*OSU Protocol #:14087*
*Version 7*
*Date: 03 August 2021*

**TITLE:** A Dose Escalation Study of Selinexor (KPT-330), a Selective Inhibitor of Nuclear Export, and Ibrutinib, a Bruton's Tyrosine Kinase Inhibitor, in Patients with Relapsed and Refractory Chronic Lymphocytic Leukemia or Aggressive Non-Hodgkin Lymphoma


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|---|---|
| **Initial Protocol** | 14 Nov 2014 |
| **Amendment 1** | 25 Jan 2016 |
| **Amendment 2** | 03 May 2016 |
| **Amendment 3** | 10 Jan 2017 |
| **Amendment 4** | 03 Oct 2017 |
| **Amendment 5** | 12 Jun 2018 |
| **Amendment 6** | 07 April 2020 |
| **Amendment 7** | 03 August 2021 |

| Investigational Agent | IND# | IND Sponsor |
|---|---|---|
| Selinexor (KPT-330) | 124150 | The Ohio State University |

**Study Cohorts:**

Cohort 1: Selinexor Dose Escalation

Cohort 2: Selinexor + Ibrutinib Expansion Cohort

Cohort 3: Selinexor added to frontline Ibrutinib in CLL

SCHEMA

| **Eligibility Criteria*** | **Required Initial Laboratory Values** |
|---|---|
| 1.Histologically confirmed chronic lymphocytic leukemia, small lymphocytic leukemia, B-cell prolymphocytic leukemia, or variants of this or B-cell non-Hodgkin's lymphoma (NHL) of any of the following subtypes recognized by the WHO classification: mantle cell lymphoma, diffuse large B-cell lymphoma not otherwise specified, or transformed lymphoma.<br>2.At least one prior therapy<br>3.ECOG performance status 0-1<br>4.Age ≥ 18 years<br>5.Patients are excluded who:<br>• Have received chemotherapy or radiotherapy ≤ 4 weeks, nitrosoureas or mitomycin C ≤ 6 weeks, or immunotherapy/ targeted agents (such as kinase inhibitors) ≤ 2 weeks (except patients already on ibrutinib).<br>• Require anticoagulation with warfarin.<br>• Require therapy with strong inducers or inhibitors of CYP3A4/5. | ANC[#] ≥ 1,000/mm$^3$<br>Platelets[$] ≥ 50,000/mm$^3$<br>Creatinine clearance ≥ 30ml/min<br>Total bilirubin[^] ≤ 2.0 x ULN<br>AST/ALT[#] < 2.5 ULN |
| [*]Please refer to Section 3 for the complete eligibility criteria. [#]Unless these values are secondary to bone marrow involvement of CLL/NHL. [$]Platelets ≥ 30,000/mm$^3$ in the setting of bone marrow involvement. [^]Unless due to Gilberts. | |

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| Agent | Precautions | Dose | Route | Schedule | Cycle Length |
| Ibrutinib | Take with 8 oz of water, 30 min before meal | Capsule or tablet* | Oral | Cycle 1 Days 8-28**, Cycles 2+ Days 1-28 | 28 days (4 weeks) |
| Selinexor | Take with at least 120 mL (4 ounces) of fluids (water, juice, etc.) | Tablet* | Oral | Days 1,8, and 15 of each cycle* | |
| *Doses/schedule as appropriate for assigned dose level. | | | | | |

| **Patients continuing on ibrutinib should take ibrutinib days 1-28 of Cycle 1 |
|---|

| Dose Level | Selinexor Dose | Selinexor Schedule | Ibrutinib Dose | Ibrutinib Schedule |
|---|---|---|---|---|
| 1* | 40 mg | Weekly (oral) | 420 mg | Daily (oral) |
| 2 | 20 mg | Bi-weekly (oral) | 420 mg | Daily (oral) |

For the phase I study, an adaptive dose finding design using a modified continuous reassessment method will be followed. Once the MTD of selinexor in combination with ibrutinib is identified, an expansion cohort of up to 10 CLL patients and 10 lymphoma patients will be accrued to better describe the toxicity profile, evaluate feasibility of pharmacodynamics studies, and to gain additional efficacy data. Dose-limiting toxicity (DLT) will be assessed during cycle 1 only. Provided the patient does not experience significant toxicity, patients may continue treatment until disease progression. Response will be assessed by PET/CT, CT, and/or peripheral blood immunophenotyping every 3 cycles during the 1st year of therapy and then every 6 months until disease progression or as medically indicated. PET/CT is preferred in lymphoma patients. In patients with bone marrow involvement at the start of therapy, a bone marrow biopsy will be performed to confirm a complete response (CR). Additionally, bone marrow biopsy will be performed at 1 year and then yearly provided other criteria for CR exist.

| **Definition of DLT for patients receiving selinexor and ibrutinib*** |
|---|
| **General** |
| • Treatment delays >28 days for any toxicity<br>• Any grade 5 toxicity |
| **Non-hematologic** |
| • Grade 3 nausea/vomiting or diarrhea lasting for ≥7 days while taking optimal supportive medications#<br>• Grade 3 anorexia or fatigue lasting for ≥7 days while taking optimal supportive care# and with correction of dehydration, anemia, endocrine, or electrolyte abnormalities<br>• Grade ≥ 3 AST or ALT elevation lasting for ≥7 days OR any Grade ≥ 3 AST or ALT elevation in the setting of bilirubin elevation > 2x ULN<br>Any other Grade 3 non-hematological toxicity except alopecia, rash that resolves to Grade 1 in ≤ 7 days, or electrolytes abnormalities correctable with supportive therapy#<br>• Any Grade 4 non-hematologic toxicity not specifically listed above |
| **Hematologic** |
| • Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm$^3$] lasting ≥7 days$^{\$}$;<br>• Grade 4 thrombocytopenia (platelet count <25,000/mm$^3$) that persists for ≥7 days$^{\$}$;<br>• Grade ≥ 3 thrombocytopenia-associated bleeding; or<br>• Grade 4 febrile neutropenia (ANC < 1000/mm3 with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour). |
| *Assessed during Cycle 1 by CTCAEv4 criteria #Section 4.4 provides detailed supportive care $Only for patients with normal cell counts at study start (See Section 4.2) ^For patients with Gilbert's syndrome: >2X baseline |

**TABLE OF CONTENTS**

# 1. OBJECTIVES

## 1.1 Primary Objectives

To determine the maximum tolerated dose for the combination of selinexor and ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia(SLL)/B-cell prolymphocytic leukemia (PLL) or aggressive non-Hodgkin lymphoma (NHL).

## 1.2 Secondary Objectives

1.2.1 To characterize the safety and tolerability of the combination of selinexor and ibrutinib in patients with relapsed or refractory CLL/SLL/PLL or aggressive NHL.

1.2.2 To obtain preliminary data on efficacy of the combination of selinexor and ibrutinib in patients with relapsed or refractory CLL/SLL/PLL or aggressive NHL.

1.2.3 To obtain preliminary data on response in CLL/SLL/PLL and diffuse large B-cell lymphoma (DLBCL) patients receiving the combination of selinexor and ibrutinib as related to CLL/SLL/PLL karyotype and IgVH mutational status and DLBCL subtype, respectively.

1.2.4 To obtain preliminary data on the ability of selinexor to improve response depth with ibrutinib when given to patients receiving initial therapy (Cohort 3)

## 1.3 Exploratory Correlative and Pharmacodynamic Objectives

1.3.1 To evaluate the inhibition of the B-cell receptor signaling pathway in patients with relapsed or refractory CLL/SLL/PLL who receive the combination of selinexor and ibrutinib.

1.3.2 To characterize the pharmacokinetic (PK) properties of the combination of selinexor and ibrutinib in patients with relapsed or refractory CLL/SLL/PLL or aggressive NHL.

1.3.3 To evaluate the change in localization of tumor suppressor and growth regulation proteins in patients with relapsed or refractory CLL/SLL/PLL following treatment with selinexor in general and as related to response.

1.3.4 To preliminarily assess potential causes for primary and secondary resistance to selinexor and ibrutinib.

1.3.5 To measure intracellular levels of selinexor and metabolites in peripheral blood mononuclear cells and to identify how this relates to pharmacodynamics effects and clinical outcomes.

# 2. BACKGROUND

## 2.1 Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma

Chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), including mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL) are the most common types of

adult hematologic malignancies in the United States[1]. In 2012, the estimated number of new cases of CLL and NHL were 16,060 and 70,130, respectively[1]. The same year, 4,580 and 18,940 people were projected to die as a cause of CLL or NHL, respectively[1]. Over the years, significant advances in the treatment of these cancers were achieved and the therapy evolved from standard chemotherapy agents to chemotherapy agents in combination with immunotherapeutic compounds such as monoclonal antibodies. However, despite this progress, there is currently no cure for relapsed or refractory CLL or NHL outside of aggressive therapy with hematopoietic stem cell transplantation. Therefore, there has been much interest in developing novel therapeutic options for this group of patients. Of late, targeted agents have shown great promise in CLL and NHL therapy with a focus on the B-cell receptor pathway.

