoietin stimulating agents as above.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Neutropenia	
Grade 3 or 4 Neutropenia (afebrile) OR Febrile Neutropenia	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reinitiate selinexor therapy and colony stimulating factors per institutional guidelines. If recurrent, continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤2 or baseline levels, and reduce dose of selinexor 1 dose level.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Sponsor-Investigator.	
Tumor lysis syndrome	
If TLS risk factors are identified, provide prophylactic IV hydration and regular monitoring of hydration (especially when increasing the dose of selinexor), renal function, urine output, and clinical laboratory measures of interest for TLS (eg, phosphorus, potassium, calcium, LDH, uric acid). Consider administration of hypouricemic agents to reduce the risk of TLS. Hold selinexor in patient with hyperkalemia (≥7.0 mmol/L) and/or symptoms of hyperkalemia, an increase in uric acid, or other changes in biochemical blood parameters suggestive of TLS. Start IV hydration, and consider hypouricemic agent until levels return to normal. Selinexor can be reintroduced at the normal or reduced dose.	
Other selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Initiate 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.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
	All dose modifications should be based on the worst preceding toxicity. [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. [c]If toxicities are suspected to be due to docetaxel rather than selinexor (eg, neutropenia occurring at expected intervals after chemotherapy), selinexor dose does not need to be modified. If, however, toxicities persist despite docetaxel dose modification and/or supportive care measures (as appropriate), then the selinexor dose should be modified. 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.

4.7.1.1 Conditions Not Requiring Selinexor Dose Reduction

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

- Alopecia of any grade.
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions.
- Isolated values of ≥Grade 3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed.
- Toxicities attributed to docetaxel. If, however, toxicities persist despite docetaxel dose modification and/or supportive care measures (as appropriate), then the selinexor dose should be modified.

4.7.1.2 Selinexor Dose Adjustment in the Setting of Infection

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

4.7.2 Missed or Vomited Doses

Weekly selinexor dosing cohorts

Missed Doses

Missed doses should be managed as follows:

- **If a dose was missed**, it may be given up to 48 hours after the planned dose and at least 36 hours before the next scheduled dose

- **If a dose must be skipped** (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

  If a patient missed a full one- or two-week period of dosing for non-study drug-related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will be replaced. For example, if patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then the patient will start the next dosing on Cycle 2 Day 7 following the break. Similarly, if a patient misses Cycle 3 Day 1 to Cycle 3 Day 15, then the patient will start the next dosing on Cycle 3 Day 1. In this fashion, laboratory and radiographic assessments remain appropriate for timing of the administration of anti-cancer therapy.

  Vomited Doses

  If a dose 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.

Twice weekly selinexor dosing cohorts

Missed Doses

If a dose of selinexor is missed or delays, patients should take the next dose at the next regularly scheduled time.

Vomited Doses

If a patient vomits a dose of selinexor, the patient should not repeat the dose. The patient should take the next dose on the next regularly scheduled day.

4.7.3 Docetaxel Dose Reduction and Supportive Care Guidelines

Each cycle of chemotherapy may be delayed until the ANC is ≥ 1500 cells/μL and the platelet count is ≥ 100,000 cells/μL and hepatic function is acceptable. Institutional standard practices may be used to adjust doses for toxicity. However, in the absence of such standard practices, suggested dose adjustments for docetaxel-related hematologic and non-hematologic toxicities are provided in Table 6 and Table 7, respectively.

NOTE: If toxicities are suspected to be due to selinexor rather than docetaxel (eg, nausea occurring on a weekly basis, coinciding with selinexor dosing), docetaxel dose does not need to be modified. If, however, toxicities persist despite selinexor dose modification and/or supportive care measures (as appropriate), then the docetaxel dose should be modified.

Anti-emetic prophylaxis and premedication for infusion reactions for docetaxel should follow institutional guidelines.

Table 6. Dose Adjustments for Docetaxel-related Hematologic Toxicities

Situation	Recommended Docetaxel Dose

	Starting Dose 75mg/m^2	**Starting Dose 60mg/m^2**
First episode of febrile neutropenia	60 mg/m^2	50mg/m^2
Second episode of febrile neutropenia	35 mg/m^2	35mg/m^2
ANC <500/mm^3	60 mg/m^2	50mg/m^2
Grade 4 thrombocytopenia or bleeding associated with thrombocytopenia	60 mg/m^2	50mg/m^2

NOTE: In addition to or in place of docetaxel dose reductions for neutropenia, patients may receive myeloid growth factors (preferably PEG-filgrastim on Day 2 of subsequent cycles).

