



## Protocol Page

Phase I/II, Study of Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) + Sorafenib in Acute Myeloid Leukemia  
2014-0975

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### Core Protocol Information

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<b>Study Chair:</b>	Naval Daver
<b>Additional Contact:</b>	Dana E. Brown Leukemia Protocol Review Group
<b>Department:</b>	Leukemia
<b>Phone:</b>	713-794-4392
<b>Unit:</b>	428
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#### Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

## Protocol Body



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**Phase I/II Investigator Sponsored Study of Selinexor (KPT-330), a  
Selective Inhibitor of Nuclear Export / SINE™ Compound + Sorafenib  
in Acute Myeloid Leukemia**

Principal Investigator: Naval Daver, M.D. and Michael Andreeff, M.D.

Sponsor: University of Texas, MD Anderson Cancer Center

IND number: 127,302

University of Texas

MD Anderson Cancer Center

Leukemia Department, Unit 428,

Houston, Texas, 77030.

**Contents**

<b>1.0 OBJECTIVES.....</b>	<b>2</b>
<b>2.0 BACKGROUND.....</b>	<b>3</b>
<b>3.0 STUDY DESIGN.....</b>	<b>11</b>
<b>4.0 PATIENT SELECTION.....</b>	<b>15</b>
<b>5.0 TREATMENT PLAN.....</b>	<b>19</b>
<b>6.0 CORRELATIVE/SPECIAL STUDIES.....</b>	<b>37</b>
<b>7.0 PATIENT EVALUATION.....</b>	<b>38</b>
<b>8.0 CRITERIA FOR RESPONSE.....</b>	<b>42</b>
<b>9.0 DISCONTINUATION OF TREATMENT.....</b>	<b>44</b>
<b>10.0 ADVERSE EVENT REPORTING.....</b>	<b>45</b>
<b>11.0 STATISTICAL CONSIDERATIONS.....</b>	<b>50</b>
<b>12.0 REFERENCES.....</b>	<b>55</b>

## **1.0 OBJECTIVES**

### **1.1 Primary Objectives**

#### **Phase I**

1. To determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) and dose limiting toxicity (DLT) of the combination of selinexor with sorafenib in FLT3-ITD and –D835 mutated patients with relapsed/refractory acute myeloid leukemia (AML).

#### **Phase II**

1. To determine the composite CR (CRc) rate including CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) within 3 months of treatment initiation in FLT3-ITD and –D835 mutated patients with relapsed/refractory AML.

### **1.2 Secondary Objectives**

#### **Phase I**

1. To determine the composite CRc rate including CR + CRp + CRi within 3 months of treatment initiation in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.
2. To determine the partial response (PR), marrow clearance rate, bone marrow blast reduction  $\geq 50\%$  within 3 months of treatment initiation in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.
3. To determine the duration of response (DOR), event-free survival (EFS), overall survival (OS), and number of patients bridged to hematopoietic stem cell transplant (HSCT) and median duration to HSCT from the initiation of the combination of selinexor with sorafenib in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.
4. To determine the safety of the combination of selinexor with sorafenib in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.

#### **Phase II**

1. To determine the PR, marrow clearance rate, bone marrow blast reduction  $\geq 50\%$  within 3 months of treatment initiation in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.
2. To determine the DOR, EFS, OS, and number of patients bridged to HSCT and median duration to HSCT from the initiation of the combination of selinexor with sorafenib in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.
3. To determine the safety of the combination of selinexor with sorafenib in FLT3-ITD and –D835 mutated patients with relapsed/ refractory AML.

### **1.3 Exploratory Objectives**

1. To evaluate the response rate, EFS and OS in FLT3 mutated/NPM1 wild-type patients versus FLT3 mutated/NPM1 mutated versus FLT3 wild-type/NPM1 mutated patients treated with the combination of selinexor and sorafenib.
2. Quantitative changes of FLT3-ITD and –D835 allelic burden with time in patients treated with the combination of selinexor and sorafenib.
3. To evaluate the extent of pharmacodynamics biomarker (such as p-FLT3, p-p70S6K, pERK) inhibition and the induction of apoptosis in the bone marrow and peripheral blasts following treatment with the combination of selinexor and sorafenib.
4. To investigate possible relationships between selinexor and other baseline gene expression signatures and clinical response.
5. To store and/or analyze surplus blood or tissue including bone marrow, if available, for potential future exploratory research into factors that may influence development of AML and/or response to selinexor (where response is defined broadly to include efficacy, tolerability or safety).
6. To evaluate the pharmacodynamic effects of treatment on induction/inhibition of XPO1 using qRT-PCR and on plasma protein/cytokine levels.

## 2. BACKGROUND

### 2.1 FLT3-mutated AML

*FLT3* (FMS-like tyrosine kinase III) belongs to the Class III family of receptor tyrosine kinases (RTKs; other members of this family include receptors for KIT, FMS, and PDGF) <sup>1</sup>. Signaling via RTKs is frequently deregulated in hematological malignancies <sup>2</sup>. *FLT3* is expressed on the leukemic cells of 70–100% of patients with AML <sup>3</sup>. Additionally, activating mutations in *FLT3* are observed in 30% of adult AML patients <sup>4</sup>. The two *FLT3* mutations found in AML include internal tandem duplications in the juxta-membrane domain (ITD, 17–34%) and mutations in the tyrosine kinase domain (TKD) activation loop (7%) <sup>5</sup>. *FLT3* stimulates survival and proliferation of leukemic blasts <sup>6</sup>. *FLT3*-ITD mutations are associated with adverse prognosis. Patients with *FLT3*-ITD have significantly elevated peripheral blood white cell counts, increased bone marrow blasts, increased relapse risk, inferior event-free survival (EFS), and decreased overall survival (OS) <sup>7-9</sup>. The *FLT3*-TKD mutations have unknown prognostic significance in AML <sup>9</sup>.

Several small-molecule *FLT3* targeted tyrosine kinase inhibitors (TKIs) that are undergoing evaluation in phase I, II, and III trials have shown promising activity as single agents and in combination with hypomethylating agents or chemotherapy. These include quizartinib (AC220), sorafenib, midostaurin (PKC412), lestaurtinib, and crenolanib<sup>10-16</sup>. These TKIs act as direct inhibitors of *FLT3* via competitive inhibition of ATP-binding sites in the *FLT3* receptor KD<sup>17, 18</sup>.

*FLT3* inhibitors demonstrate potent anti-leukemic activity and improve outcomes in patients with relapsed/refractory AML and *FLT3*-ITD mutations<sup>19</sup>. About 40-50% of

such patients achieve marrow responses to *FLT3* inhibitors, with 20-30% bridged to allogeneic stem cell transplant. Responses to *FLT3* inhibitors last 3-6 months and are invariably transient (except among patients who undergo transplantation) due to the emergence of resistance<sup>20, 21</sup>. The primary cause of resistance is the acquisition of point mutations in the *FLT3* kinase domain (KD). Heidel et al first to identified point mutations in the *FLT3-ITD* KD as a mediator of resistance to the *FLT3* inhibitor midostaurin. They reported a single amino acid substitution at position 676 (N676K) within the *FLT3* KD as the sole cause of resistance to midostaurin in a patient with AML<sup>22</sup>. Acquired point mutations in the KD may be preexisting or acquired after exposure to the *FLT3* inhibitors as has been shown with midostaurin<sup>22</sup>. Homology modeling has identified two main types of *FLT3* mutations, namely TKD1 mutations involving the ATP-binding (hinge regions) and the TKD2 mutations involving the activation loop<sup>23</sup>. Non-mutational mechanisms of resistance include up-regulation of compensatory pathways including the MAPK/ERK, *PI3K/Akt/mTOR*, *FOXO3A*, *SYK*, and *STAT5/PIM* pathways, up-regulation of the *FLT3* ligand or receptor, mutations in other kinases (e.g. *CBL*), activation of anti-apoptotic proteins *BCL2*, *MCL1* and *BCL-x(L)*, and tumor microenvironment mediated resistance<sup>23, 25 24, 25</sup>.

Sorafenib is an orally active multikinase inhibitor with potent activity against *FLT3* and the Raf/ERK/mitogen-activated protein kinase pathway<sup>26</sup>. Sorafenib is 1000-fold more active against ITD mutant *FLT3* than wild-type *FLT3* in cell based assays<sup>27</sup>. In phase I studies, sorafenib potently inhibited *FLT3-ITD* leukemic blasts. Melzelder et al reported clinical activity as a single agent in relapsed *FLT3-ITD* AML<sup>28</sup>. We performed a phase I/II study of idarubicin, high-dose cytarabine and sorafenib in AML patients (median age = 53 years)<sup>29</sup>. In this study 15 *FLT3-ITD* patients were enrolled. Fourteen patients achieved a CR and 1 patient achieved complete remission with incomplete platelet recovery (CRp). Mutant *FLT3* was suppressed in all 10 patients evaluated, with fivefold greater suppression of mutant *FLT3* as compared to wild-type *FLT3* on plasma inhibitory assays<sup>29</sup>. We recently reported the feasibility and efficacy of combining hypomethylator therapy (5-azacytidine) with sorafenib in patients with relapsed/refractory *FLT3-ITD* AML<sup>11</sup>. A total of 43 patients were treated (93% were *FLT3-ITD* mutated). Patients had received a median of 2 prior therapies. The response rate was 46% including CR, CRp and CRi (complete remission with incomplete recovery of counts). This response rate compares favorably with expected response rates in multiply relapsed AML. 64% of the patients achieved >85% *FLT3* inhibition during their first cycle of therapy. The combination was reasonably well tolerated. Although hepatotoxicity was seen, most instances were grade 1 or 2.

Over 10 major tumor suppressor pathways have evolved in order to prevent the development and progression of neoplasia. The majority of the tumor suppressor (TSP) and growth regulatory (GRP) proteins mediating these pathways act in the cell nucleus downstream of signaling pathways. Accumulating data suggest that in order to maintain their malignant behavior, neoplastic cells must inactivate most or all of the known TSP and GRP pathways<sup>30</sup>. Active nuclear export of TSP/GRP is one very efficient and rapid means of overcoming the normal cell cycle and genomic instability checkpoints mediated by these proteins. Essentially all known TSP/GRP utilize a

single nonredundant nuclear export protein complex in order to exit the nucleus. Exportin 1 (XPO1), also called chromosomal region maintenance protein 1 (CRM1), is the primary component of this export complex, and is overexpressed in many types of cancer<sup>31</sup>.