## 2.2 B-cell Receptor Pathway in Lymphoid Malignancies

Chronic activation of the B-cell receptor pathway has been shown to play a crucial role in the survival of CLL[2], MCL[3], and DLBCL cells[4]. Therefore, inhibition of the components of the B-cell receptor pathway has become an attractive therapeutic target in the treatment of these malignancies. A critical component of this pathway is Bruton's agammaglobulinemia tyrosine kinase (BTK), a non-receptor tyrosine kinase in the Tec kinase family, which is expressed predominantly in B-lymphocytes but not in T- or NK-cells and is also down-regulated in plasma cells[5]. BTK is critical for B-cell development, differentiation, signaling, proliferation, and survival[5]. Mutation of the BTK gene leads to X-linked agammaglobulinemia in humans, which results in lack of circulating B-cells, inability to produce immunoglobulins and significant susceptibility to infection[6]. Functional BTK is essential for activation of several survival pathways including the Akt, extracellular signal–regulated kinase (ERK), and nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) pathways[7]. Ibrutinib is an orally bioavailable, potent, irreversible inhibitor which covalently binds to the cysteine-481 amino acid of the BTK enzyme[8]. Over the past few years, research using ibrutinib to target multiple B-cell malignancies has been wildly successful.

## 2.3 Ibrutinib in Chronic Lymphocytic Leukemia

There is significant evidence to suggest that the viability of CLL cells is dependent on B-cell receptor signaling. Unmutated status of the immunoglobulin variable heavy chain (IgVH) is one of the strongest predictive factors for poor prognosis in CLL patients[9, 10]. This finding has been attributed to enhanced signaling and dependence on the B-cell receptor pathway in this patient subset. ZAP70 and CD38 are additional molecules that modify B-cell receptor signaling and are associated with poor prognosis in CLL patients[10, 11]. These prognostic observations gave strong rationale to use B-cell receptor pathway inhibitors, such as ibrutinib, in CLL patients.

Preclinical studies with ibrutinib in CLL cells and models have demonstrated multiple cellular effects, including abrogation of the ERK, phosphatidylinositide 3-kinase (PI3K), and NF-κB survival pathways. Ibrutinib inhibited activation-induced proliferation of CLL cells and blocked survival signals to CLL cells from the microenvironment, including soluble factors (CD40L, BAFF, IL-6, IL-4, and TNF-α), fibronectin engagement, and stromal cell contact. Importantly, ibrutinib did not interfere with T-cell survival[12].

Due to this research and other strong preclinical data, ibrutinib entered clinical trials in patients with relapsed and refractory CLL. Sixteen of the 56 patients with B-cell malignancies in an early phase I trial of ibrutinib[13] were patients with CLL. Eleven of these 16 patients experienced rapid reduction of lymphadenopathy during cycle one of treatment, which was accompanied by an increase in peripheral lymphocytosis suggesting a redistribution of CLL cells from the lymph nodes into the peripheral blood. Ibrutinib was generally well-tolerated and of all toxicities, the most common adverse events were typically grade 1 or 2, including diarrhea (42.9%), nausea (41.1%), fatigue (37.5%), myalgia (37.5%), and dyspepsia (30.4%)[13]. This trial led to a landmark phase Ib/II study in 85 relapsed and refractory CLL patients[8] where patients were assigned to receive either 420mg (n=51) or 840mg (n=34) of oral ibrutinib daily until disease progression or intolerable adverse events. The overall response rate (ORR) was 71% in both dose cohorts when based on standard response criteria[14]. An additional 20% and 15% of patients in the 420mg and 840mg cohorts, respectively, achieved a partial response with residual lymphocytosis[8]. Prolonged lymphocytosis during ibrutinib therapy has subsequently been found not to indicate a suboptimal response to therapy[15]. Response rates were not different between several known high-risk populations, with the exception of a worse response seen in patients with mutated-IgVH. Correlative analyses demonstrated a greater than 90% occupancy of the pharmacodynamics BTK probe and similar response rates between the groups that received 420 mg and 840 mg, which provided support for the use of the 420 mg dose in CLL patients. Again, ibrutinib was well-tolerated and the most common adverse events were grade 1 or 2 and included diarrhea (47%), and upper respiratory tract infection (33%), fatigue (28%), and most adverse events resolved without holding therapy. The 26-month estimated rates of progression-free survival (PFS) and overall survival (OS) were 75% and 83%, respectively. This study led to the ultimate approval of ibrutinib for relapsed/refractory CLL patients by the US Food and Drug Administration (FDA). Although these results are very promising, there remains a subset of high risk, most notably patients with del(17p13.1) karyotype, who demonstrated a shorter PFS and OS of 57% and 70%, respectively[8].

This finding indicates that there is a subset of patients that will become resistant to therapy with ibrutinib and will need alternative therapeutic options. Six CLL patients who relapsed while treated with single-agent ibrutinib on clinical trial were analyzed to detect mechanisms of resistance. Whole exome sequencing was performed at baseline and relapse on samples from these patients. In 5 of the patients, a cysteine-to-serine substitution at position of 481 of BTK (C481S; binding site of ibrutinib) was identified. In 2 patients, three distinct gain of function mutations were identified in PLC$_\gamma$2 (S707Y, R665W, and L845F), which lead to autonomous B-cell receptor signaling pathway. Both types of mutations indicate an acquired resistance to ibrutinib and further emphasize the need for alternate or combination therapies for these patients. Although only a small portion of patients have developed acquired resistance to ibrutinib, the study of the 6 patients suggest that patients with more genomic instability, including those with del(17p13.1), del(11q22.3), and complex karyotype may be at particular risk for relapse on ibrutinib[16] (unpublished data Byrd laboratory).

### 2.4 Ibrutinib in Mantle Cell Lymphoma

Preclinical data has also pointed to the importance of B-cell receptor signaling in MCL. Although IgVH stereotypes discovered in MCL were distinct from those in CLL, highly restricted immunoglobulin genes are thought to imply a role for antigen-driven selection of the clonogenic progenitors[17]. When constitutively activated, signal transducer and activator of transcription 3 (STAT3), promotes cell growth and survival through dysregulated protein expression and contributes to the malignant phenotype in numerous cancer types[18]. STAT3 was found to be activated in primary MCL cells in response to B-cell receptor engagement[3]. Another preclinical study using genomic and expression profiling identified spleen tyrosine kinase, a protein upstream from BTK in the B-cell receptor signaling pathway, as a potential therapeutic target for MCL[19]. These observations provided rationale to target the B-cell receptor pathway in clinical trials for MCL patients with agents such as ibrutinib.

In the initial ibrutinib phase I trial that encompassed multiple relapsed and refractory B-cell malignancies, seven of the nine MCL patients achieved a response with three complete responses. Pharmacodynamic studies indicated that a fixed continuous dose of 560mg daily led to full BTK occupancy in a range of individual body weights and was well tolerated, leading to the selection of this dose for phase II studies[13]. Toxicities were minimal as described above in Section 2.3.

In the landmark phase II study, 111 relapsed or refractory MCL patients were treated with 560mg daily of oral ibrutinib[20]. Again, ibrutinib was well tolerated with grade 1 or 2 diarrhea (44%), fatigue (37%), and nausea (30%) as the most common adverse events. An overall response rate of 68% was observed. The estimated PFS was 13.9 months (95%CI=7.0 to not reached) and the median OS was not reached. At 18 months, the estimated rate of OS was 58%[20]. Secondary to the response data from this trial, ibrutinib was approved by the US FDA as a single-agent in relapsed and refractory MCL patients.

In attempt to improve upon the single-agent success of ibrutinib in MCL patients, multiple trials are ongoing with ibrutinib in combination with various immunochemotherapy agents[21, 22]. There still remains a great need for combination therapy with ibrutinib and other non-cytotoxic agents, especially for elderly or unfit patients that cannot tolerate these aggressive therapies.

### 2.5 Ibrutinib in Diffuse Large B-cell Lymphoma

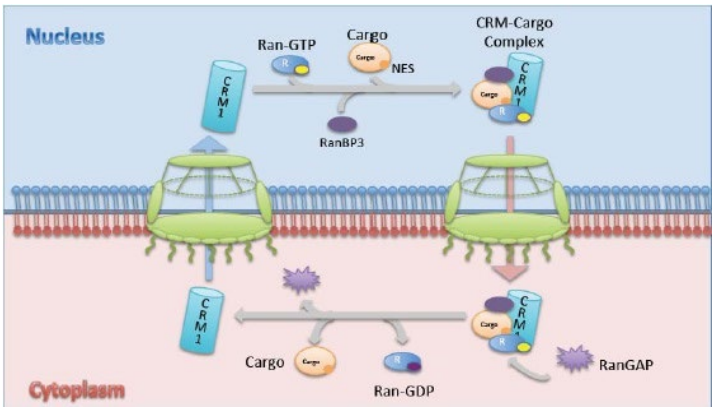
Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous diagnostic category with multiple distinct subtypes. Patients with the activated B-cell-like (ABC) subtype of DLBCL have been shown to have poor response and survival when treated with standard chemoimmunotherapy regimens[23]. This subtype has been found to rely on constituitive NFκB signaling to block apoptosis[24], which is moderated by the signaling adaptor CARD11. In ~10% of ABC DLBCL, CARD11 is mutated to cause this constituitive activation[25]. In the ABC DLBCL patients with wild-type CARD11, RNA interference genetic screen revealed that BTK is essential for the survival of these cells and knockdown of proximal B-cell receptor signaling killed these lymphoma cells[4]. These data provided preclinical rationale to targeting BTK in ABC DLBCL patients.