Table 7. Dose Adjustments for Docetaxel-related Non-hematologic Non-neuropathic Toxicities

NCI CTCAE Grade	Recommended Docetaxel Dose	
	Starting dose 75 mg/m^2	**Starting dose 60 mg/m^2**
0 to 2	75 mg/m^2	60 mg/m^2
3 (except alopecia)	60 mg/m^2	50 mg/m^2
4	35 mg/m^2	35 mg/m^2

NCI-CTCAE= National Cancer Institute (United States Common Terminology Criteria for Adverse events (Version 4.03).

In addition to the dose adjustments, patients may receive supportive care as necessary. Patients experiencing febrile neutropenia secondary to docetaxel chemotherapy may receive granulocyte colony stimulating factor therapy in association with subsequent chemotherapy doses. Erythropoietin may also be used as clinically indicated, along with other supportive care.

4.8 Supportive Care and Concomitant Therapy

4.8.1 Required Antiemetics

In order to minimize nausea, all patients should receive two anti-emetic prophylaxis. This includes (a) 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, AND (b) olanzapine 5 mg (which can be increased to 10 mg) daily starting before the first dose of treatment and continued as needed. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists.

4.8.2 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 **Error! Reference source not found.**), 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 Table 5.

4.8.3 Non-study Related Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s). Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

4.8.4 Permitted Concomitant Medication

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

4.8.5 Use of Blood Products

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

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

4.9 Other Modalities of Procedures

4.9.1 Radiation Treatment

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

4.9.2 Restrictions and Prohibited Medications

Concurrent Therapies: Concurrent therapy with glucocorticoids as specified herein is allowed. Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor-Investigator.

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

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

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. However, they are permitted if the patient has elevated liver function tests Patients must report all prescription and non-prescription medicines to their physicians during this study

4.9.3 Duration of Therapy

Review of patient accrual onto recent studies suggests that the study should enroll 3-4 patients per month. Accounting for variations in site activation time-lines, we estimate the duration of accrual to be over 36 months.

4.9.4 Discontinuation Criteria

4.9.4.1 Early Discontinuation of the Study

The study may be discontinued at the sole discretion of the Sponsor-Investigator for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients.

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

4.9.4.2 Early Discontinuation of Individual Patients

The Investigator may remove a patient from study treatment after consultation with the Sponsor-Investigator for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care (this must be linked in the study database to the AE or toxicity event to support discontinuation).
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

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

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

Patients may discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

4.9.5 Treatment Beyond Progression:

In some instances, a patient may be deemed to be receiving benefit from study therapy despite RECIST progressive disease. In these cases, study treatment may be continued if the following criteria are met:

- No ongoing intolerable treatment-related AEs
- Patient informed of available treatment options
- Case discussed with and decision to treat beyond progression approved by Study Chair

NOTE: Patients in the selinexor monotherapy cohort may be treated with selinexor + docetaxel at the time of progression. In these cases, (a) the above criteria must be met, (b) the dose and schedule of selinexor + docetaxel will be based on the currently used regimen in the combination cohort, and (c) subsequent treatment administration (dose, schedule, etc) will be based on protocol guidance for the selinexor + docetaxel cohort.

4.9.6 Removal Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator,and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.9.7 Subject Replacement

To be evaluable for DLT, a patient must receive at least one dose of docetaxel and at least three of four doses of selinexor. To be considered not to have experienced DLT, a patient must complete the first (28-day) cycle of treatment before a dose-escalation evaluation is made. Patients who are not evaluable for toxicity will be replaced.

5.0 Study Procedures

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

Screening will include the study procedures described below and will be **performed within 28 days prior to the start of therapy** as summarized in ***Error! Reference source not found.***. The Investigator should not repeat procedures that are performed as part of standard of care (SOC), if

they are within the screening window and are done prior to signing the ICF. Data from SOC procedures will be part of the patient's medical history and may be used for study purposes.

Screening may be divided into two (or more) clinic visits at the discretion of the Investigator. The procedures to be performed during screening are listed below assuming such a division; however, the decision is up to the Investigator, as long as all procedures are performed.