**Table 1: CRM1 Inhibition Enhances Multiple TSPs/GRPs**

Oncogenic Pathway	TSP/GRP Enhanced by CRM1 inhibition	Oncogenic Pathway	TSP/GRP Enhanced by CRM1 inhibition
AKT↑, PI3K↑, PTEN↓ deletion p53, MDM2↑ HER2, EGF-R p16 <sup>INK4A</sup> ↓ or p14 <sup>ARF</sup> ↓ mTOR↑ Wnt / β-Catenin ↑ deletion pRb	FOXO, p27 p21 <sup>CIP1</sup> , p53, p14 <sup>ARF</sup> FOXO, pRB pRB, p53 p53, p27, FOXO APC, HMGBP1 p27	CDK2-CyclinE-E2F1 NPM1 Mutation c-Myc ↑ Bcr-Abl Bcl2 ↑, Bcl-xL ↑ Notch ↑ NF-κB ↑	pRb, p27, p21 <sup>CIP1</sup> p53, p14 <sup>ARF</sup> PP2A, p21 <sup>CIP1</sup> PP2A, Abl p53, p16 <sup>INK4A</sup> FOXO I-κB

Selinexor is a Selective Inhibitor of Nuclear Export / SINE<sup>TM</sup> compound that slowly reversibly binds and inactivates XPO1, thereby forcing the nuclear retention of key TSP/GRP. Transient retention of TSP/GRP 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. Garzon et al identified a strong down-regulation of total FLT3 protein expression in primary AML samples after XPO-1 inhibition. This inhibition seems to occur at the post-transcriptional level<sup>32</sup>. Based on these findings, we propose Phase I combination trial of FLT3-ITD inhibitor sorafenib (Nexavar) and SINE<sup>TM</sup> compound (selinexor) in relapsed/refractory AML patients.

## 2.2 Selinexor, a Selective Inhibitor of Nuclear Export / SINE<sup>TM</sup> Compound

Selinexor is an oral, first in class, slowly reversible, potent and Selective Inhibitor of Nuclear Export / SINE<sup>TM</sup> compound that specifically blocks exportin 1 (XPO1). To date, other than XPO1, no targets of selinexor have been identified. Selinexor restores many of the tumor suppressor (TSP) and growth regulatory (GRP) proteins to the nucleus where they can carry out their normal functions. Selinexor is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both *in vitro* and *in vivo*. The nuclear export of eIF4E, a protein that binds to the mRNAs of many oncogenic and growth-promoting mediators, requires XPO1 for transport to cytoplasmic ribosomes. Selinexor blocks the XPO1-mediated nuclear export of eIF4E, preventing translation of the eIF4E-bound mRNAs on ribosomes, with a reduction in levels of the cognate oncogenic and growth-promoting proteins. All cell types exposed to a SINE<sup>TM</sup> compound *in vitro* undergo G1/S ± G2/M cell cycle arrest, followed by a ‘genomic fidelity’ review, and cells with damaged genomes are induced to undergo



apoptosis. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE<sup>TM</sup> compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

## 2.2.1 Preclinical Data

In this section a short summary of preclinical data is provided. More detailed information is presented in the selinexor Investigator's Brochure (Appendix C).

### 2.2.1.1 Pharmacology, Pharmacokinetic and Toxicology Summary:

Selinexor has shown potent apoptosis induction with a median IC50 of 90 nM across a panel of 46 tumor cell lines representing a broad spectrum of tumor types. As noted above, selinexor had little effect on normal lymphocytes or other non-transformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies, such as significant myelosuppression, alopecia, mucositis and other gastrointestinal dysfunction. Selinexor has shown substantial efficacy, with dosing regimens that match those currently under investigation in humans, in a variety of mouse models of hematological and solid tumors and, including AML, CLL, DLBCL, MCL, multiple myeloma, T-cell acute lymphoblastic leukemia (T-ALL), neuroblastoma, melanoma and prostate, breast, lung and ovarian cancer.

AML cells overexpress the nuclear exporter, Exportin 1 (XPO1/CRM1) and higher XPO1 levels correlate with poor outcome (Kojima 2013). The novel selective inhibitor of nuclear transport / SINE compound, selinexor, antagonizes XPO1 and shows potent cytotoxicity for AML and ALL cells *in vitro*, independent of genotype.

Selinexor shows potent antiproliferative effect and induced apoptosis, cell cycle arrest and myeloid differentiation in AML cell lines and patient blasts, including those from patients with *NPM1* and *FLT3*-ITD mutations (Ranganathan 2012).

Mechanistic studies show that SINE compounds induce nuclear localization and activation of multiple tumor suppressor proteins (TSPs), leading to rapid apoptosis of AML cells. In addition, a strong down-regulation of the oncogenes *FLT3* and *c-KIT* were observed after SINE treatment in both *FLT3*-ITD and wild-type cell lines (Ranganathan 2012). Selinexor treatment also restored the localization of cytoplasmic mutant *NPM1* into the nucleus.

In murine AML and ALL models, selinexor showed potent antileukemic activity without toxicity to normal hematopoietic cells (Etchin 2013a, b; Ranganathan 2012).

*In vitro* experiments with continuous (~72 hour) exposure to selinexor demonstrated potent proapoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture including multiply resistant cancers, with the majority of inhibitory concentrations, 50% (IC<sub>50</sub>s) for cytotoxicity < 800 nM and most hematologic tumor lines having IC<sub>50</sub>s of 20-400 nM for selinexor. Moreover, selinexor demonstrated cytotoxicity in multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) cells in the absence or presence of bone marrow stroma cells (BMSC). In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC<sub>50</sub>s were typically > 5 μM. As noted above, selinexor had little effect on normal (non-malignant) lymphocytes or other nontransformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction.

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

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

See the selinexor Investigator's Brochure for more information (Appendix C).

### **2.2.2. Clinical Experience**

KCP-330-001: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced Hematological Malignancies  
*Study Design:* This is a Phase-1, open-label, parallel-group study, with dose escalation and expansion phases, to determine the MTD, preliminary safety,

preliminary response, and PK of various selinexor dose schedules (3 to 85 mg/m<sup>2</sup> dosed 1-3 times weekly) in patients with RR hematologic malignancies, including:

- \_Chronic hematological malignancies (B-cell) – Multiple myeloma (MM), Waldenström’s Macroglobulinemia (WM), Non-Hodgkin’s Lymphoma (NHL), chronic lymphocytic leukemia (CLL)
- \_Acute Myeloid Leukemia (AML) - Any subtype except M4 (Acute Promyelocytic Leukemia [APL])
- \_Peripheral (PTCL) and Cutaneous (CTCL) T-Cell Lymphoma
- \_Acute Lymphoblastic Leukemia (ALL) - B- or T-cell
- \_Chronic Myelocytic Leukemia (CML)

This study is registered on ClinTrials.gov at NCT01607892.

Preliminary, unaudited response data (as of 04 Dec 2014) and safety reports (as of 01 Feb 2015) for AML patients are included in the attached IB v4.0\_03 April 2015 (Appendix C).

*Study Design:* Sixty-five heavily pretreated patients with progressive RR AML, most with  $\geq$  3 prior lines of treatment, were enrolled in the KCP-330-001 AML treatment arm and received selinexor 16.8-70 mg/m<sup>2</sup> in four-week cycles.

*Preliminary Response Results:* Among 63 evaluable patients, the CR rate, with or without full hematologic recovery, was 11%, ORR was 16%, and DCR was 49%. (Note: 16 patients [25%] were non-evaluable but were included in the AML response rate calculation, based on the ITT approach.) Best response results in AML patients as of 13 May 2014 are shown in Table 1. Patients could be deemed non evaluable due to either lack of post-dosing bone marrow assessments, failure to take the required number of doses of study medication, withdrawal of consent, or death during Cycle 1 prior to response determination. During this study, sixteen patients died during Cycle 1, including patients who were evaluable due to PD prior to death.

Table 1 Best responses in AML patients as of May 13. 2014

N	DCR	ORR	CR	CR(i/p)	PR	MLFS	SD	PD	NE
63	31	10	5	2	1	2	21	16	16
(100%)	(49%)	(16%)	(8%)	(3%)	(2%)	(3%)	(33%)	(25%)	(25%)

*Preliminary Safety Results:* Grade 3/4 TEAEs that were reported in > 3 patients include: fatigue (18%), and nausea (8%). Grade 3/4 thrombocytopenia (15%) and neutropenia (11%) were observed, however a majority of patients enrolled with baseline high-grade thrombocytopenia and neutropenia as part of progressive disease (which is associated with reduced hematopoietic function). The most

common Grade 1/2 TEAEs were diarrhea (82%), anorexia (78%), nausea (74%), and fatigue (65%). No DLTs were reported during the dose escalation phase, however due to SAEs that were seen at 85 mg/m<sup>2</sup> in study KCP-330-002, a maximum allowable dose of 70 mg/m<sup>2</sup> twice weekly was assigned for this and future studies. The anticipated selinexor dose for patients in future AML studies will be 80-100 mg (35-60 mg/m<sup>2</sup>) twice weekly. For details of overall safety results in the AML patients and in all hematologic clinical studies please see the attached IB (Appendix C)

### **Potential Risks**

Selinexor is currently in clinical development and has not been approved by the Food and Drug Administration (FDA) for commercial use. Human experience with selinexor is currently limited and the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

Side effects observed to date in patients are shown below. Please see Selinexor for Oral Administration Investigator's Brochure (Appendix C) for most up-to-date information.

#### **Most common side effects:**

- nausea
- loss of appetite
- fatigue
- vomiting
- weight loss
- diarrhea

#### **Less common:**

- change in taste
- changes in vision including blurred vision
- low platelets
- decrease in red blood cells
- low sodium without symptoms

#### **Rare (< 5%):**

- worsening of pre-existing cataracts
- elevated levels of bilirubin
- elevated levels liver enzymes (ALT and AST)

One patient, heavily pre-treated for recurrent pancreatic cancer, developed, ‘acute cerebellar syndrome’ following 4 doses of selinexor at 85 mg/m<sup>2</sup> twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. No other patients have reported such symptoms to date.

### **Reproductive risks**

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. It is not anticipated that female patients enrolling in this study will be able to conceive. However, in the rare event that this is possible, female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

**2.2.3** For further details of selinexor and sorafenib preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the selinexor Investigator Brochure (Appendix C) and sorafenib drug label (Appendix D).