In the initial phase I study of ibrutinib in relapsed/refractory hematologic malignancy, two of the seven DLBCL patients achieved response[13]. Secondary to preclinical data indicating that the ABC subtype is more dependent on the B-cell receptor signaling pathway, a phase II study was designed to test the hypothesis that ibrutinib would be more active in these patients than an alternative germinal center B-cell-like (GCB) subtype[26]. Seventy patients with relapsed/refractory DLBCL enrolled on the trial received 560 mg of oral ibrutinib daily. Of the 25 evaluable ABC DLBCL patients, 10 (40%) achieved response with 2 (8%) complete responses. In the ABC DLBCL responders, the median PFS was 5.5 months at the time of analysis. In contrast, only 1 of the 19 (5.3%) GCB DLBCL patients achieved a partial response. The results of this trial were consistent with an essential role of B-cell receptor signaling in ABC DLBCL patients[26]. As the response rate was 40% in these patients, there is room to augment the success of ibrutinib in these patients via combining this agent with other agents with alternative targets and mechanism of action.

## 2.6 Tumor Suppressor Protein (TSP) and Growth Regulatory Protein (GRP) Nuclear Export

Many important TSP/GRPs have been identified in cancer pathogenesis, including but not limited to TP53, FOXO3a, iκB, BRCA1, APC, and Rb[27]. TSP/GRPs mediate tumor suppression pathways via various functions including recognition of cellular damage, arrest of the cell cycle until repairs can be made, and induction of apoptosis in cells that are beyond repair[28].

These proteins function primarily in the nucleus and exportation out of the nucleus can inactivate their abilities to regulate cellular processes[29] and cancer cells can exploit these normal functions to successfully evade anti-neoplastic therapy. The majority of known TSP/GRPs must traverse structures imbedded in the nuclear envelope called nuclear pore complexes (NPC)[27]. One primary component of the NPC is called chromosomal region maintenance protein 1 (CRM1) in mice or exportin 1 (XPO1) in humans[27]. XPO1 can identify these cargo proteins (including TSP/GRPs) via canonical Nuclear Export Sequences (NES), which are typically leucine-rich repeats in the cargo protein, which are exposed on the protein surface in response to microenvironment signals[29]. Once the cargo protein forms a complex with XPO1 (CRM1) and RanGTP (energy source) the protein can be transported out of the nucleus[30], in a process promoted by Ran-binding protein RanBP3[27] (as shown in Figure 1). XPO1 overexpression has been reported in many types of human cancer, including both solid tumors and hematologic malignancies[27]. XPO1 overexpression and subsequent increased export and inactivation of TSP/CRPs may fuel the growth of these cancers and lead to chemotherapy resistance.



## 2.7 Inhibition of XPO1 in Human Cancer

FOXO3 is a transcription factor that is a crucial regulator of hematopoietic cell fate that plays a role in proliferation and apoptosis as a component of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway[31] that is commonly activated in various cancers. FOXO3 was found to be constitutively inactivated in mantle cell lymphoma cell lines and to have cytoplasmic localization in patient-derived cells[31]. These FOXO3 defective cells were resistant to PI3K/AKT inhibitors in vitro[31]. Non-specific inhibition of nuclear export with a non-specific small molecule (Psammaplysene A), drastically reduced viability of the malignant cells and made those cells more susceptible to cytotoxicity from doxorubicin[31]. Another group showed that plasmid-based overexpression of constitutively active FOXO3 in cells from chronic lymphocytic leukemia (CLL) reduced their survival[32].

Based on the suspected mechanism of CRM1 in driving malignancy and chemotherapy resistance, the molecule is promising as an oncologic therapeutic target. CRM1 blockade of causes a transient nuclear retention of TSP/GRPs, re-establishing their tumor suppressing effects on cancer cells and potentially reversing mechanisms leading to chemotherapy resistance (which holds possible future implications for combination therapies)[33]. In normal cells, XPO1 inhibition transiently arrests cell cycle without cytotoxicity followed by recovery after the inhibitor is removed[33]. Several attempts to develop this class of anti-cancer drug have failed secondary to off target effects of the drugs, which led to significant fatigue and weight loss in the early clinical trials[34-36].

## 2.8 Selective Inhibitors of Nuclear Export (SINE)

SINE, a new generation of CRM1/XPO1 inhibitors, was designed to more selectively inhibit XPO1 for increased efficacy and reduced toxicity secondary to off-target effects. KPT-185 and KPT-251, two SINEs, were initially evaluated for CLL in our laboratory at Ohio State University (OSU)[37]. These data showed that the SINEs induced significant time and dose-dependent cytotoxicity in CLL cells (even in patient samples with known poor prognostic factors such as unmutated IgVH status), while causing only modest apoptosis in normal B-cells[37]. In CLL cells, the SINEs demonstrated specific inhibition of nuclear export via analysis of increased accumulation of important TSP/GRPs (AKT, p53, FOXO3a, and IκB) in the nucleus[37]. In a mouse model of CLL (Eμ-TCL1-SCID mouse), treatment with KPT-251 showed a significant improvement over survival when compared to fludarabine- or vehicle-treated mice. The drug was well tolerated, resulting on only moderate wt loss (≤10% of body wt)[37]. Another group studied SINEs (KPT-185 and KPT-276) in mantle cell lymphoma (MCL), an aggressive subtype of non-Hodgkin's (NHL) B-cell lymphoma[38]. In MCL cell lines and primary cells, the SINEs induced significant apoptosis in a manner independent of p53 status[38]. Oral administration of KPT-276 significantly suppressed tumor growth in a MCL-bearing SCID mouse, with minimal wt loss and no other clinically observed toxicities[38]. Another similar SINE (KPT-335) was administered to dogs with spontaneous NHL at doses up to 2mg/kg twice weekly[39]. This single-agent therapy demonstrated disease stabilization and tumor reduction with a main side effect of anorexia, which was largely overcome by food supplementation[39]. Secondary to the success of these SINEs in preclinical study, selinexor (KPT-330) was developed with the goal of improved

pharmacokinetic (PK) and oral bioavailability.

## 2.9 Selinexor Preclinical and Clinical Data

Selinexor, the newest generation of SINE, has been tested in our lab and in our clinics with a nearly complete phase I study in advanced hematologic malignancy. In CLL cells, selinexor induced similar levels of cytotoxicity while preserving normal B-cells when compared to KPT-251[40]. The compound also showed enhanced cytotoxicity in high-risk CLL cells including patient samples with del(17p) cytogenetics and unmutated IgVH status[40]. In CLL patient samples with unmutated IgVH status, XPO1 inhibition prevents CpG-induced phosphorylation of ERK and AKT, thereby preventing expression of cMyc and cyclin A2 and downstream proliferation of these CLL cells. SINEs induce BTK downmodultion in CLL cells. Selinexor abrogated phosphorylation of AKT and ERK in primary CLL cells, possibly through targeted inhibition of AKT or ERK pathways[40]. Additionally, selinexor was found to significantly inhibit CXCL12-mediated signaling in CLL cells, which prevents trafficking of CLL cells to the protective stromal environment and decreases the cells ability to survive[40].

In Eμ-TCL1-SCID mouse model of CLL, mice were treated with selinexor either twice (BIW; 5 or 15mg/mL) or thrice (TIW; 3 or 10mg/mL) weekly and compared with vehicle-treated mice for 36 weeks. The mice treated with 15mg/mL BIW and all mice treated TIW, showed significant survival improvement over vehicle[40]. Additionally, selinexor was well-tolerated with initial weight loss, which was fully reversed by the end of the study and did not appear to adversely affect the animals[40].

Preclinical PK and toxicology parameters have been studied in mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus) models (unpublished data from Karyopharm Therapeutics, Natick, MA). Oral bioavailability was consistently >60% in all species. Based on these studies and work with similar compounds in dogs, the minimal area under the curve (AUC) values were determined to be ~5,000ng*hr/mL in mice and ~2,000ng*hr/mL in dogs. These values correspond to anticipated AUC values of >3,000ng*hr/mL in humans, which should be achieved at projected doses of 15-45mg/m$^2$. In toxicology studies, the rats and monkeys demonstrated a dose limiting toxicity (DLT) of wt loss with atrophy of the gastrointestinal tract and noncritical effects on other major organs. Majority of adverse events (AEs) were completely reversed after a 2-week break period. At projected doses of ≤45mg/m$^2$, observed AEs were rare. For the rats, the severely toxic dose (STD) was found to be 30mg/m$^2$ and for monkeys, the highest non-severely toxic dose (HNSTD) was 18mg/m$^2$. Therefore, based on International Conference in Harmonization (ICH) guidelines, the initial starting dose for selinexor humans in the phase I trial was 3mg/m2 (rat STD/10=3mg/m$^2$; monkey HNSTD/6=3mg/m$^2$).