Screening (Performed within 4 weeks prior to start of study therapy)

- A complete medical history (all significant conditions that have previously existed and are now resolved as well as current conditions)
- Documentation of concomitant medications (including alternative medications)
- Physical examination including body weight, height, and vital signs (heart rate, blood pressure, temperature)
- BSA baseline calculation
- Histological or cytological confirmation of NSCLC and molecular identification of *KRAS* mutation. Molecular identification of a *KRAS* mutation (codons 12, 13, or 61 mutations detected by sequencing) is to be performed by a CLIA-certified assay (source documentation required)
- Nutritional Consultation
- Serum pregnancy test for women of childbearing potential (must be within 72 hours of administration of study treatment)
- Urinalysis
- CBC w/differential
- Comprehensive Metabolic Panel (CMP)
- Other Study Requirements will include: , PT/INR, PTT, Uric Acid,, , Magnesium, Phosphate, LDH,
- Viral Hepatitis to include: HCV antibody, HAV IgM antibody, HBsAg, HBcAB IgM
- CXR
- EKG
- ECOG performance status

The following radiologic assessment will be performed within 4 weeks prior to study start:

- CT/MRI scans of the chest and upper abdomen (CT scan with contract preferred)
- RECIST Tumor Assessment Form

Brain imaging will be performed only if clinically indicated (headache, focal neurological findings) or if known history of treated brain metastases. For patients with baseline abnormalities on brain imaging, brain imaging should be repeated every 4 cycles (ie, every 12 weeks)

5.2 Procedures During Treatment

5.2.1 Cycle 1 Day -7 (docetaxel + selinecor cohort only)

- Limited physical examination including body weight, and vital signs (heart rate, blood pressure, temperature)
- Serum pregnancy test for women of childbearing potential (must be within 72 hours of administration of study treatment)
- CBC w/Differential
- Comprehensive Metabolic Panel (CMP)
- LDH
- ECOG performance status
- Documentation of concomitant medications (including alternative medications)
- Toxicity assessment/Documentation of Adverse Events
- Selinexor Dispensation
- Provide Study Drug Diary
- Blood draws for PD analysis will be performed pre-dose and 4 hours post-dose,

5.2.2 Cycle 1 Day 1

- Limited physical examination including body weight, height, and vital signs (heart rate, blood pressure, temperature)
- BSA calculation
- CBC w/Differential
- Comprehensive Metabolic Panel (CMP)
- LDH
- Other Study Requirements will include: Uric Acid, Magnesium, Phosphate,
- Documentation of concomitant medications (including alternative medications)
- Toxicity assessment/Documentation of Adverse Events
- Docetaxel administration (unless in the selixenor monotherapy cohort)
- Selinexor Dispensation
- Provide Study Drug Diary (selinexor monotherapy cohort)
- Review patients dosing diary for dosing compliance (docetaxel + selinexor cohort)
- Blood draws for PD analysis will be performed pre-dose and 4 hours post-dose

5.2.3 Cycle 1 Day 3 or Cycle 1 Day 4 (contact)

- Telephone call with patient to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 or C1D4 following the Cycle 1 Day 1 selinexor and docetaxel dosing.

5.2.4 Cycle 1 Day 8 (±1 day)

- Limited Physical examination including body weight, and vital signs (heart rate, blood pressure, temperature)
- CBC w/Differential
- Comprehensive Metabolic Panel (CMP)
- LDH
- Review patients dosing diary for dosing compliance
- Documentation of concomitant medications (including alternative medications)
- Toxicity assessment/Documentation of Adverse Events

5.2.5 Cycle 1 Day 15 (±1 day)

- Limited Physical examination including body weight, and vital signs (heart rate, blood pressure, temperature)
- CBC w/Differential
- Comprehensive Metabolic Panel (CMP)
- LDH
- Review patients dosing diary for dosing compliance
- Documentation of concomitant medications (including alternative medications)
- Toxicity assessment/Documentation of Adverse Events

5.2.6 Cycles ≥ 2 Day 1 + 3 days

During these visits the following assessments will be completed:

- Physical examination including body weight, height, and vital signs (heart rate, blood pressure, temperature)
- BSA Calculation
- ECOG performance status
- CBC w/differential
- Comprehensive Metabolic Panel (CMP)
- LDH
- Other Study Requirements will include: Uric Acid, Magnesium, Phosphate
- Urinalysis
- Coagulation tests – PT/INR, PTT
- Documentation of concomitant medications (including alternative medications)
- Toxicity assessment/Documentation of Adverse Events
- Provide Study Drug Diary
- Review patients dosing diary for dosing compliance
- Docetaxel Administration (unless in the selinexor monotherapy cohort)
- Blood draw for PD testing will be performed pre-dose (cycle 2 only)

- Tumor assessment by RECIST 1.1 may be performed at any points Days 16-21 ; even-numbered cycles only. NOTE: for subjects who have been on treatment for one year or more, tumor assessment may be performed every 4 cycles.

5.3 End-of-Treatment Visit (≥ 30 Days after Last Dose)

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

- Assessment of adverse events
- Documentation of concomitant medications (including alternative medications)
- Physical examination including body weight, and vital signs (heart rate, blood pressure, temperature)
- CBC w/differential
- Comprehensive Metabolic Panel (CMP)
- Other labs as follows: LDH, Uric Acid, Magnesium, Phosphate, EKG

▪ Blood draw for PD testing

5.4 Follow-up Procedures

After treatment discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's NSCLC status, general health, and information on any antineoplastic therapies utilized since discontinuation of study treatment. Alternatively, review of medical records may be performed for collection of follow-up information.