### **2.3 Rationale for study:**

FLT3 inhibitors demonstrate potent anti-leukemic activity and improve outcomes in patients with relapsed/refractory AML and *FLT3-ITD* mutations<sup>19</sup>. About 40-50% of such patients achieve marrow responses to FLT3 inhibitors, with 20-30% bridged to allogeneic stem cell transplant. Responses to *FLT3* inhibitors are usually maintained for 3-6 months but invariably these responses are transient (except among patients who undergo transplantation) due to the emergence of resistance<sup>20, 21</sup>. The causes of resistance include the acquisition of point mutations in the *FLT3* KD and non-mutational mechanisms of resistance include up-regulation of compensatory pathways including the *PI3K/Akt/mTOR*, *FOXO3A*, *SYK*, *RAS* and *STAT5/PIM* pathways, up-regulation of the *FLT3* ligand or receptor, mutations in other kinases (e.g. *CBL*), activation of anti-apoptotic proteins *BCL2*, *MCL1* and *BCL-x(L)*, and tumor microenvironment mediated resistance<sup>23, 25 24</sup>.

Selinexor is a first in class Selective Inhibitor of Nuclear Export / SINE<sup>TM</sup> compound that specifically binds and inactivates XPO1, thereby forcing the nuclear retention of key TSP/GRP implicated in non-mutational resistance to FLT3-inhibitors including *AKT*,

*PI3K, mTOR, FOXO, STAT5, BCL2, BCL-x(L)*. Nuclear retention of these known mediators of non-mutational resistance may improve the efficacy and duration of response to FLT3 inhibitor sorafenib. Furthermore, Garzon et al identified a direct inhibition of FLT3 protein expression in AML samples after XPO1 inhibition. The indirect and direct impact of XPO1 inhibition on the FLT3 pathway support combining a XPO1 inhibitor (selinexor) with a FLT3 inhibitor (sorafenib). We have preclinical data recently generated showing activity of the KPT330+sorafenib combination in patients with D835 alone, double mutant D835+ITD and D842+ITD (Zhang et al., ASH poster, December 2015 – attached as appendix K). Based on this data we will evaluate in addition to FLT3-ITD also double mutant ITD+D835 as well as D835 alone FLT3 mutated patients. We do not have active therapies for D835 alone or double mutant AML patients and the preclinical data suggests this therapy may be active. In this initial trial, we propose to investigate whether selinexor in combination with sorafenib improves the response rates in patients with FLT3-ITD and –D835 mutated relapsed/refractory AML. If the combination proves to be well tolerated and results in improved response rates, we would expand the use of this approach in the frontline setting for FLT3-ITD and –D835 mutated AML.

### 3.0 STUDY DESIGN:

#### 3.1 General

The study will be a phase I/II, single-institution, open-label, non-randomized, parallel group clinical trial. The phase II will include two separate cohorts to be enrolled simultaneously. All patients will be registered through CORE/PDMS.

- **Phase I**
  - This will include FLT3-ITD and –D835 mutated patients with relapsed/refractory AML, including patients who may have been previously exposed to one or more FLT3-inhibitors. Relapsed/refractory status defined by the failure of at least one prior cycle of chemotherapy (including but not limited to cytotoxic chemotherapy, hypomethylator therapy, immune-based therapy, stem cell transplant or stem cell therapy, FLT3-inhibitor therapy, investigational therapy, and others).
  - The DLT assessment period will be performed only during Cycle 1 of Phase I.
  
- **Phase II in two cohorts**
  1. **Cohort 1 (FLT3 inhibitor failure cohort)** in FLT3-ITD and –D835 mutated relapsed/refractory AML who have failed therapy with up to two prior salvage regimens (HSCT or stem cell therapy for patients who previously underwent HSCT/stem cell therapy in remission will not be considered a salvage regimen) and have previously been exposed to at least one prior FLT3 inhibitor.

2. **Cohort 2 (FLT3 inhibitor naive cohort)** in FLT3-ITD and –D835 mutated relapsed/refractory AML who have failed therapy with up to two prior salvage regimens (HSCT or stem cell therapy for patients who previously underwent HSCT/stem cell therapy in remission will not be considered a salvage regimen) with no prior exposure to any FLT3 inhibitor.

### 3.2 Study Design

- The phase I portion is aimed at finding the MTD and RP2D of the combination drugs. We will use the standard “3+3” design. The target dose is dose level +1, and the starting dose will be dose level 0. The first 3 patients on study will receive dose level 0.
- Other dose levels will be used for dose adjustments for toxicity during therapy (Table 3).
- Prior to advancing/changing dose levels, a cohort summary will be completed and submitted to the IND Office Medical Monitor for review and approval. A copy of the cohort summary should be placed in the Investigator’s Regulatory Binder under “sponsor correspondence”.
- The dosing schema is shown in Table 3 below.

**Table 3: Dosing schema**

Dose level	Sorafenib (in mg)	Selinexor (in mg) on days 1 and 3 of weeks 1-3 of each 4 week cycle
+1 (Target dose)	400 twice daily	100 mg* twice weekly
<b>0 (Starting dose)</b>	<b>400 twice daily</b>	<b>80 mg twice weekly</b>
-1	400 twice daily	60 mg twice weekly
-2	400 twice daily	40 mg twice weekly

\*not to exceed 70 mg/m<sup>2</sup> based on BSA

### 3.3 3+3 algorithm

The 3+3 algorithm that we will follow in the phase I is described below.

- Enroll 3 patients at the dose level 0
- Proceed to the next higher dose level with a cohort of 3 patients until at least 1 patient experiences the dose-limiting toxicity (DLT)
- If only 1 of 3 patients experiences the DLT at a given dose level, enter 3 additional patients at the current dose level
- If only 1 of 6 patients experiences the DLT at a given dose level, proceed to the next higher dose level with a cohort of 3 patients or open broadly for phase II if at maximum escalation dose
- If at least 2 of 3 or 2 of 6 patients experience the DLT at a given dose level, then the MTD has been exceeded
- Once the MTD has been exceeded, treat another 3 patients at the previous dose level if there were only 3 patients treated at that dose level

- The MTD is the highest dose level in which we have treated 6 patients with at most 1 experiencing the DLT
- If  $\geq 2/6$  patients experience DLT at dose level -2, the study will be revised to consider additional lower dose levels.

\*With up to 2 potential dose de-escalation level (-1 and -2) to be studied and up to 6 patients to be treated at a given dose, the target maximum number of patients enrolled in the phase I part of the trial will be 12.

### 3.4 Definition of dose-limiting toxicity (DLT)

DLT is defined as clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle on study and at least possibly related to the study drugs that meets any of the following criteria:

- CTCAE Grade 3 AST (SGOT) or ALT (SGPT) for  $\geq 7$  days
- CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration
- Grade 3 nausea/vomiting, dehydration or diarrhea lasting more than 3 days in the setting of optimal supportive medications
- Grade 3 fatigue lasting more than 5 days in the setting of optimal supportive medications
- Grade 3 biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences. Grade 3 electrolyte abnormalities will only be considered DLT if possibly related to study drug and not corrected by optimal replacement therapy or if the Grade 3 electrolyte abnormalities persist after 7 days of optimal replacement therapy
- All Grade 4 non-hematologic toxicities of any duration
- For the purposes of DLT assessment, asymptomatic hyponatremia will be “graded” not by the NCI CTCAE version 4.03 but rather by clinically meaningful criterion of  $<125\text{mmol/L}$ . Sodium  $<125\text{mmol/L}$  will be graded as DLT with the exception of asymptomatic translational hyponatremia due to hyperglycemia (see footnote below for calculation).  
*\*In marked hyperglycemia, ECF osmolality rises and exceeds that of ICF, since glucose penetrates cell membranes slowly in the absence of insulin, resulting in movement of water out of cells into the ECF. Serum Na concentration falls in proportion to the dilution of the ECF, declining 1.6 mEq/L for every 100 mg/dL (5.55 mmol/L) increment in*



*the plasma glucose level above normal. This condition has been called translational hyponatremia because no net change in total body water (TBW) has occurred. No specific therapy is indicated, because Na concentration will return to normal once the plasma glucose concentration is lowered. Corrected Sodium (Hillier, 1999) = Measured sodium + 0.024 \* (Serum glucose - 100)<sup>33</sup>.*

- All other clinically significant non-hematological adverse event that is Grade 3 according to the NCI CTCAE version 4.03.
- Myelosuppression and cytopenias are expected outcomes of leukemia treatment and per se will not constitute DLT. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity < 5% on Day 42 or later (6 weeks) from start of therapy without any evidence of leukemia, will be considered in defining DLT. In case of a normocellular bone marrow with <5% blasts, 8 weeks with pancytopenia will be considered DLT. Anemia will not be considered for the definition of DLT.

Any patients who stop treatment prior to completing evaluation for the DLT observation period (first 28 days) due to disease progression or refusal for further participation for reasons other than toxicity during the DLT defining phase I portion of the study will be replaced at that dose level for a full evaluation of that dose level before a decision regarding dose escalation can be made.

### 3.5 Phase II expansion

Once MTD is defined, the RP2D will be selected based on efficacy and safety result from the phase I in discussion with the PI, the sponsor and the supporting company (Karyopharm). The Investigator is responsible for completing the cohort summary template prior to advancing subjects to the phase II portion. The phase II portion will start in two cohorts as defined previously with 20 patients per cohort. Any patients still on study from the phase I portion at a dose lower than RP2D can be dose escalated up to RP2D in accordance with the dose escalation guidelines in section 5.2.3.

However, the dose for any patient may never exceed the RP2D.

## 4.0 PATIENT SELECTION

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written

informed consent must be obtained from the patient prior to initiating treatment or any study-specific procedures. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

#### 4.1 Inclusion Criteria

##### 4.1.1 Phase I

FLT3-ITD and/or FLT3-D835 mutated patients 18 years of age or older with relapsed/ refractory AML (any number of relapses) including patients who may have been previously exposed to one or more FLT3-inhibitor therapies will be eligible for the phase I portion of this study.

##### 4.1.2 Phase II

**FLT3-ITD and/or FLT3-D835 mutated relapsed/refractory patients:** Patients should have a diagnosis of AML (de novo or transformed from hematologic malignancies). Patients with high-risk myelodysplastic syndrome (MDS) (defined as having  $\geq 10\%$  blasts in the bone marrow) or patients with Chronic Myelomonocytic Leukemia (CMML) (having  $\geq 10\%$  blasts in the bone marrow) may also be eligible after discussion with Principal Investigator (PI).

The patients should have one of the following features:

1. Patients with AML should have failed any prior induction therapy or have relapsed after prior therapy.
2. Patients with high-risk MDS or high-risk CMML should have failed any prior therapy for the MDS or CMML.
3. Patients with MDS or CMML who received therapy for the MDS or CMML and progress to AML are eligible at the time of diagnosis of AML regardless any prior therapy for AML. The WHO classification will be used for AML.