Selinexor is currently under clinical investigation for the treatment of patients with advanced hematologic and advanced solid malignancies. Three Phase 1 studies (KCP-330-001 in hematologic malignancies, KCP-330-002 in solid tumor malignancies, KCP-330-00: food effect in sarcoma) are in progress. In addition, Phase 2 studies in multiple hematologic and solid tumor indications are currently ongoing or in process of being initiated (protocol submitted to FDA). These studies and current safety and efficacy results are described in detail in the

Investigator's Brochure.

In a food effect study, the presence of food (high- or low-fat meals) delayed selinexor absorption (tmax from 1.7 to approximately 4 hours), however, there was minimal impact on exposures (geometric mean ratio [GMR] was 114.7% and 125.5% for low- and high-fat meals, respectively) and this was not clinically relevant. Therefore, selinexor should be taken with water and can be administered with or without food.

To date, broad anti-tumor activity has been reported during the dose-escalation phase with single agent selinexor in patients heavily pretreated, with relapsed/refractory, progressive solid tumor and hematologic malignancies. The most common adverse effects (AEs) have been similar to those reported in nonclinical studies and include anorexia, weight loss, nausea and fatigue. These AEs can be prevented or mitigated with dietary counselling and prophylactic supportive medications. No major organ toxicities have been observed to date, and no clinically significant cumulative toxicities have been observed in >10 months of dosing. Overall, oral selinexor pharmacokinetics was predictable, reasonably dose-proportional, and exhibited moderate to moderately high inter-patient variability across a wide dose range in male and female patients with advanced solid tumor or hematological malignancies.

The phase I study in advanced hematologic malignancies (KCP-330-001) is ongoing at multiple institutions, with 148 patients enrolled as of 28 February 2014. Of the 68 patients assessed for efficacy in Arm 1 (B cell malignancies) as of 28 February 2014, 55 patients (81%) had partial responses (14 patients, 21%), minimal responses (6 patients, 9%), or stable disease (35 patients, 51%). A total of 13 patients (19%) had progressive disease. These data are summarized in the table below.

**Best Responses in Patients with B Cell Malignancies in KCP-330-001 as of 28 February 2014**

| Cancer Type | Number of Patients Evaluated | Total PRs, MRs and SD (%) | PR (%) | MR (%) | SD (%) | PD (%) |
|---|---|---|---|---|---|---|
| Multiple Myeloma | 28 | 22 (79%) | 1 (4%) | 4 (14%) | 17 (61%) | 6 (35%) |
| CLL | 4 | 4 (100%) | 2* (50%) | -- | 2 (50%) | -- |
| Richter's Transformation | 4 | 3 (100%) | 1 (25%) | -- | 2 (50%) | 1 (25%) |
| Other types | 1 | 1 (100%) | -- | -- | 1 (100%) | -- |
| **Non-Hodgkin's lymphomas** | | | | | | |
| Diffuse Large B Cell Lymphoma | 18 | 13 (72%) | 5 (28%) | -- | 8 (44%) | 5 (28%) |
| Follicular Lymphoma | 6 | 6 (100%) | 1 (17%) | -- | 5 (83%) | -- |
| Mantle Cell Lymphoma | 2 | 2 (100%) | 1 (50%) | -- | 1 (50%) | -- |
| Transformed DLBCL | 3 | 1 (33%) | 1 (33%) | -- | -- | 2 (67%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Waldenstrom's Macroglobulinemia | 3 | 3 (100%) | 1 (33%) | 2 (67%) | -- | -- |
| **Total** | **68** | **55 (81%)** | 14 (21%) | 6 (9%) | 36 (51%) | **13 (19%)** |

Abbreviations: PR=partial response, MR=minimal response, SD=stable disease, PD=progressive disease, NE=not evaluable, WC=withdrew consent. *These PRs in CLL patients refer to Lymph Node responses only.

In summary, this early analysis has also demonstrated tolerability and preliminary signals of response in the hematologic malignancies population (unpublished data Karyopharm). Constitutional symptoms of weight loss, fatigue, and anorexia were common but can be prevented or mitigated using aggressive prophylactic supportive measures.

## 2.10 Rationale for the Study

Although ibrutinib has shown significant efficacy in CLL and NHL as a single agent, relapses have occurred via binding site mutations and certain subgroups of each disease continue to lag in PFS. Additionally, this treatment requires continuous treatment and does not produce complete remissions. Thus, efforts to diminish the frequency of ibrutinib relapse and also increase the depth of remission with combination based therapies is a priority moving forward in the field of CLL and NHL. In both CLL and NHL the importance of BTK as a true therapeutic target has been genetically, pharmacologically, and clinically validated. Preclinical and clinical data have shown that CLL and NHL are susceptible to single-agent cytotoxicity by selinexor. Selinexor has been shown to inhibit the BCR pathway in an alternate way than ibrutinib by depleting BTK protein level, which provides rationale to combine these drugs. Indeed, targeting a kinase/protein/pathway in two or more different ways is a classic pharmacologic strategy to prevent emergence of drug resistance. In phase I clinical trials in this population, selinexor has shown tolerability and early signals of clinical efficacy. Ibrutinib which is approved for NHL and CLL has similar promising results. We hypothesize the combination will be active and tolerable in this population and want to proceed with phase I investigation. Ultimately, we anticipate this approach moving to larger randomized phase II trials comparing the combination treatment to monotherapy with ibrutinib.

## 2.11 Rationale for the Dose/Dosing Schedule

Recent analysis of the existing PK data from Phase 1 trials KCP-330-001 and KCP-330-002 supports the use of fixed rather than BSA-based dosing. The 5$^{th}$ and 95$^{th}$ percentile for BSA values encountered to date in Phase 1 trials KCP-330-001 and KCP-330-002 are 1.5 and 2.3 $m^2$, respectively (N=331). PK values ($C_{max}$ and $AUC^{(0-\infty)}$) for a given flat (fixed) dose of selinexor were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA.

In Phase I study, the lowest dose that selinexor inhibits XPO1 completely for ~24 hours is 12mg/$m^2$ (about 20 mg) on a 10 doses per cycle schedule, however, prolonged inhibition of XPO1 mRNA were observed at doses >23 mg/m2, allowing twice weekly dosing. Therefore, 40 mg weekly will be our lowest dose administered, with goals to use twice weekly dosing if

tolerated. The phase I study has reached a dose level of 60mg/$m^2$ twice weekly, and our proposed study's top dose level (100 mg twice weekly) is equivalent to this dose. We are starting at this lower dose of selinexor to assure tolerability of the combination.

The starting dose of 420 mg of ibrutinib for CLL patients is based on the standard recommended dosing from the phase II study of patients with relapsed/refractory CLL. In this study, correlative analyses demonstrated a greater than 90% occupancy of the pharmacodynamics BTK probe and similar response rates between the groups that received 420 mg and 840 mg, which provided support for the use of the 420 mg dose in CLL patients[8].

The starting dose of 560 mg of ibrutinib for NHL patients is based on the standard recommended dosing from the phase I study of patients with relapsed/refractory lymphoid malignancies. In this trial, pharmacodynamic studies indicated that a fixed continuous dose of 560mg daily led to full BTK occupancy in a range of individual body weights and was well tolerated, leading to the selection of this dose for phase II studies[13].

## 2.12 Correlative Studies Background

We plan to evaluate the inhibition of the B-cell receptor signaling pathway via assessment of phosphorylation of BTK, PLc$_\gamma$, AKT, and ERK in patients with relapsed or refractory CLL who receive the combination of selinexor and ibrutinib. In primary CLL cells, ibrutinib has been shown to inhibit these components of the B-cell receptor signaling pathway[12]. In CLL patient samples with unmutated IgVH status, XPO1 inhibition with selinexor prevents CpG-induced phosphorylation of ERK and AKT, thereby preventing expression of cMyc and cyclin A2 and downstream proliferation of these CLL cells. Selinexor induced BTK downmodulation in CLL cells. Selinexor abrogated phosphorylation of AKT and ERK in primary CLL cells, possibly through targeted inhibition of AKT or ERK pathways[40]. Evaluation of B-cell receptor pathway inhibition in patients on this trial will provide evidence for potential drug synergy or interactions.

We plan to evaluate the change in localization of tumor suppressor proteins in patients with relapsed or refractory CLL following treatment with selinexor with the aid of confocal microscopy and immunoblot of downstream targets of these proteins (NFKB, Mcl1, Tcl1, BTK, p21, BCLxL, cMyc). As selinexor inhibits the exportation of nuclear tumor suppressor proteins[40], this correlative study will allow exploratory investigation of potential drug interactions on this clinical trial.