5.5 Schedule of Study Activities and Assessments

Activity/Assessment	Screening (28 days prior to start of treatment)	Cycle 1				Cycles ≥ 2	End of cycle 2	End-of-Treatment (EoT) Visit	Survival Follow-up[17] (Every 3 mo.)
		Day -7	Day 1	Day 8	Day 15	Day 1		30 Days Post-Last Dose	
		± 1 day				+ 3 days		± 7 days	± 14 days
Informed consent[1]	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history[2]	X								
Patient height	X		X			X			
Patient weight	X	X	X			X		X	
Body Surface Area (BSA)[3]	X		X			X			
Vital signs[4]	X	X	X	X	X	X		X	
Physical examination, full[5]	X					X		X	
Physical examination, limited[6]		X	X	X	X				
ECOG[7]	X	X				X		X	
12-lead ECG[8]	X							X	
Urinalysis[9]	X					X		X[9]	
CBC with differential[10]	X	X	X	X	X	X		X	

Activity/Assessment	**Screening (28 days prior to start of treatment)**	**Cycle 1**				**Cycles ≥ 2**	**End of cycle 2**	**End-of-Treatment (EoT) Visit**	**Survival Follow-up[17] (Every 3 mo.)**
		Day -7	Day 1	Day 8	Day 15	Day 1		30 Days Post-Last Dose	
		± 1 day				+ 3 days		± 7 days	± 14 days
Comprehensive Metabolic Panel (CMP)[11]	X	X	X	X	X	X		X	
LDH	X	X	X	X	X	X		X	
Other Labs: • Uric Acid • Magnesium • Phosphorus	X		X			X		X	
CT/MRI scans (CT with contract preferred) • Chest • Upper Abdomen [12]	X						X		
RECIST Tumor Assessment Form	X						X		
Brain imaging[20]	X								
Chest radiograph[13]	X								
Serum pregnancy test[14]	X	X							
Docetaxel administration[21]			X			**X**			
Study drug dosing			See Table 1						

Activity/Assessment	**Screening (28 days prior to start of treatment)**	**Cycle 1**				**Cycles ≥ 2**	**End of cycle 2**	**End-of-Treatment (EoT) Visit**	**Survival Follow-up[17] (Every 3 mo.)**
		Day -7	Day 1	Day 8	Day 15	Day 1		30 Days Post-Last Dose	
		± 1 day				+ 3 days		± 7 days	± 14 days
Provide Study Drug Dosing Diary		X				X			
Compliance Review of Study Drug Dosing Diary			X	X	X	X			
Blood draw for PD testing[15]		X	X			X (C2 only)		X	
Adverse events	X	X	X	X	X	X		**X**	
Concomitant medication	X	X	X	X	X	X		X	
Nutritional consultation[19]	X								
Telephone contact[16,17]			On C1D3 *or* C1D4						X
Antineoplastic therapy after EoT treatment									X
Viral hepatitis labs[18]	X								

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment (Visit); MM = multiple myeloma, PD = Pharmacodynamic; PK = Pharmacokinetic; QoL = Quality of Life; CBC = complete blood count;

[1] Prior to the first study-specific measures. However, the Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF.

[2] Including details of all prior anti-NSCLC therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Body Surface Area (BSA) will be calculated (by *Dubois 1916* or *Mosteller 1987* method) during screening and on Day 1 of each cycle. When calculating the dose of Docetaxel, rounding the BSA according to instutitional practice is permitted. The dose may be capped at the dose corresponding to a BSA of $2m^2$ if necessary to comply with institutional practices.

[4] Blood pressure, pulse and temperature, unless this data was obtained during the vital signs assessment.

[5] Full physical examination (PE) for baseline, start of every new cycle and EoT visit.

[6] Limited PEs during the study should be symptom directed.

[7] ECOG performance status assessments will be done on Day 1 of each Cycle, however the assessment for Cycle 1 Day 1 may be done during Screening or pre-dose C1 D-7.

[8] ECG will be performed during Screening (or pre-dose Cycle 1 Day 1) and the EoT Visit.

[9] Includes appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

[10] CBC with differential includes hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, RBC count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be performed when clinically indicated

[11] Complete serum chemistry at Screening or Cycle 1 Day, then Day 1 of each Cycle and EoT visit. Parameters to be assessed for complete serum chemistry are presented in Table 8 and include serum sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin LDH, calcium, magnesium, phosphorus, total protein, albumin, , uric acid.