##### 4.1.3 Patients must be eligible for one of two cohorts:

**Cohort 1 (FLT3 inhibitor failure cohort)** in FLT3-ITD and/or FLT3-D835 mutated relapsed/refractory AML who have failed therapy with up to two prior salvage regimens (SCT or stem cell therapy for patients who previously underwent SCT/stem cell therapy in remission will not be considered a salvage regimen) and have previously been exposed at least one prior FLT3 inhibitor.

**Cohort 2 (FLT3 inhibitor naive cohort)** in FLT3-ITD and/or FLT3-D835 mutated relapsed/refractory who have failed therapy with up to two prior salvage regimens (SCT or stem cell therapy for patients who previously underwent SCT/stem cell therapy in remission will not be considered a salvage regimen) with no prior exposure to any FLT3 inhibitor.

- 4.1.4 Age  $\geq$ 18 years.
- 4.1.5 ECOG Performance Status  $\leq$ 2.
- 4.1.6 Patients should have estimated life expectancy of  $>$ 3 months at study entry.
- 4.1.7 Adequate hepatic (serum direct bilirubin  $\leq$  2.0 x upper limit normal (ULN) (or  $\leq$  3.0 x ULN if deemed to be elevated due to leukemia), alanine aminotransferase and/or aspartate transaminase  $\leq$  3.0 x ULN (or  $\leq$  5.0 x ULN if deemed to be elevated due to leukemia), and renal function (creatinine  $\leq$  2.0 mg/dL).
- 4.1.8 Patients must provide written informed consent.
- 4.1.9 In the absence of rapidly progressing disease, the interval from prior treatment to time of initiation of selinexor and sorafenib administration will be at least 2 weeks for cytotoxic agents or at least 5 half-lives for cytotoxic/noncytotoxic agents. The half-life for the therapy in question will be based on published pharmacokinetic literature (abstracts, manuscripts, investigator brochure's, or drug-administration manuals) and will be documented in the protocol eligibility document. The use of chemotherapeutic or anti-leukemic agents is not permitted during the study with the following exceptions: (1) intrathecal (IT) therapy for patients with controlled CNS leukemia at the discretion of the PI and with the agreement of the Sponsor. Controlled CNS leukemia is defined by the absence of active clinical signs of CNS disease and no evidence of CNS leukemia on the most recent 2 simultaneous CSF evaluations. (2) Use of one dose of cytarabine (up to 2 g/m<sup>2</sup>) or hydroxyurea for patients with rapidly proliferative disease is allowed before the start of study therapy and for the first four weeks on therapy. These medications will be recorded in the case-report form.
- 4.1.10 Baseline ejection fraction must be  $\geq$  40%.

- 4.1.11** Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment.
- 4.1.12** Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Combination of any of the two following (a+b or a+c or b+c)
  - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

**Note:** Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g.

age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

## 4.2 Exclusion Criteria

- 4.2.1 Patients with known allergy or hypersensitivity to selinexor, sorafenib or any of its components.
- 4.2.2 Subject has concurrent, uncontrolled medical condition, laboratory abnormality, or psychiatric illness, which could place him/her at unacceptable risk.
- 4.2.3 Patients who have had any major surgical procedure within 14 days of Day 1.
- 4.2.4 Patients currently receiving any other standard or investigational therapy for the treatment of AML.
- 4.2.5 Patients unwilling or unable to comply with the protocol.
- 4.2.6 Patients receiving concomitant treatment with strong CYP3A4 inhibitors, unless such drugs are considered critical for the well being of the patient and not adequate alternatives are available. Strong CYP3A4 inhibitors include the following medications: itraconazole, ketoconazole, miconazole, voriconazole; amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir; ciprofloxacin, clarithromycin, diclofenac, doxycycline, enoxacin, isoniazid, ketamine, nefazodone, nicardipine, propofol, quinidine, telithromycin.
- 4.2.7 Patients with any severe gastrointestinal or metabolic condition that could interfere with absorption of oral medications.
- 4.2.8 Patients who are in blast transformation of chronic myeloid leukemia (CML). Prior MDS or CMML is acceptable.
- 4.2.9 Patient has a concurrent active malignancy under treatment.
- 4.2.10 Unstable cardiovascular function:
- Symptomatic ischemia, or
  - Uncontrolled clinically significant conduction

abnormalities (i.e., ventricular tachycardia on antiarrhythmic agents are excluded; 1<sup>st</sup> degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or

- Congestive heart failure (CHF) NYHA Class  $\geq 3$ , or
- Myocardial infarction (MI) within 3 months.
- Left ventricular ejection fraction  $< 40\%$ .
- Hypertension  $> 140$  mm Hg systolic or  $> 90$  mm Hg diastolic with or without antihypertensive therapy.

- 4.2.11** Uncontrolled infection at the time of enrollment. Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines is acceptable.
- 4.2.12** Known active hepatitis B virus (HBV) or C virus (HCV) infection; or known to be positive for HCV ribonucleic acid (RNA) or HBsAg (HBV surface *antigen*).
- 4.2.13** Known human immunodeficiency virus (HIV) infection.
- 4.2.14** Female subjects who are pregnant or breastfeeding.
- 4.2.15** Acute promyelocytic leukemia.
- 4.2.16** Any medical condition, which in the investigator's opinion, could compromise the patient's safety.

## **5.0 TREATMENT PLAN:**

### **5.1 Schedule**

All patients will be registered through CORE/PDMS.

5.1.1 Selinexor will be administered orally twice a week (e.g. Monday/Wednesday or Tuesday/Thursday or Wednesday/Friday) for 3 weeks of a 28-day cycle. Selinexor will not be dosed the last week of the cycle (week 4). After initiation of sorafenib on cycle 1 day 1, sorafenib will be administered orally daily twice continuously for the duration of the study with no interruptions unless there are adverse events as described in Section 5.2 below. Sorafenib doses will be separated by intervals of approximately 12 hours (+/- 2 hours). Sorafenib will be administered without food, at least 1 hour before or 2 hours after eating. If a dose is missed, the

next dose will not be increased to account for missing a dose. The patient will take the next regular dose at the scheduled time. Patients will receive one cycle of therapy every 28 days (+/- 7 days).

On the day when both drugs, Selinexor and Sorafenib, will be administered:

- Selinexor needs to be taken with food.
- Sorafenib should not be taken with food. Therefore, patient should take Sorafenib at least 1 hour before eating or 2 hours after eating.

**5.1.1.1** Cycles may be started early (but not earlier than day 21) for patients with active disease if judged in the best interest of the patient.

\*For the phase I, DLT defining period is 28 days. As such, cycle 2 should not be started before 28 days for the patients being treated on the phase I cohort to allow for adequate evaluation of DLTs.

**5.1.1.2** Subsequent cycles may be delayed for recovery of toxicity or other medical conditions. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator and the sponsor of potential risk/benefit ratio and complete documentation of the degree of clinical benefit and reason for continuation on this regimen.

**5.1.1.3** In instances where one drug has to be discontinued transiently because of safety, the administration of the other drug may continue as scheduled. If the drug that is held can resume at a later time, no doses will be made up and the administration will follow the originally defined schedule calendar according to the drug that was continued.

**5.1.1.4** For patients who discontinue therapy, the reason for treatment discontinuation will be documented.

**5.1.1.5** Patients must receive at least 4 doses of selinexor and at least 44 doses of sorafenib during the first 28 days on trial (i.e. during cycle 1) to be evaluated for DLT. Patients who receive less than 4 doses of selinexor and/or less than 44 doses of sorafenib during the first 28 days on trial will not be evaluable for DLT. Patients not evaluable for DLT will be replaced. These patients may continue therapy on trial

after discussion with the PI if they are having clinical benefit and the reasons for continuation and potential benefit/risk profile for the patient must be clearly documented in the medical records.

## 5.2 Dose Adjustments

### 5.2.1 Selinexor and sorafenib dose adjustments for drug-related hematological adverse events (AEs):

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 4.03 (Appendix E) of the toxicity and the guidelines provided below.

- Patients with acute leukemia's usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemia's. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles and/or in the presence of residual leukemia. After that, treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of residual leukemia.
  - Patients with a response (e.g., no evidence of residual leukemia or cytopenias not considered to be related to leukemia) and pre-cycle counts of neutrophils  $>1.0 \times 10^9/L$  and platelets  $>50 \times 10^9/L$  who have sustained low counts of neutrophils  $<0.5 \times 10^9/L$  or a platelet count  $<20 \times 10^9/L$  for more than 2 consecutive weeks in the current cycle, may have the treatment with selinexor and sorafenib interrupted at the discretion of the treating physician after discussing with the PI until neutrophils recover to  $\geq 0.5 \times 10^9/L$  and platelets to  $\geq 30 \times 10^9/L$ . If prolonged myelosuppression defined as  $ANC < 0.5 \times 10^9/L$  and platelets  $< 20 \times 10^9/L$  (more than 8 weeks) with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed in these patients, both selinexor and sorafenib will be discontinued. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio and complete documentation of the degree of clinical benefit and reason for continuation on this regimen.



- If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or evidence of leukemia, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of selinexor and sorafenib in these patients should be considered on an individual case and discussed with the PI and the sponsor.
- Patients with a response (no marrow evidence of leukemia) and pre-cycle counts of neutrophils  $<1 \times 10^9/L$  and platelets  $<50 \times 10^9/L$  may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these patients should be considered on an individual case and discussed with the PI and the sponsor.
- Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce selinexor and/or sorafenib, as applicable.

### 5.2.2 Selinexor and sorafenib dose adjustments for non-hematologic drug-related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce selinexor and/or interrupt sorafenib, as applicable. Thus, if dose level 0 is established as the MTD, one and two dose level reductions of selinexor will be selinexor 60 mg twice weekly and selinexor 40 mg twice weekly, respectively. If the MTD is below dose level 0 further dose reduction levels of selinexor will be defined before moving to the phase II portion of the study. Dose reductions of sorafenib will be as follows: Starting dose = sorafenib 400 mg BID, -1 dose level = 400 mg in the AM and 200 mg in the PM, -2 dose level = 200 mg BID, -3 dose level = 200 mg Qday. The sorafenib dose will not be reduced beyond 200 mg Qday.