Baseline characteristics of tumor samples, plasma and microenvironment will be assessed at baseline to preliminary examine for features of primary resistance. For patients who respond to therapy and then relapse, we will characterize the features of resistance to ibrutinib and selinexor. As both of these are irreversible inhibitors, we will focus on the primary target (BTK, XPO1) and also down-stream molecules (PLCγ2) . We will also take a more global approach through examination of next generation sequencing methods examining the genome, transcriptome, and epigenetic changes from baseline samples to those obtained at relapse. Expression and biochemical studies of pathways of resistance will also be pursued. For CLL this will be done on blood, bone marrow aspirate, and lymph nodes (when available). For NHL, this

will be examined predominately from nodal material (including archival material if available from previous biopsy) along with blood/marrow if positive for NHL. Buccal swabs or other germ line material (marrow fibroblasts, saliva) will be collected for interpretation of next generation sequencing data differentiation of SNP versus acquired mutations.

We also plan to characterize plasma pharmacokinetics of selinexor and steady-state plasma concentrations of ibrutinib. We will compare selinexor pharmacokinetics (full 24-hour profiles) in the absence and presence of ibrutinib, and we will compare ibrutinib steady state concentrations with historical data to identify any significant differences in pharmacokinetics since there is a small potential for drug-drug interactions via CYP3A4/5. We will also characterize concentration vs. time of selinexor in white blood cells. These cells will be obtained from samples collected at the same time points as the plasma pharmacokinetic samples for selinexor. Given KPT-330 chemically reacts with glutathione and may also be metabolized to form glutathione and glucuronide conjugates, we hypothesize intracellular conjugation will vary among patients, and intracellular selinexor exposures will better correlate with pharmacodynamic measures and clinical response to this agent relative to plasma exposures. In addition to selinexor, we will also measure and pseudo-quantify selinexor hydroxylated and conjugated (glutathione and glucuronide) metabolites. The ratio of intracellular metabolites to parent drug may be expected to be higher at baseline or to increase during the first few weeks of combined therapy for patients less sensitive or resistant to selinexor.

A single whole blood sample or lymph node aspirate and buccal swab will be obtained for DNA extraction. DNA will be extracted and stored for potential analysis later if patients relapse on therapy or if relevant pharmacogenetic questions arise during clinical development of selinexor.

## 3. PATIENT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Patients must have:

- A histologically confirmed diagnosis of CLL/SLL/B-cell PLL according the International Workshop on CLL/SLL/B-cell PLL or variant of these [IWCLL[14] or World Health Organization (WHO) Criteria] and meet criteria for treatment or have need for cytoreduction for stem cell transplantation or alternative cell therapy.

*OR*

A histologically confirmed diagnosis of mantle cell lymphoma (MCL) or diffuse large B-cell lymphoma (DLBCL) de novo or in the setting of transformation from an indolent lymphoma (including DLBCL not otherwise specified) according to the World Health Organization criteria for diagnosis of NHL.

*AND*

- Patients must have received at least one prior therapy for CLL or NHL, need additional treatment (or have need for cytoreduction as mentioned above), and meet criteria for relapsed or refractory disease. They may not be a candidate for curative therapy. **Relapsed disease** is defined as a patient who previously achieved a CR or a PR, but after a period of six or more months demonstrates evidence of disease progression. **Refractory disease** is defined as progression within six months of the last anti-leukemic or anti-lymphoma therapy, or any response less than a CR or PR.

*EXCEPT*

- Patients in Cohort 3 (selinexor added to ibrutinib for patients receiving frontline therapy) must be receiving ibrutinib as their initial therapy for CLL or SLL. These patients must have been receiving ibrutinib for at least 1 year before enrollment

3.1.2 Patients must be ≥ 18 years of age.

3.1.3 Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of < 2. (See Appendix A.)

3.1.4 Patients with NHL must have objective, documented evidence of disease prior to study entry.

3.1.5 Patients must have normal organ function defined as:

- Platelet count ≥ 50,000/$mm^3$ in the absence of bone marrow involvement; patients with bone marrow involvement only require a platelet count of ≥ 30,000/$mm^3$
- Absolute neutrophil count ≥ 1000/$mm^3$ in the absence of bone marrow involvement; patients with bone marrow involvement are not required to have a minimum absolute neutrophil count
- Creatinine clearance [as calculated by Cockroft Gault equation=(140-age) * Mass (kg)*(0.85 if female)/(72 * creatinine mg/dL] ≥ 30mL/min
- AST/ALT < 2.5 times upper limit of normal (ULN)
- Total bilirubin ≤ 2.0 x ULN.

3.1.6 Female patients capable of reproduction and male patients who have partners capable of reproduction must agree to use an effective contraceptive method during the course of the study and for -1 month following the completion of their last treatment. 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.

3.1.7 Female of childbearing potential must have a negative serum β-Hcg pregnancy test result within 3 days of first study dose. Female patients who are surgically sterilized or who are > 45 years old and have not experienced menses for > 2 years may have β-Hcg pregnancy test waived.

3.1.8 Patients with a history of hepatitis B (surface antigen or core antibody positive and PCR positive) must take lamivudine or equivalent drug during study therapy and for one year after completion of all therapy. Patients on IVIG who are core antibody positive but PCR negative are not mandated to take prophylaxis.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.1.10 Patients enrolled into cohort 3 must have high-risk disease with higher risk of relapse on ibrutinib. This includes patients with complex karyotype (3 or more cytogenetic abnormalities) or high/very high risk by CLL-IPI (https://www.mdcalc.com/international-prognostic-index-chronic-lymphocytic-leukemia-cll-ipi)

## 3.2 Exclusion Criteria

3.2.1 Patients who are concurrently receiving any other investigational agents.

3.2.2 Patients who have received:
-Radiation or chemotherapy ≤ 4 weeks,
-Mitomycin C, nitrosureas, or radio-immunotherapy ≤ 6 weeks, or
-Immunotherapy or targeted therapy (such as kinase inhibitors) ≤2 weeks prior to cycle 1 day 1. Patients who are on ibrutinib at study entry are not required to discontinue ibrutinib for any period of time.
Palliative steroids for disease related symptoms are allowed as long as dose is tapered down to an equivalent of ≤ 10mg of oral prednisone daily on cycle 1 day 1.

3.2.3 Patients who have underwent autologous or allogeneic stem cell transplant ≤ 4 weeks prior to cycle 1 day 1 or have active graft-versus-host disease are excluded.

3.2.4 Patients unable to swallow tablets or capsules, those with uncontrolled vomiting or diarrhea or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine

3.2.5 Patients who are 20% below their ideal body weight (BMI calculator can be found at http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html)

3.2.6 Patients must not be receiving systemic anticoagulation with warfarin. Patients must be off warfarin for 30 days prior to enrollment. Patients who require anticoagulation with an agent other than warfarin will not be excluded, but must be reviewed by the principal investigator prior to enrollment.

3.2.7 As ibrutinib is extensively metabolized by CYP3A4/5, and patients must not require continued therapy with a strong inhibitor or inducer of CYP3A4/5. See Appendix B for a list of these medications.

3.2.8 Patients with active HIV or Hepatitis C. (HIV-positive patients on combination antiretroviral therapy or Hepatitis C-positive patients on antiviral therapy are ineligible because of the potential for pharmacokinetic interactions with ibrutinib or selinexor. In addition, HIV patients are at increased risk of lethal infections when treated with potentially marrow-suppressive therapy.)

3.2.9 Patients with secondary malignancy that requires active systemic therapy that will interfere with interpretation of efficacy or toxicity of selinexor. (Note: Patients with basal or squamous skin carcinoma, cervical carcinoma in situ, localized breast cancer requiring hormonal therapy or localized prostate cancer (Gleason score <5 are allowed).

3.2.10 Patients with active known central nervous system (CNS) involvement of CLL or lymphoma. (Patients with history of CNS CLL or lymphoma now in remission are eligible for the trial.)

3.2.11 Patients who are pregnant or breast feeding. (Pregnant women are excluded from this study because it is unknown if selinexor has teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with selinexor, breastfeeding should be discontinued if the mother is treated with selinexor.)

3.2.12 Patients must have recovered all toxicities from prior therapy or radiation to grade 1 or less (excluding alopecia).

3.2.13 Patients may not have had major surgery within 10 days of enrollment, or minor surgery within 7 days of enrollment. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration of a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.

3.2.14 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.15 Patients enrolling in Cohort 3 must not have ongoing Grade 3 or higher toxicity due to ibrutinib at study entry (except hypertension that is medically managed).

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

For subsite patients, sites must send the signed consent form, documentation of the consent process, and the Screening Form (refer to Supplemental Forms Document) within 2 business days of initial consent.

Patients will be registered after meeting all entry requirements, clearance by the Protocol Coordinator, and signing of the informed consent.

OSU patients will be registered by the OSU research coordinator, as per their standard practice.