[1] Limited chemistry for Cycle 1 (Day -7, Days 8 and 15). Laboratory parameters to be assessed for limited serum chemistry are presented in Table 8 and include serum sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, ALP, total bilirubin LDH.

[12] Disease status will be measured once at the end of every two cycles and as clinically indicated (±5 days). Response will be evaluated as per RECIST v1.1 criteria. Computed tomography (CT)/magnetic resonance imaging (MRI) scans for disease evaluation need not be

repeated at the final visit if one has been performed within 6 weeks of the final visit date. Baseline scans required within 4 weeks of study treatment initiation. For subjects who have been on treatment for one year or more, tumor assessment may be performed every 4 cycles.

[13] Both posteroanterior and lateral films should be obtained at baseline. Note that this test does not need to be repeated if results are available from a test performed within 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any adverse events during the study.

[14] For women of childbearing potential; negative serum hCG pregnancy test ≤ 3 days (72 hours) of Cycle 1 Day -7

[15] Blood draws for PD analysis will be performed Cycle 1 Day -7 pre-dose and 4 hours post-dose, Cycle 1 Day 1 pre-dose and 4 hours post-dose, Cycle 2 Day 1 pre-dose, and at end of treatment

[16] Telephone call (or visit) with patient to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 or C1D4 following the Cycle 1 Day 1 selinexor and docetaxel dosing.

[17] After study discontinuation, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's NSCLC status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment. Alternatively, the medical record may be reviewed to obtain this information; if needed, a phone call will be made.

[18] Viral hepatitis labs includes HAV IgM antibody, HBsAg and HBcAb IgM and HCV antibody.

[19] Patients must be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between enrollment and (or on) cycle 1 day -7.

[20] Brain imaging (preferably MRI) will be performed only if clinically indicated (headache, focal neurological findings) or if known history of treated brain metastases. For patients with baseline abnormalities on brain imaging, brain imaging will be repeated every 4 cycles (ie, every 12 weeks). Baseline scans required within 4 weeks of study treatment initiation.

[21] Docetaxel will not be administered in the selinexor monotherapy cohort

Table 1A: Dosing Schedule—combination therapy

	Cycle 1																									
								Cycles 1+																		
Treatment	Week -1							Week 1							Week 2							Week 3						
	D-7	**D-6**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**	**D17**	**D18**	**D19**	**D20**	**D21**
Selinexor	X							X							X[1]							X[1]						
Docetaxel								X[2]																				

[1]If a dose is missed, it may be given up to 48 hours after the planned dose and at least 36 hours before the next scheduled dose

[2]Docetaxel may be administered up to 3 days after Day 1 of each cycle

Table 2B: Dosing Schedule—selinexor monotherapy

	Cycles 1+																		
Treatment[1]	Week 1							Week 2							Week 3						
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**	**D17**	**D18**	**D19**	**D20**	**D21**
Selinexor—weekly cohort	X[2]							X[2]							X[2]						
Selinexor—twice weekly cohort	X[3]		X[3]					X[3]		X[3]					X[3]		X[3]				

[1]Based on the totality of clinical data, after 6 patients are treated in each selinexor monotherapy cohort (weekly and twice weekly), one schedule will be selected for further study in the expansion cohort.

[2]In the weekly dosing cohort, if a dose is missed, it may be given up to 48 hours after the planned dose and at least 36 hours before the next scheduled dose.

[3]In the twice weekly dosing cohort, if a dose is missed or delayed, patients should take the next dose at the regularly scheduled time.

5.6 Removal Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.6.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.6.2 Subject withdraws consent (termination of treatment and follow-up);

5.6.3 Subject is unable to comply with protocol requirements;

5.6.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.6.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.6.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.6.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.6.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.6.9 Lost to follow-up.

6.0 MEASUREMENT OF EFFECT

6.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) Committee [Eur J Cancer. 2009;45(2):228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.2 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

If using RECIST, state:

6.3 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Disease assessment via RECIST v1.1[1] will be performed at the end of even-numbered cycles beginning with Cycle 2 (Day 42); the assessment may be performed up to 5 days before Day 42 (Day 38 - Day 42) but attempts should be made to conduct the assessment as close to Day 42 as possible. Disease assessment may be performed prior to initiation of the next cycle, but results must be available prior to initiation of treatment and must confirm continued eligibility for next cycle). Patients who require extended dose interruptions without disease progression (e.g. unacceptable toxicities) will remain on study and continue with tumor scans per schedule of assessments as specified until disease progression or start of alternative treatment.