**Table 4 Dose adjustments for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator**

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction.
3  (Persistent grade 2: Consider	1st and 2nd time	Hold selinexor and/or sorafenib. Resume selinexor and/or sorafenib at prior dose if recovery to $\leq$ Grade 1 or baseline occurs within 14 days. If toxicity persists for 15-28 days, hold therapy and resume at ONE dose level below current dose for selinexor OR sorafenib

similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)		OR both based on which medication is likely causing the toxicity ONLY after recovery of toxicity to $\leq$ Grade 2. Dose re-escalation to prior dose of selinexor OR sorafenib OR both is permitted if tolerated and no recurrent Grade 3 or 4 toxicities occur over 4 weeks while on the lower dose level.
	3 <sup>rd</sup> and 4th time	Hold selinexor and/or sorafenib. Follow until toxicity $\leq$ Grade 2. Resume at TWO dose level below current dose for selinexor OR sorafenib OR both based on which medication is likely causing the toxicity ONLY after recovery of toxicity to $\leq$ Grade 2. Dose re-escalation by one dose level every 4 weeks of selinexor OR sorafenib OR both is permitted if tolerated and no recurrent Grade 3 or 4 toxicities occur over the 4 weeks while on the lower dose level.
	5th time	Stop selinexor and sorafenib and discontinue patient. (For patients with clinical benefit/response from the combination we will consider continuation if toxicities resolve to $\leq$ grade 1 and with proper dose adjustments after consultation with the PI and the sponsor)
4	Any time	Stop selinexor and sorafenib and discontinue patient. (For patients with clinical benefit/response from the combination we will consider continuation if toxicities resolve to $\leq$ grade 1 and with proper dose adjustments after consultation with the PI and the sponsor)

- If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.
- Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions for either selinexor or sorafenib or both agents (based on attribution of the specific toxicity to selinexor or sorafenib or both) implemented in subsequent cycles provided the toxicity has resolved as specified in table 4 above.
- These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor in specific cases.
- Guidelines for dose adjustment for toxicities that are likely related to selinexor are given below:

**Table 5 – Specific supportive Care and Dose Adjustment Guidelines for Selinexor-Related Toxicities**

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
<b>Fatigue (common)</b>			
Grade 1	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status.	Maintain dose.	
Grade 2	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status. For additional support see NCCN guidelines.	Maintain dose. Consult medical monitor for additional option such as temporary dose reduction or short dose interruptions.	
Grade 3	See guidelines for Grade 2 fatigue	Interrupt selinexor dosing until resolved to Grade $\leq$ 2, For first occurrence of Grade 3, if adequate supportive care resulted in fatigue improving to Grade $\leq$ 1 within 7 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below (Table 3).	
<b>Anorexia or Weight loss</b>			

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
Grade 1	<p>Rule out other causes of anorexia.</p> <p>Assess dietary options (e.g., try a variety of other foods).</p> <p>Add high-calorie supplements (e.g., Ensure<sup>®</sup>).</p> <p>Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.</p>	Maintain dose.	
Grade 2	<p>Rule out other causes of anorexia.</p> <p>Assess dietary options (e.g., try a variety of other foods).</p> <p>Add high-calorie supplements (e.g., Ensure<sup>®</sup>).</p> <p>Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.</p> <p>Consider megestrol acetate 80-400 mg daily.</p> <p>Consider anabolic steroids such as oxandrolone, or dronabinol (Marinol<sup>®</sup>) or other cannabinoid, mainly for patients who can't tolerate steroids or at high risk to progress.</p> <p>For additional supportive care see NCCN guidelines<sup>b</sup></p>	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.	
Grade 3	See guidelines for Grade 2 anorexia.	<p>Interrupt dosing with selinexor.</p> <p>Restart selinexor at 1 dose level reduction (Table 3) once anorexia resolves to Grade <math>\leq 2</math> and patient is clinically stable.</p>	

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia.	Stop dosing of selinexor. Restart selinexor at 1 dose level reduction (Table 3) only if anorexia resolves to Grade $\leq$ 2, patient is clinically stable other contributing factors have been addressed.	
<b>Nausea/ - acute (common)</b>			
Grade 1	Insure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed. Consider addition of NK1 antagonists. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.	Maintain dose.	
Grade 2	See guidelines for Grade 1 nausea.  For additional options see NCCN guidelines for antiemesis <sup>c</sup>	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.	

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
Grade 3	<p>See guidelines for Grade 1 nausea</p> <p>For additional options see NCCN guidelines for antiemesis<sup>c</sup></p>	<p>Interrupt selinexor dosing until resolved to Grade <math>\leq 2</math>, For first occurrence of Grade 3, if adequate supportive care resulted in nausea improving to Grade <math>\leq 1</math> within 3 days, restart selinexor at current dose.</p> <p>Otherwise, restart selinexor at one dose level below (Table 3). If nausea stabilizes for at least 4 weeks at Grade <math>\leq 1</math>, then original dose of selinexor may be resumed.</p>	
<b>Hyponatremia (common)</b>			
Grade 1 (sodium levels $<$ Normal to 130 nM)	<p>Be certain sodium level is corrected for hyperglycemia (serum glucose <math>&gt;150</math>mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use).</p> <p>Consider salt supplementation one – two times per day.</p>	Maintain dose.	

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
Grade 3 (sodium levels 126-129nM) without Symptoms	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Initiate salt supplementation two-three times per day.	Hold selinexor until Grade $\leq 1$ ( $\geq 130$ nM), restart on the same dose level.	
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with Symptoms	Correct sodium as per institutional guideline Initiate salt supplementation two-three times per day.	Hold selinexor until resolved to Grade $\leq 1$ ( $\geq 130$ nM) then reduce selinexor dose by 1 level (Table 3). For Grade 3 hyponatremia, if serum sodium stabilizes to grade $\leq 1$ for at least 4 weeks, then original dose of selinexor may be resumed.	
<b>Diarrhea (common)</b>			
Grade 1+2	Diet recommendation as per guidelines (Benson, 2004) <sup>d</sup> . Institute standard anti-diarrheal therapy. After the first occurrence of diarrhea, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	For Grade 2 only, reduce selinexor one dose level (Table 3) until resolved to $\leq$ Grade 1, then re-start at the current dose level.	

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
Grade 3	<p>Institute IV fluids                      Diet recommendation as per guidelines (Benson, 2004)<sup>d</sup>.</p> <p>Institute standard anti-diarrheal therapy.</p> <p>Once the symptoms resolve to <math>\leq</math>Grade 1, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.</p>	<p>Delay selinexor until resolved to <math>\leq</math> Grade 1, then reduce selinexor dose by one dose level (Table 3).</p> <p>If diarrhea stabilizes for at least 4 weeks at Grade <math>\leq</math>1, then original dose of selinexor may be resumed.</p>	
Grade 4	<p>Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative. Follow institutional guidelines for Grade 4 diarrhea.</p>	<p>Delay selinexor until resolved to <math>\leq</math> Grade 1, then reduce selinexor dose by one dose level (Table 3).</p>	
<b>Other selinexor-related adverse events*</b>			
Grade 1 or 2	<p>Initiate standard supportive care and follow institutional guidelines.</p>	<p>Maintain dose.</p>	
Grade 3	<p>Initiate standard supportive care and follow institutional guidelines.</p>	<p>Delay dose until resolved to Grade <math>\leq</math> 1 or baseline, then reduce by one dose level (Table 3).</p>	
Grade 4	<p>Initiate standard supportive care and follow institutional guidelines.</p>	<p>Delay dose until resolved to Grade <math>\leq</math>1 or baseline, then reduce by two dose levels (Table 3).</p>	



Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification	
All dose modifications should be based on the worst preceding toxicity.			
* Isolated values of $\geq$ Grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed.			
<sup>a</sup> <b>National Comprehensive Cancer Network®</b> . NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. Available at <a href="http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf">http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf</a>			
<sup>b</sup> <b>National Comprehensive Cancer Network®</b> . NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 1.2014. Fort Washington, NY. April 2014. Available at: <a href="http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf">http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf</a> .			
<sup>c</sup> <b>National Comprehensive Cancer Network®</b> . NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 2.2014. Fort Washington, NY. April 2014. Available at: <a href="http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf">http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf</a> .			
<sup>d</sup> Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.			

### 5.2.3 Intra-patient dose escalation

Intra-patient dose escalation of selinexor and sorafenib (in accordance with the dosing schema in table 3) will be permitted provided:

- Patient has completed  $\geq 1$  cycle at their current dose level
- Patient has not experienced any grade 3 or higher non-hematologic drug-related toxicity, and
- Patient has not experienced hematologic DLT, and
- At least 3 patients have been treated at the next higher dose level and followed for at least 28 days without experiencing DLT.
- The dose may be escalated by one dose level per cycle (per table 3) provided such dose level does not exceed RP2D.
- Dose escalation of only one of the two agents is allowed if judged in the best interest of the patient (e.g., in patients with anorexia this would be likely secondary to selinexor, in patients with skin rash this would be likely secondary to sorafenib). However, the dose of any agent cannot be escalated beyond the established RP2D for that agent.

**5.2.4 Modifications of dose schedules other than the above** will be allowed within the following guidelines:

- 5.2.4.1 Further dose reductions can be made to keep clinically significant toxicities grade  $\leq 2$ .
- 5.2.4.2 Dose adjustments by more than 1 dose level at a time (e.g., from selinexor 80 mg twice weekly to 40 mg twice weekly) can be considered when judged in the best interest of the patient (e.g. severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.
- 5.2.4.3 A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.
- 5.2.4.4 Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI, sponsor and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator (e.g., in patients with anorexia this would be likely secondary to selinexor, in patients with skin rash this would be likely secondary to sorafenib).

**5.3 Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease, or
2. Intercurrent illness that prevents further administration of treatment, or
3. Patient request, or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

- 5.3.1 It is planned that up to a total of 24 cycles of therapy will be administered for patients deriving benefit from this regimen.

Continuation of therapy for patients completing 24 cycles of therapy may be considered on a case-by-case basis after discussion with the principal investigator.

- 5.3.2. All patients receiving at least one dose of any of the two drugs will be considered evaluable for toxicity.

## 5.4 Drug administration

### (A) Selinexor administration

#### 5.4.1 Dosage form

Selinexor tablets are manufactured by KABS Laboratories (Montreal, ON) for Karyopharm, Therapeutics (Newton, MA) using methods in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of antineoplastic agents for human use. The tablets are prepared from a common blend of excipients and all tablet excipients are GRAS (generally regarded as safe) listed and suitable for use in pharmaceuticals. Selinexor is an investigational agent supplied to investigators of this study by Karyopharm Therapeutics at no cost.

Selinexor will be supplied as clear-coated white to off-white tablets for oral administration in two (2) dose strengths: 10 and 25 mg of active ingredient per tablet, with transition to the 20 mg tablets as these supplies become available. The tablets are distinguishable by size and debossing (K10 and K25 respectively). Bulk bottles of 50 tablets per bottle will be supplied for each of the two strengths. The 20 mg tablets will be supplied in blister packs. Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

#### 20 mg Tablets in Blister Packs

- Selinexor tablets (20 mg) are currently in ongoing 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.
- All selinexor tablets must be kept in an appropriate, limited access, secure place until dispensed, destroyed or returned to Karyopharm Therapeutics, Inc. or designee for destruction.
- Selinexor tablets can be stored at room temperature or refrigerated, at or below 86 °F or 30 °C, do not freeze. Room temperature storage is recommended. The study site

will be required to maintain a log of the temperature where the study medication is stored.