Subsite patients will have eligibility verified and will be entered on study centrally at the Ohio State University by the Multi-Center Trial Program (MCTP_. All subsites must email the MCTP to verify slot availability prior to consenting patients. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the MCTP:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form
- Signed Patient HIPAA Authorization Form
- Consent Documentation Note

- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria
    - Note: every inclusion and exclusion criteria must be documented in the patient's medical record (emails or other notes outside the medical record will not be considered source documentation)

Upon receipt of registration documents, the MCTP will send an email confirmation of receipt. If confirmation of receipt is not received within 1 hour of submission, please call or page the MCTP.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the MCTP will:

- Register the patient on the study
- Fax and/or e-mail to the subsite the completed Registration Form with the assigned study ID as confirmation of patient registration

Following registration, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator and MCTP as soon as possible. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled, after discussion with the PI and MCTP.

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the MCTP.

# 5. TREATMENT

## 5.1 Overview

The study will enroll patients with CLL and NHL in a dose escalation and subsequent expansion. First, patients with relapsed or refractory disease will be enrolled in a dose finding study that will assign doses for each patient using a modified continuous reassessment method using software developed by Piantadosi (Modified Continual Reassessment Method, version 4.0). Up to 10 patients with CLL and 10 patients with NHL will be treated at the estimated MTD as part of the expansion.

In August 2016 after 2 patients were treated at dose level 2 for 1 cycle, both reported significant fatigue and anorexia. While not technically DLT, these AEs were concerning to the investigators, and after discussion with the DSMC it was decided to return to dose level 1 for continued expansion. This was discussed with Karyopharm, who reported increased tolerability

and efficacy using once weekly dosing strategies in other studies.

Cohort 3, which will initiate after the dose escalation and expansion, will add selinexor administered weekly (days 1, 8, and 15 of each cycle) at 40 mg PO, to patients receiving ibrutinib as frontline therapy for at least 12 months. Selinexor plus ibrutinib will be administered for 14 cycles, with discontinuation of selinexor after 14 cycles. At the end of 14 cycles, patients who achieve a minimal residual disease (MRD) negative response may have both drugs discontinued at the discretion of the treating physician. Patients who are MRD positive at the end of 14 cycles will discontinue selinexor and are recommended to continue ibrutinib.

## 5.2 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| Agent | Precautions | Dose | Route | Schedule | Cycle Length |
| Ibrutinib | Take with 8 oz of water, 30 min before meal | Capsule or tablet* | Oral | Cycle 1 Days 8-28**, Cycles 2+ Days 1-28 | 28 days (4 weeks) |
| Selinexor | Take with at least 120 mL (4 ounces) of fluids (water, juice, etc.) | Tablet* | Oral | Days 1, 8, and 15 of each cycle* | |
| *Doses/schedule as appropriate for assigned dose level.<br>**Patients continuing on ibrutinib should take ibrutinib days 1-28 of Cycle 1 | | | | | |

| **Dose Level** | **Selinexor Dose** | **Selinexor Schedule** | **Ibrutinib Dose** | **Ibrutinib Schedule** |
|---|---|---|---|---|
| 1* | 40 mg | Weekly (oral) | 420 mg | Daily (oral) |
| 2 | 20 mg | Bi-weekly (oral) | 420 mg | Daily (oral) |

### 5.2.1 Study Drugs Description

5.2.1.1 Selinexor is an oral selective inhibitor of nuclear export.

Selinexor is 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.

5.2.1.2 Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase. The compound is manufactured by Pharmacyclics, Inc (Sunnyvale, CA) using methods in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of antineoplastic agents for human use.

5.2.2 Drug Products Composition and Preparation

5.2.2.1 Selinexor

Selinexor will be supplied in 20 mg tablets in wallet-sized blister packs (12 tablets per blister pack). Each wallet-size blister package of selinexor tablets will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada, EMA, etc. Blister packages for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws.

5.2.2.2 Ibrutinib

Ibrutinib for oral administration is supplied as either capsules or tablets. The capsules are hard gelatin capsules containing micronized ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are manufactured as 140mg in a size 0, gray, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 capsules. Ibrutinib capsules are to be dispensed in their original containers. The tablet formulation is manufactured as 140, 280, or 420 mg and is dispensed as a blister pack.

5.2.3 Selinexor Administration

Each dose will consist of selinexor tablet(s) for oral administration on a fixed dose basis. Dose levels for the study are 40 mg once weekly and 20 mg twice weekly. If needed, the level (-1) de-escalation dose level will be 20 mg weekly. Selinexor oral doses are given Days 1, 8, and 15 of each 28 day cycle.

Selinexor tablets are to be taken with at least 120 mL (4 ounces) of fluids (water, juice, etc.) at approximately the same time each day. Selinexor tablets should not be crushed because of increased risk of dermatologic toxicity if the powder comes in contact with skin.

### 5.2.4 Ibrutinib Administration

Ibrutinib should be taken with 8 ounces (approximately 240 mL) of water (avoid grapefruit or Seville orange juice due to CYP450 3A4 inhibition). Each dose of ibrutinib should be taken at least 30 minutes before meal, at approximately the same time each day. The capsules or tablets should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be reported at the next scheduled visit.

Ibrutinib should be held for any procedure using the following guidelines:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (i.e. such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

### 5.2.5 Patient Compliance and Replacement

To the extent possible, patients must strictly follow the standard dosing schedule. Patients who miss 2 of the doses of selinexor or 1/4 of the doses of ibrutinib within the first cycle of treatment in the absence of study drug related toxicity will be discontinued unless these are consecutively missed doses due to a required medical procedure that is unrelated to study drug or an anticipated personal emergency, in which case they should restart the cycle.

Compliance to study medication will be ascertained by use of patient diaries for the days where patient administers the study drug themselves at home and for the drug administration days in the clinic, compliance to study medication will be done by the investigator or delegate and recorded in source documents. The date, time and number of capsules or tablets consumed will be recorded as per study drug schedule. The principal investigator or the designee will account for the number of capsules or tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the case report form and drug accountability logs for verification with the reasons. The investigator / designee will try to ensure complete compliance

with the dosing schedule by providing timely instructions to the patients. Patients withdrawn in cycle 1 because of non-compliance not related to study drug related toxicity will be replaced.

### 5.3 Definition of Dose Limiting Toxicity

CTCAE version 4.0 is used to grade all adverse events and to provide management guidelines for administrational toxicity. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

| **Definition of DLT for patients receiving selinexor and ibrutinib*** |
|---|
| **General** |
| • Treatment delays >28 days for any toxicity<br>• Any grade 5 toxicity |
| **Non-hematologic** |
| • Grade 3 nausea/vomiting or diarrhea lasting for ≥7 days while taking optimal supportive medications#<br>• Grade 3 anorexia or fatigue lasting for ≥7 days while taking optimal supportive care# and with correction of dehydration, anemia, endocrine, or electrolyte abnormalities<br>• Grade ≥ 3 AST or ALT elevation lasting for ≥7 days OR any Grade ≥ 3 AST or ALT elevation in the setting of bilirubin elevation > 2x ULN<br>• Any other Grade 3 non-hematological toxicity except alopecia, rash that resolves to Grade 1 in ≤ 7 days, or electrolytes abnormalities correctable with supportive therapy#<br>Any Grade 4 non-hematologic toxicity not specifically listed above |
| **Hematologic** |
| • Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm$^3$] (for patients with baseline ANC ≥ 1000/mm$^3$) or ≥ 75% reduction of neutrophils (for patients with baseline ANC < 1000/mm$^3$) lasting ≥7 days;<br>• Grade 4 thrombocytopenia [platelet count <25,000/mm$^3$] (for patients with baseline platelets ≥ 100,000/mm$^3$) ≥ 75% reduction of platelets (for patients with baseline platelets < 100,000/mm$^3$) that persists for ≥7 days;<br>• Grade ≥ 3 thrombocytopenia-associated bleeding; or<br>• Grade 4 febrile neutropenia (ANC < 1000/mm$^3$ with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour). |
| *Assessed during Cycle 1 by CTCAEv4 criteria #Section 4.4 provides detailed supportive care ^For patients with Gilbert's syndrome: >2X baseline |

AEs meeting the above definitions but that are clearly unrelated to study drugs will not be considered DLTs.

Patients will be considered eligible for DLT assessment if they receive at least 2 of 3 planned doses of selinexor and 19 of 21 planned doses of ibrutinib.

In rare instances, an event may fall within the definition of a DLT as defined above, but the event may not be considered a DLT (ie: not clinically meaningful/significant). If this occurs, a meeting

with all investigators, PI and Sponsor will take place to thoroughly review the event and supporting data and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. Conversely, other events may occur which do not meet the definition of a DLT but are concerning to the investigators and sponsor and may be then considered to be DLTs. We will also consult the DSMC team for input.

Management and dose modifications associated with the above adverse events are outlined in Section 5.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

## 5.4 Concomitant Medications

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

5.4.1.1 Permitted Concomitant Medications

## 5.5 Prevention of Pregnancy

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 - one month following the last dose.