6.5 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

(Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

6.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.8 Safety/tolerability

Safety evaluations will be conducted at Cycle 1 Day -7 and Cycle 1 Day 1 and on Days 8 and 15 of Cycle 1; Days 1 for Cycles ≥ 2, and the EoT Visit

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 4.03 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

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

Analyses of AEs will be performed for those events that are considered to be treatment emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

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

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

Serious AEs (SAEs) will also be tabulated.

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

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

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

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are assessed in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.3 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 30 days post treatment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.4 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory

agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.5 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03).

Step 2: Grade the adverse event using the NCI CTCAE v4.03.

Step 3: Determine whether the adverse event is related to the protocol therapy.
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment or until another anti-cancer therapy is started (whichever occurs sooner) (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).

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);

- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.6 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Written reports to: **Investigator: David Gerber, MD** David.Gerber@utsouthwestern.edu **c/o Phase 1 Manager** **5323 Harry Hines Blvd, NB2.402** **Dallas, Texas 75390** **214-648-1578 fax** UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu

Fax: 214-648-5949 or deliver to BLB.306

Completed and signed SAE report forms must be emailed or faxed to:

Email : Pharmacovigilance@karyopharm.com

Fax: 1-617-334-7617

UTSW Institutional Review Board (IRB)
Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation (for coordinating center per institutional guidelines)

Karyopharm Pharmaceuticals, Inc. Serious Adverse Event Reporting

The Investigator will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance every 6 months in the form of line-listings. The line listings required template will be provided by Karyopharm Therapeutics, Inc.

Serious Adverse Events

The investigator/coordinator shall report all SAEs, regardless of the causal relationship to the Karyopharm medications, occurring after the patient has signed informed consent until 30 days after the patient has stopped study treatment or until another anti-cancer therapy is started (whichever occurs sooner) to the Karyopharm Pharmacovigilance within *24 hours* of awareness. A Karyopharm SAE Report Form template is provided for this purpose. For reporting any SAE to Karyopharm Pharmacovigilance Department, a completed and signed (by the Investigator) SAE Report Form will be submitted by the sponsor investigator or designee to Karyopharm Pharmacovigilance:

Completed and signed SAE report forms must be emailed or faxed to:

Email : Pharmacovigilance@karyopharm.com

Fax: 1-617-334-7617

Pharmacovigilance Department

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 study treatment.

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

progression of the initial SAE must be reported as follow-up to the initial report within 24 hours of the Investigator receiving the follow-up information.

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 Therapeutics will report applicable SAEs to other applicable Regulatory Agencies and Investigators utilizing the Karyopharm product, as may be required.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered.

SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's 'Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies' or as per national regulatory requirements in participating countries.

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT

Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.7 Unblinding Procedures

Subjects or study personnel will are not blinded in this open-label trial.

7.8 Stopping Rules

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

8.0 DRUG/TREATMENT INFORMATION

8.1 Study Drugs

The following drug(s) will be used in this study:

Selinexor: Provided as 20 mg coated, immediate-release tablets for oral administration.

Docetaxel: Commercially available docetaxel will be used for this study. It will be supplied in accordance with applicable local laws and regulations.

Docetaxel 60 mg/m^2 or 75 mg/m^2 depending on the dose level will be administered per institutional practice (generally as a 1-hour IV infusion). The amount of docetaxel administered will be determined on Day 1 of each cycle, or per intuitional guidelines, by calculating the patient's BSA. When calculating the dose of docetaxel, rounding the BSA according to institutional practice is permitted. The dose of docetaxel may be capped at the dose corresponding to a BSA of 2 m^2 if necessary to comply with institutional practices. Premedication for docetaxel will follow the local institutional standard of care guidelines.

8.2 Placebo or Control

No placebo or control is being proposed. Historical control data (docetaxel monotherapy) will be used to compare responses and toxicities.

8.3 Labeling

Each wallet-size blister package selinexor tablets will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada, EMA, etc. Blister packages and/or containers for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws.

All treatments will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practices (GCP), FDA, HC, and EMA regulations and guidelines. Labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of Canada, EU, and the US.

8.4 Dosing Information

Selinexor dosing will be done based on the dose level the patient is receiving, ranging from 40 mg weekly to 100 mg weekly (see Table 3). When Selinexor is administered on the same day as Docetaxel, it may be administered at any time prior to the start of infusion.

8.5 Dosing Instructions for Patients

Study medications will be dosed according to the schedules provided below and in *Table 1.* For doses of oral medications to be taken on non-clinic days, patients will be provided with medication to take home.

Selinexor should be given with at least 120 mL (4 ounces) of fluids (water, milk, etc.) For details of drug formulation, preparation, and administration, please refer to *Appendix 2.*

Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Sample Collection, Storage, and Shipping

Information on sample collection, storage and shipping will be provided in the *Lab Manual*.