Each bottle of selinexor tablets will be labelled in accordance with current International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), FDA and specific national requirements.

Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The Investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

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

#### **5.4.2 Drug Storage**

Selinexor tablets will be stored at room or refrigerated temperatures between 5-30°C (41-86°F) in a locked and secured area with restricted access. Room temperature storage is recommended. The tablets should not be stored at freezer temperatures or allowed to freeze. Tablets will be supplied in white high-density polyethylene (HDPE) bottles. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

#### **5.4.3 Accountability and Destruction of Investigational Medicinal Product**

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

#### **5.4.4 Drug Administration**

Each dose will consist of selinexor for oral administration on a fixed dose basis. Patients should not receive more than a 70 mg/m<sup>2</sup> dose, so the dose given is subject to a BSA limit (example for 100 mg, a BSA is limited to > 1.43 m<sup>2</sup>).

Selinexor doses planned for this study are 80 mg twice weekly and 100 mg twice weekly. Potential de-escalation doses are 60 mg twice weekly and 40 mg twice weekly.

Selinexor tablets are to be taken within 30-minutes of solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.). Selinexor tablets should not be crushed because of increased risk of dermatologic toxicity if the powder comes in contact with skin.

#### **(B) Sorafenib administration**

Sorafenib is supplied as an immediate-release film-coated, round, and salmon color tablet containing 200 mg of the free base, Sorafenib, and the excipient croscarmellose sodium, microcrystalline cellulose, hydroxypropyl methylcellulose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.

If sorafenib is administered on a BID schedule, sorafenib drug doses must be separated by intervals of approximately 12 hours (+/-3 hours).

If a dose is missed, the next dose should not be increased to account for missing a dose. The subject should take the next regular dose at the regularly scheduled time. If a dose is vomited, do not take another dose of medication. Wait until the next dose is due. Take the next regular dose and do not increase it to account for missing a dose.

Modifications to the schedule and/or dose of both/either drugs that are thought to be in the best interest of the patient are allowed after discussion with and approval by the PI.

### **5.5 Supportive Care Recommendations for Selinexor-Related Adverse Events**

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 400 adult patients treated with selinexor as of 01 October 2014, the main side effects are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.

#### **Required Supportive Care Medication**

*5-HT<sub>3</sub> Antagonists*

In order to minimize nausea, unless contraindicated, all patients must receive 5-HT<sub>3</sub> antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued twice daily (bid) – three times a day (tid) as needed (prn).

Besides the required 5-HT<sub>3</sub>, supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H<sub>2</sub>-blockers) and other treatments may be administered as described below:

- Glucocorticoids: dexamethasone (4-12 mg) or equivalent glucocorticoid (e.g., prednisone 10-20 mg) on days of, and 1 day after, selinexor dosing may improve appetite, reduce nausea or vomiting, and minimize fatigue. A maximum of 40 mg dexamethasone or equivalent may be given per week.
- Appetite stimulants: megestrol acetate at a dose of 80-400 mg daily.
- Centrally acting agents: per National Comprehensive Cancer Network<sup>®</sup> [NCCN] Clinical Practice Guidelines<sup>®</sup> for antiemesis and anorexia/cachexia [palliative care]).
- NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

## 5.6 Concomitant medications

### 5.6.1 Required Concomitant/Supportive Care Medications

- Oral dexamethasone (4 mg) will be given to all patients with each dose of selinexor ( $\pm$ 1 day after) to improve tolerability. Co-administration was found to improve appetite, reduce nausea/vomiting, and minimize fatigue in patients treated with selinexor. Higher doses of dexamethasone (or an equivalent corticosteroids) may be appropriate for short periods of time. For all patients, maximum of 40 mg dexamethasone or equivalent per week is permitted.

#### *5-HT<sub>3</sub> Antagonists*

In order to minimize nausea, unless contraindicated, all patients must receive 5-HT<sub>3</sub> Antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued twice daily (bid) – three times a day (tid) as needed (prn).

**5.6.2** In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted. Since the effect of both selinexor and sorafenib may be delayed for up to 4 weeks, patients with high WBC counts may receive hydroxyurea prior to study entry. Hydroxyurea is allowed before the start of study therapy

and for the first four weeks on therapy. Hydroxyurea is allowed after completion of first cycle of treatment to control high WBC with PI approval. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted as defined in inclusion criteria 4.1.8. With the exception of these agents, concomitant systemic chemotherapy is not permitted.

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 5.

**Table 5: Instructions for the use of concomitant medications and therapies**

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of care at MDACC	Before induction 1 day 1 only
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MDACC	None
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MDACC	None
	Erythropoietin or darbepoetin	At investigators discretion according to standard of care at MDACC	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None

### **5.6.3 Use of Blood Products**

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

Myelosuppression is expected in patients with AML due to underlying disease, as well as due to therapies (such as selinexor and sorafenib), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support including G-CSF, GM-CSF and platelet growth factors and erythropoietin/darbopoetin/blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

### **5.6.4 Radiation Treatment**

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but interruption of study drug is not required based on preclinical data and limited clinical observations. Treatment with selinexor shall not be discontinued solely due to palliative radiation.

### **5.6.5 Prohibited Concomitant medications**

Erythropoietin and growth factors are not permitted to be used prophylactically in cycle 1 but allowed if needed in cycle 2 and onwards. However, these can be used therapeutically throughout the study (see section 5.6.3 above).

### **5.6.6 Drugs undergoing Glutathione conjugation**

The primary metabolism of selinexor in vitro and in vivo appears to be inactivation by glutathione conjugation. In vitro studies using human liver microsomes confirm in vivo findings that selinexor undergoes minimal CYP450 metabolism. Therefore, administration of selinexor with drugs that undergo substantial glutathione conjugation should be minimized. These drugs include acetaminophen (paracetamol), which should be avoided 2 hours before and four hours after selinexor dosing. Studies of selinexor in combination with acetaminophen are ongoing in separate protocols. It should also be noted that ethanol ingestion is associated with glutathione depletion, therefore use of products containing ethanol should be minimized or avoided on selinexor dosing days.

### **5.6.7 Strong CYP3A4 inducers**

Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) as they make decrease the systemic exposure to sorafenib.



- Other restrictions and precautions:
  - Alcohol: Ethanol should be avoided on selinexor dosing days as it may compete for glutathione-mediated metabolism.
  - Fasting: Patients on the selinexor arm should maintain an adequate diet.
  - Medications: Acetaminophen (paracetamol, Tylenol) and products containing acetaminophen (paracetamol) should be avoided 2 hours before and 2 hours after dosing with selinexor as it may compete with glutathione mediated metabolism.
  - Diet: There are no dietary restrictions on this study. Patients on the selinexor arm should maintain adequate caloric and fluid intake.

## 6.0 CORRELATIVE/SPECIAL STUDIES (Optional)

### 6.1 Effect of MAPK, AKT signaling and apoptosis induction

The timetable for collection of peripheral blood will be as defined in section 7.2 below.

Vectra testing will be done for p53, survivin, FLT3, pPI3K, pAKT, pERK. Reverse phase protein assay (RPPA) will be utilized to assess activation of FLT3, MAPK, AKT (via detection of phosphorylated FLT3, ERK, pS6, p4EBP1 and pAKT). We will analyze induction of apoptosis in AML stem cells by 3-color flow cytometry assay (CD34/annexin V/CMXRos) established in Dr Andreeff's laboratory. RT-PCR analysis on selected markers will be done only on bone marrow samples.

Peripheral blood for these studies (Vectra, 3-color flow, RPPA) will be collected prior to the first dose of selinexor (baseline: day 1) in cycle 1, 24 (+/- 4) hours post the first dose of selinexor in cycle 1, cycle 1 day 28 (+/- 7 days), and at progression/relapse (if available). Bone marrow samples for studies (Vectra, 3-color flow, RPPA, PCR) will be collected at baseline (within the last 7 days preceding the first dose of selinexor), cycle 1 day 28 (+/- 7 days), and at progression/relapse (if available). Correlative studies and biomarker evaluation will be performed by Dr Andreeff's lab.

### 6.2 XPO1 induction/inhibition

Whole blood (2 tubes X 2.5 mL) will be obtained to assess XPO1 induction/inhibition in leukocytes prior to the first dose of selinexor and 4 hours (+/- 1) hours post the first dose of selinexor on cycle 1 day 1 only, by quantitative real time polymerase chain reaction (qRT-PCR). Karyopharm Therapeutics will be responsible for this testing. Karyopharm will also analyze a panel of additional genes as well as microRNA expression on the blood samples from these time points.

A Karyopharm Therapeutics laboratory manual (Appendix F) and supplies has been provided to facilitate testing. Sample collection and shipment details will be included in the laboratory manual.

### **6.3 Plasma protein/cytokine analysis**

Plasma samples (2 ml) will be collected prior to the first dose of selinexor and 4 hours (+/-1) hours post the first dose of selinexor on cycle 1 day 1 only, and will be analyzed for plasma proteins/cytokine concentrations. Karyopharm Therapeutics will be responsible for this testing. A Karyopharm Therapeutics laboratory manual and supplies has been provided to the site in order to facilitate testing. Sample collection and shipment details will be included in the lab manual.

## **7.0 PATIENT EVALUATION**

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such correlative assays.

### **7.1 Pre-Treatment Evaluation**

All pretreatment studies should be obtained within 14 days from time of first dose of the study drug administration, unless otherwise specified:

- 7.1.1 A complete history and physical, concomitant medications and performance status.
- 7.1.2 CBC, platelet count, hemoglobin, differential (differential can be omitted if WBC is  $\leq 0.5 \times 10^9/L$ ).
- 7.1.3 Creatinine, BUN, direct bilirubin, total bilirubin, AST, ALT.
- 7.1.4 Serum or urine pregnancy test in females of childbearing potential, should be performed within 72 hours before the initiation of therapy.
- 7.1.5 Bone marrow aspirate within the last 7 days preceding study initiation.
- 7.1.6 Evaluation of FLT3-ITD and -D835, NPM1, IDH1 & 2 should have been done within 60 days preceding study initiation.
- 7.1.7 12-lead EKG and ECHO and/or MUGA.
- 7.1.8 A baseline neurological examination will be documented for all patients within the last 7 days preceding study initiation. MRI Brain will be performed at the discretion of the treating physician and/or the PI if clinically indicated.