## 5.6 Blood Products

During the administration of selinexor and ibrutinib, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. These transfusions should be leukopore filtered and irradiated. Patients who require repeated transfusion support should be discussed with the principal investigator.

Patients may receive supportive care with G-CSF or GM-CSF in accordance with institutional guidelines prior to entry and throughout the study.

## 5.7 Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drug should be held for 3-5 days before the start of palliative radiation therapy and 3-5 days after

palliative radiation therapy. Treatment with selinexor and ibrutinib shall not be discontinued solely due to palliative radiation. Additionally for patients responding to this treatment, if local radiation to a secondary cancer (prostate, skin, DCIS, etc.) is required, this can be considered after discussion with the PI.

## 5.8 Glucocorticoid Therapy

Glucocorticoids ≤ 10 mg oral prednisone (or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma, IBD, etc.) as needed.

As part of supportive care (e.g. for nausea or anorexia), oral or parenteral dexamethasone, up to 30 mg/week, may be given to patients, in consultation with the principal investigator. Doses of 2-4mg po qd, or 10mg with each dose of selinexor, can reduce fatigue, increase appetite, and improve energy in patients on study.

## 5.9 Anti-diarrheal Medications

Over-the-counter anti-diarrheal medications (such as loperamide or equivalent) may be used by the patient to control loose stools associated with the study medications. The medications should be used as directed by the package insert, pharmacist or treating physician.

## 5.10 General Medications

Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

## 5.11 Procedures

Refer to section 5.2.4 for guidelines on holding ibrutinib for procedures.

5.11.1.1 Prohibited Concomitant medications

Patients should minimize the use of products containing Acetaminophen. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted.

## 5.12 Anticancer Therapy

Concurrent therapy with a systemic approved or investigative anticancer therapeutic, other than glucocorticoids as specified herein, is not allowed (this includes bone marrow transplantation for any reasons). Hormonal therapy is permitted.

## 5.13 Investigational Agents

Other investigational agents should not be used during the study.

### 5.14 Drugs undergoing Glutathione conjugation

The primary metabolism of selinexor *in vitro* appears to inactivation by glutathione conjugation. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. In vitro studies using human liver microsomes confirm in vivo findings that selinexor undergoes minimal CYP450 metabolism. Therefore, administration of selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen (paracetamol). It should be noted that no studies selinexor in combination with acetaminophen have been performed to date and that these recommendations are empirical. There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen use must not exceed a total daily dose of 1 g.

### 5.15 Drugs that inhibit or induce CYP 3A4/5

Because there is a potential for interaction of ibrutinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix B presents guidelines for identifying medications/substances that could potentially interact with ibrutinib.

### 5.16 Warfarin

Patients who must receive systemic anticoagulation with warfarin will be excluded secondary to severe bleeding when ibrutinb and warfarin have been used concurrently. Patients must be off warfarin for 30 days prior to enrollment. If individuals develop a DVT or other complications requiring anticoagulation, low molecular weight heparin or thrombin inhibitors may be used. Ibrutinib should be held for a minimum of 7 days to assure acceptable tolerance of this treatment. For patients with low risk atrial fibrillation, aspirin (325 mg/day) is recommended unless the patient is at high risk for thromboembolic complications.

### 5.17 Concomitant Treatments for Selinexor

Dexamethasone (12 mg) will be given as a concomitant medication with each dose of selinexor. For patients with partial intolerance to glucocorticoids, a minimum dose of 8 mg dexamethasone is permitted. Patients who are tolerating selinexor well may have the dose of dexamethasone decreased or eliminated at the discretion of the treating physician. Dexamethasone, like the other recommended prophylactic treatments in this study, is an approved drug. It will be provided in tablet form by prescription from the treating physician and obtained from the clinic pharmacy.

Required 5-HT3 Antagonists: In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 Antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued bid – tid prn.

## 5.18 Supportive Care Guidelines for selinexor

**TABLE: SUPPORTIVE CARE AND SELINEXOR DOSE ADJUSTMENT GUIDELINES FOR AES RELATED TO SELINEXOR[A,B]**

| Toxicity and Intensity | Supportive Care and Dose Adjustment Guidelines |
|---|---|
| **Fatigue** | |
| Grade 1 | Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8 g/dL (anemia Grade <3).<br>Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. |
| Grade 2 lasting ≤7 days | As per the NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. |
| Grade 2 lasting >7 days or<br>Grade ≥3 | Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for Hb <8 g/dL (Grade ≥3). Interrupt selinexor dosing until resolved to Grade 1 or baseline.<br>For first occurrence, restart selinexor at current dose.<br>For ≥ second occurrence, reduce selinexor by 1 dose level.<br>Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.<br>As per the NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only. |
| **Anorexia or Weight loss** | |
| Grade 1 anorexia | Maintain dose. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®).<br>For persistent symptoms, start appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), per NCCN guidelines. |
| Grade1 weight loss<br>Grade 2 anorexia | Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines. |
| Grade 2 weight loss<br>Grade 3 anorexia,<br>or Grade 3 weight loss | Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level.<br>Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®)<br>Start appetite stimulants as above, |

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

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

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

1. **[A]FOR ALL GRADE ≥3 HEMATOLOGIC OR NON-HEMATOLOGIC AES THAT ARE NOT SELINEXOR RELATED, AFTER CONSULTATION WITH THE MEDICAL MONITOR AND AT THE DISCRETION OF THE INVESTIGATOR, SELINEXOR DOSING MAY BE MAINTAINED.**
2. **[B]FOR ALL SELINEXOR-RELATED AE'S, IF THE BELOW PRESCRIBED DOSE REDUCTIONS/INTERRUPTIONS RESULT IN A STABILIZATION OF ≥4 WEEKS, A RE-ESCALATION MAY BE CONSIDERED AFTER APPROVAL FROM THE MEDICAL MONITOR.**
3. **ALL DOSE MODIFICATIONS SHOULD BE BASED ON THE WORST PRECEDING TOXICITY.**
4. **NOTE: WHEN TOXICITIES DUE TO SELINEXOR HAVE RETURNED TO BASELINE LEVELS OR THE PATIENT HAS STABILIZED, THE DOSE OF SELINEXOR MAY BE RE-ESCALATED IN CONSULTATION WITH THE MEDICAL MONITOR.**

## 5.19 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patients enrolled in Cohort 3 will discontinue therapy in a response-adapted manner. All patients will discontinue selinexor after 14 cycles. Patients who achieve a MRD negative CR at 14 cycles will discontinue both selinexor and ibrutinib. Patients who achieve a MRD – PR will discontinue both selinexor and ibrutinib at discretion of treating physician. Patients with any other response are recommended to continue ibrutinib indefinitely.

### 5.20 Duration of Follow Up

Patients will be followed every 6 months until progression or an alternative therapy is started. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Follow-up data will be required unless consent is withdrawn.

### 5.21 Criteria for Removal from Treatment

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

- Death,
- Disease progression,
- Noncompliance with study procedures,
- Intercurrent illness that prevents further administration of treatment,
- Need of treatment with medications not allowed by the study protocol,
- Unacceptable adverse event(s),
- Other treatments become available,
- Treatment delays exceeding 28 days,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Patients who are removed from protocol therapy will still be followed for progression and survival.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Toxicities that occur in cycle 1 that are DLTs (Section 4.2) will result in protocol removal. Adverse events that are not defined as DLTs and / or occur in cycles 2 and higher will lead to dose delays and modifications as detailed below. No dose reduction below ibrutinib 140 mg and selinexor 20 mg/week will be allowed. If a patient experiences several adverse events, and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level. Missed doses will not be replaced. Treatment delays for adverse events exceeding 28 days will lead to protocol removal unless approved by the principal investigator.

Ibrutinib-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared with baseline count in conjunction with unequivocal improvement in at least 1 other disease-related parameter including lymph node size, spleen size,

hematologic parameters (hemoglobin or platelets), or disease-related symptoms. Ibrutinib-associated treatment-related lymphocytosis generally occurs within the first few weeks of therapy, peaks within the first few months, and resolves slowly. Patients with isolated lymphocytosis in the setting of reduced disease burden or improvement in hemoglobin/platelets should not be considered to have progressive disease.

Asymptomatic treatment-related lymphocytosis should not be considered an adverse event. Subjects with treatment-related lymphocytosis in the absence of other disease-related symptoms should be encouraged to remain on study treatment and continue with all study-related procedures.