9.2 Pharmacodynamic Assessments

Predictive and Pharmacodynamic Biomarkers: If applicable, archival tumor tissue (10 unstained slides plus 1 H+E slide) will be evaluated for predictive and pharmacodynamic biomarkers. These may include but are not limited to the following: YAP1, FSTL5, LATS 1/2, and nuclear IkB expression. Additionally, in patients for whom a post-progression biopsy is performed as standard of care, additional tumor tissue submission is requested. These analyses are designed to identify early biomarkers predictive of benefit of selinexor and also

to demonstrate the in vivo specificity for molecular targeting of XPO1 cargo function via pharmacological blockade by selinexor.

Blood draws for PD analysis will be performed pre-dose and 4 hours post-dose on Cycle 1 Day -7, Cycle 1 Day 1 pre-dose and 4 hours post-dose on Cycle 2 Day 1 and at end of treatment.

10.0 STATISTICAL CONSIDERATIONS

This is a Phase 1/2 study. UT Southwestern will be the coordinating center for this study;

UT Southwestern will be responsible for registering patients and for maintaining a complete database of the study information.

The design of this Phase 1/2 trial is described above; along with the definition of MTD and the rules for dose escalation.

The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.0 and nadir or maximum values for the laboratory measures), time of onset (i.e., cycle number), duration, and reversibility or outcome.

Tables will be created to summarize these toxicities and side effects by dose and by cycle. Toxicities will be reported for all patients receiving study drug. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented to describe the patients treated in this Phase I study. All responses will be reported. Survival and time to failure will be summarized with Kaplan-Meier plots to describe the outcome of patients treated on this protocol.

10.1 Study Design/Study Endpoints

10.2 Sample Size and Accrual

In the docetaxel plus selinexor cohort, depending on cohort expansion requirements, a total of 9-24 patients will be accrued to the dose-escalation phase 1 pilot trial. A total of 35 patients will be enrolled to this expansion cohort, for a total of 31-46 patients. For the selinexor monotherapy cohort, up to 28 patients will be accrued to the recommended monotherapy regimen (either 80 mg PO weekly or 60 mg PO twice weekly). Because the trial population will be drawn from a multi-institution base, it is anticipated that accrual will be completed over 36 months.

In the docetaxel plus selinexor expansion cohort, enrollment of 35 patients will provide 90% power to detect an improvement in the primary endpoint of radiographic response rate from 10% (historical control) to 35%, with a two-sided alpha of 0.05. The sample size estimate is based on the exact one-sample binomial test for proportions.

Of note, the trial is taking a conservative approach to generating assumptions for the primary endpoint analysis. While reported response rates to docetaxel monotherapy have been as low

as 0% in *KRAS* mutant NSCLC,[9] we are employing a value more closely resembling that in unselected NSCLC populations.[10]

10.3 Data Analyses

10.3.1 Safety Population

The safety population includes patients who have received at least one dose of docetaxel and at least one dose of selinexor.

10.4 Efficacy Analysis

Tumor size will be assessed at baseline and every 2 cycles (ie, after 7 weeks for first 2 cycles, and then every 6 weeks) during the treatment period using the RECIST v1.1 criterion.

10.5 Pharmacodynamic Variables

As an exploratory endpoint, treatment efficacy (RR, PFS) will be correlated with correlative biomarkers.

10.6 Safety Analysis

The NCI CTCAE v4 will be used to collect data regarding safety events

10.7 Laboratory Data

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

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

10.8 Vital Signs and Physical Examinations

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

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

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any sub-site, the following documentation must be provided to the Phase 1 Regulatory Associate, Ashish Shaha.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract (or filed per institutional guidelines)

11.4 Registration/Randomization Procedures

For UT Southwestern Medical Center:
The coordinating center for the trial will be UT Southwestern. Patients who are candidates for registration into the study will be evaluated for eligibility by the Investigator once consent has been obtained to ensure that the inclusion and exclusion criteria have been satisfied and that the patient is eligible for participation in this clinical study. The phase 1 research manager will confirm eligibility for all patients prior to receipt of the first dose of study drug. The completed patient eligibility verification registration form (Appendix 6) and inclusion/exclusion checklist (Appendix 7) will be provided to the phase 1 manager for review. The manager will complete the dose level and patient ID assignment on the patient eligibility verification registration form (Appendix 6) and provide this completed form back to the study coordinator. The site should maintain a log of all patients who are consented but do not qualify for the study or who do not receive study drug. The reason for disqualification should be documented on the log.