7.1.9 A baseline full Ophthalmological and Visual Acuity Examination, including slit lamp examination and anterior segment photographs for cataracts or other abnormalities must be performed at screening and must be document for all patients. Follow-up ophthalmologic evaluations will be performed if clinically indicated during the study.

7.1.10 Pretreatment optional correlative studies (see section 6.0)

Peripheral blood (up to 35 cc) – (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA, (4) RT-PCR for selected genes, and (5) XPO1 induction/inhibition in leukocytes and plasma protein/cytokine analysis in the blood prior to first dose of selinexor at baseline (Cycle 1 Day 1)

Bone marrow samples (up to 10 cc): (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA in the bone marrow at baseline, and (4) RT-PCR for selected genes (within the last 7 days preceding study initiation)

## 7.2 Evaluation During Treatment

7.2.1 Physical exam on day 1 of each cycle ( $\pm$  1 days) for the first 4 cycles, then every 1-2 cycles.

7.2.2 CBC, platelet count, hemoglobin, differential at least once weekly for the first 3 cycles, then every 2-4 weeks (differential can be omitted if WBC is  $\leq 0.5 \times 10^9/L$ ). Outside labs may be used, but the PI/Treating physician must review all protocol specific outside lab results and determine the clinical significance of abnormal values then sign/date the results or dictate this process in the medical record.

7.2.3 Creatinine, BUN, total bilirubin, ALT, AST weekly ( $\pm 4$  days) for the first 3 cycles, then every 2-4 weeks.

7.2.4 Laboratory tests can be ordered more frequently if mandated by development of peripheral blast/blood counts or electrolyte/liver function test abnormalities.

7.2.5 Bone marrow aspiration for differential and PCR for FLT3 on day 28 ( $\pm 7$  days) of cycle 1, day 28 of cycle 3 ( $\pm 7$  days), then every 1-3 cycles. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC  $< 0.3$  if the bone marrow test is considered noncontributory by the investigator at any time point.

- 7.2.6 Concomitant medication data will not be collected or entered into the case report form (PDMS is the case report form for this study). Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea if administered during the first cycle; however, the subject's medication record will contain a list of concomitant medications.
- 7.2.7 12-lead EKG will be performed on day 1 ( $\pm 1$  day) of each cycle for the first 4 cycles, then every 1-3 cycles
- 7.2.8 Peripheral blood (up to 35 cc each time) and bone marrow (up to 10 cc each time) for pharmacodynamic studies (Optional) as defined in section 6.2 on
- **Peripheral blood:**
  - Prior to first dose of selinexor at baseline (Cycle 1 Day 1) as per section 7.1.10.
  - Cycle 1 Day 1: 4 (+/- 1) hours after the first dose of selinexor to evaluate (1) XPO1 induction/inhibition in leukocytes and (2) plasma protein/cytokine analysis
  - Cycle 1 Day 2: 24 (+/-4) hours after first dose of selinexor for evaluation of (1) Flow cytometry for CD34/annexin V/CMXRos, (2) Vectra, (3) RPPA, and (4) RT-PCR for selected genes
  - Cycle 1 Day 28 (+/- 7 days): for evaluation of (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA, and (4) RT-PCR for selected genes
  - At progression/relapse (if sample available): for evaluation of (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA, and (4) RT-PCR for selected genes
  - **Bone marrow samples:**
  - At screening (within the last 7 days preceding study initiation) as per section 7.1.10.
  - At the time of disease assessment on day 28 (+/- 7 days): for evaluation of (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA, and (4) RT-PCR for selected genes
  - At progression/relapse (if sample available): for evaluation of (1) Flow cytometry for CD34/annexinV/CMXRos, (2) Vectra, (3) RPPA, and (4) RT-PCR for selected genes
  - Missed samples for correlative studies will not constitute protocol deviations. These studies are optional on this protocol.

7.2.9 All treatment prescriptions for sorafenib and selinexor must be written by the patient's attending physician at MDACC or the PI of the study. We do not intend for the subjects to receive prescriptions for sorafenib or selinexor at an outside physician's office. During the first cycle all the protocol required laboratory evaluations will be done at MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

### **Outside Physician Participation During Treatment**

1. MDACC Physician communications with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix G).
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. The PI/treating physician must review the labs, determine clinical significance and sign and date the report.
4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
6. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
7. All follow-up visits will be performed at MDACC.
8. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

- 7.2.10 For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the PI. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated) and other laboratory tests to once every cycle.
- 7.2.11 Pregnancy test (urine or serum) in females of childbearing potential every 3 months ( $\pm 2$  weeks).
- 7.2.12 Patients with an objective response will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months after the end of treatment visit for up to 5 years after completion of active treatment. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

## **8.0 CRITERIA FOR RESPONSE**

Response criteria will be modified from the International Working Group for AML<sup>34</sup>. Responders are patients who obtain a Composite Complete Remission Rate (CRc) with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. CRc rate is defined as the confirmed remission rate of all complete and incomplete CRs (i.e., CR+ CRp + CRi).

### **8.1 Complete Remission (CR)**

For patients to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC  $> 1 \times 10^9/L$  and platelet count  $\geq 100 \times 10^9/L$ , and normal marrow differential with  $< 5\%$  blasts, and patients will be red blood cell (RBC) and platelet transfusion independent (defined as 4 weeks without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.

### **8.2 Complete Remission with Incomplete Platelet Recovery (CRp)**

For patients to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery ( $< 100 \times 10^9/L$ ).

### **8.3 Complete Remission with Incomplete Hematological Recovery (CRi)**

For patients to be classified as being in CRi, they must fulfill the criteria for CR except for incomplete hematological recovery with residual neutropenia (ANC  $\leq 1 \times 10^9/L$ ) with or without thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ). In addition, patients do not need to be RBC or platelet transfusion independent (modification to Cheson criteria).

### **8.4 Partial Remission (PR)**

For patients to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the

percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%.

### **8.5 Morphologic leukemia-free state:**

Bone marrow:  $\leq 5\%$  myeloblasts

**8.6 Hematologic Improvement (HI):** Hematologic response must be described by the number of positively affected cell lines.

- ◆ **Erythroid response (E)** (pretreatment Hgb  $< 11$  g/dL)  
Hgb increase by  $\geq 1.5$  g/dL
- ◆ **Platelet response (P)** (pretreatment platelets  $< 100 \times 10^9/L$ )  
Absolute increase of  $\geq 30 \times 10^9/L$  for patients starting with  $> 20 \times 10^9/L$  platelets  
Increase from  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  and by at least 100%
- ◆ **Neutrophil response (N)** (pretreatment ANC  $< 1.0 \times 10^9/L$ )  
At least 100% increase and an absolute increase  $> 0.5 \times 10^9/L$
- ◆ **Blast response (B)**  
 $\geq 50\%$  reduction in peripheral blood or bone marrow blasts but still  $> 5\%$

### **8.7 Recurrence of Disease**

Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or  $\geq 5\%$  blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to  $> 25\%$  not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

### **8.8 Best Response measurement**

Response will be measured and defined for primary endpoints as the best response achieved during the first 3 cycles of therapy, or at time off study, for those patients discontinuing treatment before the completion of 3 cycles of therapy. Best response is defined to be the best-measured response (CRc=CR+CRp+CRi, PR, or marrow clearance) post-treatment up to that time. Best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

## **9.0 DISCONTINUATION OF TREATMENT:**

### **9.1 Discontinuation Criteria for Individual Patients**

#### **9.1.1 Patient Withdrawal**

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

### **9.1.2 Investigator Discontinuation of Patient**

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

### **9.1.3 Criteria for Protocol-Defined Required Discontinuation of Treatment**

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
3. Clinically significant progressive disease.
4. Investigator discretion.

### **9.1.4 Follow-Up at Treatment Discontinuation or Early Withdrawal**

Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30-day (+/-7 days) follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient's condition. The phone conversation will then be documented in the patient's charts.

## **9.2 Study Stopping Rules**

The principal investigator and MDACC IND office have the right to terminate this clinical study at any time. The principal investigator and MDACC IND office, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Data recording is significantly inaccurate or incomplete



- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

### **9.3 Protocol Violations and Deviations**

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits) except for those allowed per protocol
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

## **10.0 ADVERSE EVENT REPORTING**

- 10.1** Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

- 10.2** Adverse Events (AEs) will be evaluated against the most current version of the selinexor and sorafenib Investigator Brochure (Appendix C and D) for expectedness. Adverse Events (AEs) will be evaluated according to the latest CTCAE version 4.03 (Appendix E) and documented in medical record. AEs will be recorded in the Case Report Form (CRF) as per appendix I. Expected events during leukemia therapy are:

### **10.2.1 Myelosuppression related events (due to disease or leukemia therapy)**

10.2.1.1 febrile or infection episodes not requiring management in the intensive care unit

10.2.1.2 epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage

10.2.1.3 anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia

## **10.2.2 Disease related events**

10.2.2.1 symptoms associated with anemia

-fatigue

-weakness

-shortness of breath

10.2.2.2 electrolyte abnormalities (sodium, potassium, bicarbonate, CO<sub>2</sub>, magnesium)

10.2.2.3 chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

10.2.2.4 coagulation abnormalities

10.2.2.5 disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

10.2.2.6 alopecia

10.2.2.7 bone, joint, or muscle pain

10.2.2.8 liver function test abnormalities associated with infection or disease progression

10.2.2.9 disease progression

10.2.2.10 abnormal hematologic values

## **10.2.3 General therapy related events**

10.2.3.1 catheter related events

10.2.3.2 renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy

10.2.3.3 rash related to antibiotic use

**10.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form, unless the event is considered a DLT as listed in section 3.4.**

#### **10.4 Serious Adverse Event Reporting (SAE)**

An adverse event (AE) or suspected adverse event is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that might have caused death if it had occurred in a more severe form,.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol that meet the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs

and Devices.” Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30-day time period that is related to the study treatment must be reported to the IND Office and Karyopharm Therapeutics, Inc. This may include the development of a secondary malignancy.
- All cases of selinexor or sorfenib overdose (defined as accidental or intentional ingestion of any dose of the product that is considered excessive and medically important) must be reported as an SAE to the Sponsor (MDACC IND office) and to the supporting company on the SAE Form.
- Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment or within 4 weeks of ending treatment, even if the subject is withdrawn from the study, the pregnancy must be reported immediately to the sponsor (MDACC IND office) on the MD Anderson SAE Form and to the supporting company within 1 days of the Investigator’s knowledge of the pregnancy. The investigator should abide by necessary regulation for medical release from a female partner of a male subject prior to obtaining follow up. The investigator will follow the pregnancy to term or termination, will collect data on both the maternal and fetal outcome and will report all outcomes as a follow-up report to the initial pregnancy notification to the supporting company, Karyopharm Inc..  
Notwithstanding, all pregnancy outcomes that meet the regulatory definition of serious (i.e. spontaneous abortion, neonatal death,

congenital anomaly in an aborted fetus or neonate) will be reported on the MD Anderson SAE Form to the sponsor (MDACC IND office) and the supporting companies within 24 hours of Investigator knowledge of the outcome.

### 10.5 Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI, and the research team, to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

### 10.6 Serious Adverse event Reporting to Karyopharm Inc.

All SAEs, whether related or unrelated to selinexor, pregnancies and reports of overdose regardless of suspected causality and expectedness will be reported immediately but not later than 24 hours of the PI becoming aware of the SAE to Karyopharm's SAE Management team who will ensure data is captured in Karyopharm's Pharmacovigilance system. The PI will forward completed SAE and pregnancy forms by email to [pvg@karyopharm.com](mailto:pvg@karyopharm.com).

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

## 11.0 STATISTICAL CONSIDERATIONS

The primary objectives of the study are to evaluate safety and efficacy of selinexor in combination with sorafenib in patients with FLT3-ITD and -D835 mutated AML. The total accrual is 52 patients (Phase I: up to 12 patients and Phase II: 20 patients per cohort).

### 11.1 Phase I

In order to determine the MTD of selinexor in combination with sorafenib, we will use the standard 3+3 design for dose finding. The MTD is defined as the highest dose level with  $\leq 1$  out of 6 patients experience a DLT during the first 28 days of treatment. **DLT is defined in section 3.4 (page 13)**. The 3+3-dosing algorithm is presented in section 3.3 and the dosing schema for the combination treatment is shown in Table 3. The RP2D will be selected at the end of the phase I portion based on safety and efficacy of selinexor and sorafenib after discussion with the sponsor and the supporting company (Karyopharm). The Investigator is responsible for completing the cohort summary template prior to advancing subjects to the phase II part. Once RP2D has been established, any patients

still on study at a dose lower than RP2D can be dose escalated up to RP2D in accordance with the dose-escalation guidelines in section 5.2.3.

## 11.2 Phase II

The primary objective of the phase II is to evaluate the efficacy of the combination. The study has two cohorts (maximum of 20 patients for each cohort): (1) FLT3-ITD and –D835 mutated relapsed/refractory AML previously exposed to any FLT3 inhibitor, and (2) FLT3-ITD and –D835 mutated relapsed/refractory AML with no prior exposure to any FLT3 inhibitor.

For all the cohorts, the primary endpoint is the achievement of CRc (CRc=CR/CRp/CRi) at any time during the first three cycles of therapy and toxicity assessed at the end of one cycle of therapy. CRc and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998) separately for each cohort. Multic Lean Desktop (version 2.1) was used to generate the stopping boundaries and the OC tables for futility and toxicity monitoring.

- **Cohort #1: Patients with relapse FLT3-ITD and –D835 mutant AML (FLT3 inhibitor naïve cohort):**

The historical data suggested a CRc rate of 20% for this population and the target CRc with selinexor and sorafenib combination is 35%. The treatment will be considered worthy of further investigation if it elicits an increase in CRc to 35% with acceptable toxicity. A >30% therapy related non-hematological grade 3/4 toxicity rate is considered unacceptable. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

- 1)  $\Pr(\text{CR}_{cE} > \text{CR}_{cH} + 0.15 | \text{data}) < 0.025$  or
- 2)  $\Pr(\text{TOX}_E > 0.30 | \text{data}) > 0.90$

Here  $\text{CR}_{cE}$  and  $\text{CR}_{cH}$  are the CRc rate for selinexor in combination with sorafenib and the historical treatment, respectively.  $\text{TOX}_E$  is the toxicity rate for selinexor in combination with sorafenib. That is, if at any time during the study we determine that there is a less than 2.5% chance that the average CRc rate improves over historical CRc rate by more than 15% we will stop enrollment to this cohort. The second condition will stop the study early if excessive therapy-related non-hematological grade 3/4 toxicity (>30%) is highly probable (i.e., probability >90.0%) for the CRcE and CRcH are assumed to follow a prior of Beta (0.4, 1.6) and a constant of 20%, respectively. The stopping boundaries for CRc, based on these assumptions and monitoring conditions are found in **Table 6**. We will apply these stopping boundaries continuously starting from the fifth patient in a cohort size of 5 patients. For example, accrual will cease if 0 patients experiences CRc among the first 10 patients treated.

**Table 6. Stopping boundaries for CRc rate**

Stop accrual if the number with overall response is less than or equal to indicated (i.e., #
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patients with overall response) among the number of patients evaluated				
Number of patients evaluated for CRc	5	10	15	20
Number of patients with CRc (i.e., CR, CRp, or CRi) is less than or equal to	0	0-1	0-2	Always stop with this many patients

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in **Table 7**. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.

**Table 7. Stopping boundaries for Toxicity**

Stop accrual if the number of drug-related non-hematological grade 3/4 toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated				
# patients evaluated	5	10	15	20
# patients with toxicities	4-5	6-10	8-15	Always stop with this many patients

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 8). In order to utilize the software for the design, a 20.0% ORR and beta (0.4, 1.6) priors were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a 30% toxicity constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity constant rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true ORR of the combination treatment was 35% and the true toxicity rate was 30% was 23.8%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 63.3% when the true ORR was 35% and 57.5% when true ORR rate was 50%.

Table 8. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment		
True Toxicity Rate	True ORR	Prob(stop the trial early)
0.10	0.20	0.5391
	0.25	0.3835
	0.35	0.1686
	0.45	0.0642
	0.50	0.0378
0.20	0.20	0.5450
	0.25	0.3913
	0.35	0.1791

Table 8. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment		
True Toxicity Rate	True ORR	Prob(stop the trial early)
	0.45	0.0760
	0.50	0.0499
0.30	0.20	0.5778
	0.25	0.4352
	<b>0.35</b>	<b>0.2384</b>
	0.45	0.1427
	0.50	0.1185
0.40	0.20	0.6650
	0.25	0.5519
	0.35	0.3957
	0.45	0.3198
	0.50	0.3006
0.50	0.20	0.7965
	0.25	0.7278
	0.35	0.6330
	0.45	0.5869
	0.50	0.5752

- **Cohort #2: Patients with relapsed FLT3-ITD and –D835 mutant AML (FLT3 inhibitor failure cohort)**

The historical data suggested a CR<sub>c</sub> rate of 10% for this population and the target CR<sub>c</sub> rate with selinexor ad sorafenib combination is 20%. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

- 1)  $\Pr(\text{CR}_{cE} > \text{CR}_{cH} + 0.10 | \text{data}) < 0.025$
- 2)  $\Pr(\text{TOX}_E > 0.30 | \text{data}) > 0.875$

Here CR<sub>cE</sub> and CR<sub>cH</sub> are the CR<sub>c</sub> rate for selinexor in combination with sorafenib and historical treatment, respectively. TOX<sub>E</sub> is the toxicity rate for selinexor in combination with sorafenib. That is, if at any time during the study we determine that there is a less than 2.5% chance that the average CR<sub>c</sub> rate improves over historical rate by more than 10% we will stop enrollment to this cohort. CR<sub>cE</sub> and CR<sub>cH</sub> are assumed to follow a prior of Beta (0.2, 1.8) and constant of 10%, respectively. The second condition will stop the study early if excessive therapy-related non-hematological grade 3/4 toxicity (>30%) is highly probable (i.e., probability >95.0%). The stopping boundaries for CR<sub>c</sub> rate, based on these assumptions and monitoring conditions are found in **Table 9**. We



will apply these stopping boundaries continuously starting from the fifth patient and in cohort size of 5 patients. For example, accrual will cease if no patient experiences CRc among the first 10 patients treated.

**Table 9. Stopping boundaries for CRc rate**

Stop accrual if the number with overall response is less than or equal to indicated (i.e., # patients with overall response) among the number of patients evaluated			
Number of patients evaluated for CRc	5	10-15	20
Number of patients with CRc (i.e., CR, CRp, or CRi) is less than or equal to	Never stop with this many patients	0	Always stop with this many patients

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in **Table 10**. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.

**Table 10. Stopping boundaries for Toxicity**

Stop accrual if the number of drug-related non-hematological grade 3/4 toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated				
# patients evaluated	5	10	15	20
# patients with toxicities	4-5	5-10	7-15	Always stop with this many patients

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 11). In order to utilize the software for the design, a 10.0% ORR and beta (0.2, 1.8) priors were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a 30% toxicity constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity constant rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true ORR of the combination treatment was 30% and the true toxicity rate was 20% was 28.2%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 77.8% when the true ORR was 20% and 75.8% when true ORR rate was 30%.

**Table 11. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment**

True Toxicity Rate	True ORR	Prob(stop the trial early)
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Table 11. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment		
True Toxicity Rate	True ORR	Prob(stop the trial early)
0.10	0.10	0.3500
	0.15	0.1985
	0.20	0.1092
	0.25	0.0582
	0.30	0.0302
0.20	0.10	0.3756
	0.15	0.2301
	0.20	0.1443
	0.25	0.0953
	0.30	0.0684
0.30	0.10	0.4761
	0.15	0.3540
	<b>0.20</b>	<b>0.2820</b>
	0.25	0.2410
	0.30	0.2184
0.40	0.10	0.6552
	0.15	0.5748
	0.20	0.5274
	0.25	0.5004
	0.30	0.4855
0.50	0.10	0.8381
	0.15	0.8003
	0.20	0.7781
	0.25	0.7654
	0.30	0.7584

### 11.3 Statistical Analysis Plan

All patients who received any dose of the study agent will be included in the analysis for efficacy and safety. Demographic/clinical characteristics (including duration of response) and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. For the primary efficacy analysis, we will estimate the ORR for the combination treatment, along with the 95% confidence interval. In addition, we will estimate composite CRc rate, partial response and marrow clearance rate within 3 months by FLT3 mutation. Patients who drop out of the study before completing all the cycles will be treated as “failures” for the primary analysis. ORR during the study period will also be presented with the 95% confidence interval. The association between ORR and patient’s clinical characteristics will be examined by Wilcoxon’s rank sum test or Fisher’s exact test, as appropriate. Toxicity type, severity and attribution will be summarized for each patient using frequency tables.

The distribution of time-to-event endpoints (DFS and OS) including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. Paired t-tests will be used to determine the immunological and molecular changes in the peripheral blood and bone marrow from baseline to the time of response, and to the time of disease progression.

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