For Sub-Site Management:
The coordinating center for the trial will be UT Southwestern. Patients who are candidates for registration into the study will be approved by UTSW after confirmation of eligibility of the inclusion and exclusion criteria have been satisfied. UTSW will confirm eligibility for all patients prior to receipt of the first dose of study drug.

For patients who pass screening the following items will be required for registration:

- copy of the signed patient treatment consent
- completed patient eligibility verification registration form (Appendix 6)
- completed inclusion/exclusion checklist (Appendix 7)
- source documentation (which includes, but not limited to, pathology, labs, progress notes, etc) that confirms all eligibility items on the inclusion -exclusion checklist has been met

This information will be provided no later than 48 hours prior to the planned cycle 1 day 1 treatment to allow adequate time for review. These items can be faxed with the provided cover sheet (located in the study binder) to:

Phase 1 QA Coordinator or Designee
UT Southwestern
Fax 214-648-1578

The Phase 1 MQA Coordinator or Designee will complete the dose level and patient ID assignment on the patient eligibility verification registration form and provide this completed form back within 48 hours of receipt of the package.

The site should maintain a log of all patients who are consented but do not qualify for the study or who do not receive study drug. The reason for disqualification should be documented on the log.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

Note: For multi-center studies, suggest assigning a lead-in identifier for each site and defining in the protocol. For example, for a study which includes two sites, the first patient consented and enrolled at the first site will be subject 01-001-01. The second subject enrolled at the second site might be 02-003-02.]

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.5 Patient Updates

The sub-sites will be invited to participate in a monthly meeting teleconference conducted by the Phase 1 manager and Principal Investigator to discuss all active treatment patients. In addition both UT Southwestern and all participating sub-sites will be expected to provide a weekly update in writing or via email to the phase 1 manager . The patient updates should include, but not limited to, the following information:

Pt initials:	Study ID:	Cohort:	Dose:
Visit: (cycle/day)		Date of visit:	
Summary of visit including AE's with grades and attributions, labs, and any other pertinent information			

11.6 Data Management and Monitoring/Auditing

The UTSW Simmons Comprehensive Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research

documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed.

Trial monitoring will be conducted according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.7 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

 Reporting requirement*: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.7.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

 Reporting requirement*: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

 Reporting requirement*: Serious Noncompliance must be promptly reported tothe IRB within 5 working days of discovery.

3.1.1 **Continuing Noncompliance:** includes a pattern of repeated noncompliance (in one or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

 Reporting requirement*: Continuing Noncompliance must be promptly reported to

the IRB within 5 working days of discovery.

11.6.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance

 Reporting requirement*: Noncompliance that is neither serious nor

continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first..

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

11.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.10 Obligations of the Investigator

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of

the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

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APPENDICES

Appendix 1: Eastern Cooperative Oncology Group Performance Status Criteria

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

Source: Oken MM et al

Appendix 2: Selinexor Formulation and Administration

Description of Selinexor (KPT-330)

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

The chemical name is: (*Z*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide

The *molecular formula* is: $C_{17}H_{11}F_6N_7O$.

The *molecular weight* is: 443.31.

Form

Selinexor will be supplied and administered as coated, immediate-release oral tablets in 20 mg tablets in wallet-sized blister packs of 12 tablets each.

Storage and Stability

Selinexor should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at or below 30˚C (86˚F). Room temperature storage is recommended, refrigerated is acceptable. Tablets should not be stored frozen.

Selinexor tablets are currently in on-going stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Availability

Selinexor is an investigational agent and will be supplied free-of-charge from Karyopharm Therapeutics, Inc.

Preparation

No special preparation required.

NOTE: Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

Administration

Selinexor will be provided as tablets to be administered by mouth. Selinexor is to be taken within 30 minutes of solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.).

Ordering

Drug order forms with all the needed contact information will be provided at the start of the trial, along with recommended initial and resupply stock orders. Orders submitted via e-mail will be filled within 5 business days of receipt.

Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (see the Cancer Therapy Evaluation Program [CTEP] website at http://ctep.cancer.gov/ protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form).

Destruction and Return

At the end of the study, unused supplies of selinexor should be destroyed and documented according to institutional policies.

Appendix 3: RECIST v1.1 criteria[1]

EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as
follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph
node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'(more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

RESPONSE CRITERIA

Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions,

taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to

qualify for PD, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions

Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be

designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive
FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up
CT scans are needed to determine if there is truly progression occurring at that site (if so, the
date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET
at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the
basis of the anatomic images, this is not PD.

Response Assessment

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. The Table below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, a different Table is to be used.

Time Point Response: Patients With Target (+/- Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum criteria for SD duration is 6 weeks.

Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.