### 6.1 Dose adjustment guidelines for hematologic ibrutinib or selinexor-related toxicities

Toxicities that are clearly not related to ibrutinib or selinexor will not require a dosing modification. Similarly, toxicities that are clearly attributable to an individual drug will only require modification of that drug, with modifications following the tables below.

| **Event Name** | **Neutropenia, Anemia, or Thrombocytopenia For Patients with Baseline Absolute Neutrophil Count ≥ 1000/mm$^3$; Hemoglobin ≥ 11g/dL; or Platelets ≥ 100,000/mm$^3$** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib* | Management/Next Dose of Selinexor* |
| < Grade 3 | No change in dose | No change in dose |
| ≥ Grade 3 | Hold until neutrophils, hemoglobin, or platelets have returned to < Grade 3.<br>• 1st occurrence: No change in dose<br>• 2nd occurrence: Cohort 1 and 3= No change in dose; Cohort 2 = Decrease ibrutinib to next lowest dose level<br>• 3rd occurrence: Decrease ibrutinib to next lowest dose level<br>• 4th occurrence: Patient comes off study | Hold until neutrophils, hemoglobin, or platelets have returned to < Grade 3.<br>• 1st occurrence: No change in dose<br>• 2nd occurrence: Decrease selinexor to next lowest dose.<br>• 3rd occurrence: No change in dose<br>• 4th occurrence: Patient comes off study |
| *Dose reductions < ibrutinib 140mg daily or selinexor 20 mg weekly are not permitted.<br>Recommendations:<br>-Full supportive care, growth factors, and transfusions should be given as medically indicated.<br>- If the patient tolerates a reduced dose for two cycles, patient may be dose escalated to the dose they received prior to the reduction after authorization from Principal Investigator. | | |

| **Event Name** | **Neutropenia, Anemia, or Thrombocytopenia For Patients with Baseline Absolute Neutrophil Count ≤ 1000/mm$^3$; Hemoglobin ≤ 11g/dL; or Platelets ≤ 100,000/mm$^3$** |
|---|---|

| Grade of AE | Management/Next Dose Ibrutinib* | Management/Next Dose of Selinexor* |
|---|---|---|
| <Grade 3 | No change in dose | No change in dose |
| ≥ Grade 3 | Hold until neutrophils, hemoglobin, or platelets have returned to within 50% of pretreatment values. If initial value is within 50% of pretreatment value, no hold is needed.<br>• 1st occurrence: No change in dose<br>• 2nd occurrence: Cohort 1 and 3= No change in dose; Cohort 2 = Decrease ibrutinib to the next lowest dose level.<br>• 3rd occurrence: Decrease ibrutinib to the next lowest dose level.<br>• 4th occurrence: Patient comes off study | Hold until neutrophils, hemoglobin, or platelets have returned to within 50% of pretreatment values. If initial value is within 50% of pretreatment value, no hold is needed.<br>• 1st occurrence: No change in dose. Initiate granulocyte colony-stimulating factors for grade >3 neutropenia.<br>• 2nd occurrence: Decrease selinexor to next lowest dose.<br>• 3rd occurrence: No change in dose<br>• 4th occurrence: Decrease selinexor to the next lowest dose<br>• 5th occurrence: No change in dose<br>• 6th occurrence: Discontinue selinexor |
| *Dose reductions < ibrutinib 140mg daily or selinexor 20 mg weekly are not permitted.<br>Recommendations:<br>-Full supportive care, growth factors, and transfusions should be given as medically indicated.<br>- If the patient tolerates a reduced dose for two cycles, patient may be dose escalated to the dose they received prior to the reduction after authorization from Principal Investigator. | | |

| **Event Name** | **Bleeding** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib* | Management/Next Dose of Selinexor* |
| ≤ Grade 2 (mild to moderate) | Hold ibrutinib for at least 7 days after last bleeding and until platelets return to ≥ 50% of baseline value.<br>• 1st occurrence: Restart ibrutinib at next lowest dose level. In cases where no bleeding is observed after 6 days of dosing return to full dose at the physician's discretion.<br>• 2nd occurrence: Restart ibrutinib at next lowest dose level.<br>• 3rd occurrence: Patient comes off study. | Hold selinexor for at least 7 days after last bleeding and until platelets return to ≥ 50% of baseline value.<br>• 1st occurrence: Restart selinexor at next lowest dose level. In cases where no bleeding is observed after 6 days of dosing return to full dose at the physician's discretion.<br>• 2nd occurrence: Restart selinexor at next lowest dose level.<br>• 3rd occurrence: Patient comes off study. |

| | | |
|---|---|---|
| ≥ Grade 3 (severe) | Hold ibrutinib for at least 7 days after last bleeding and until platelets return to ≥ 50% of baseline value.<br>• 1st occurrence: Restart ibrutinib at next lowest dose level.<br>• 2nd occurrence: Patient comes off study. | Hold selinexor for at least 7 days after last bleeding and until platelets return to ≥ 50% of baseline value.<br>• 1st occurrence: Restart selinexor at next lowest dose level.<br>• 2nd occurrence: Patient comes off study. |
| *Dose reductions < ibrutinib 140mg daily or selinexor 20 mg weekly are not permitted.<br>Recommendations:<br>-Full supportive care, growth factors, and transfusions should be given as medically indicated. | | |

| **Event Name** | **Neutropenic Fever** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib* | Management/Next Dose of Selinexor* |
| Grade 3 | Hold until toxicity ≤ Grade 2 or baseline.<br>• 1st occurrence: No change in dose.<br>• 2nd occurrence: Decrease ibrutinib to next lowest dose level.<br>• 3rd occurrence: Patient comes off study. | Hold until toxicity ≤ Grade 2 or baseline.<br>• 1st occurrence: Decrease selinexor to next lowest dose.<br>• 2nd occurrence: No change in dose.<br>• 3rd occurrence: Patient comes off study. |
| Grade 4 | Hold until toxicity ≤ Grade 2 or baseline.<br>• 1st occurrence: Decrease ibrutinib to next lowest dose level.<br>• 2nd occurrence: Decrease ibrutinib to next lowest dose level.<br>• 3rd occurrence: Patient comes off study | Hold until toxicity ≤ Grade 2 or baseline.<br>• 1st occurrence: Decrease selinexor to next lowest dose.<br>• 2nd occurrence: Decrease selinexor to next lowest dose level.<br>• 3rd occurrence: Patient comes off study |
| *Dose reductions < ibrutinib 140mg daily or selinexor 20 mg weekly are not permitted.<br>Recommendations:<br>-Full supportive care and/or growth factors should be given as medically indicated. | | |

## 6.2 Dose adjustment guidelines for non-hematologic ibrutinib or selinexor-related toxicities

Specific guidelines are provided below for non-hematologic toxicities. For all other grade 3 non-hematologic toxicities possibly related to study therapy, hold the causative agent, or if the causative agent cannot be determined, hold both ibrutinib and selinexor. Once the toxicity is improved to ≤ Grade 2 or until baseline pre-treatment value, resume treatment with a decrease in the dose of ibrutinib by 140 mg or selinexor by one dose level. No dose reduction below ibrutinib 140 mg and selinexor 20 mg/week will be allowed. If a patient experiences several adverse events, and there are conflicting recommendations, the investigator should use the

recommended dose adjustment that reduces the dose to the lowest level. Missed doses will not be replaced. Treatment delays for adverse events exceeding 28 days will lead to protocol removal.

Any Grade 4 toxicities (lasting ≥7 days for transaminase or electrolyte abnormalities) that are at least possibly attributed to selinexor or ibrutinib should result in permanent discontinuation of the causative agent. If attribution to a single drug cannot be made, both drugs should be discontinued.

| **Event Name** | **Nausea** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| Grade 1 | No change in dose | 5-HT3-antagonists, D2-antagonists or NK1 antagonists, or dronabinol or combinations can prevent nausea in the majority of patients. Consider additional anti-emetics (see the NCCN Clinical Practice Guideline for antiemesis). Provide guidance on diet as described above for anorexia as increased caloric intake may reduce nausea. |
| Grade 2 | No change in dose | Implement one or more combinations of anti-nausea medications. Consider additional anti-emetics (see the NCCN Clinical Practice Guideline for antiemesis). If Grade 2 nausea persists, reduce dose of selinexor by one dose level. If patient's nausea is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |
| Grade 3 | No change in dose | Interrupt dosing of selinexor and implement one or more combinations of anti-nausea medications. Consider additional anti-emetics (see the NCCN Clinical Practice Guideline for antiemesis). Ensure adequate caloric and fluid intake. Restart selinexor with one dose level reduction when nausea is Grade ≤ 2 and adequate caloric and fluid intake have been achieved. If patient's nausea is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |

| |
|---|
| Recommendations:<br>-Full supportive care and antiemetics. See Section 4.4.<br>- If the patient tolerates a reduced dose for two cycles, patient may be dose escalated to the dose they received prior to the reduction after authorization from Principal Investigator. |

| **Event Name** | **Vomiting** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| ≤ Grade 2 | No change in dose | No change in dose |
| Grade 3 | No change in dose | Hold until toxicity ≤ Grade 1. Decrease by one dose level. |
| Recommendations:<br>-Full supportive care and antiemetics. See Section 4.4. | | |

| **Event Name** | **Diarrhea** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| Grade 1 | No change in dose | Rule out other causes of diarrhea, including infectious agents. At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care, e.g., loperamide (Immodium®). Maintain dose level of selinexor. |
| Grade 2 | No change in dose | If diarrhea is present despite maximal anti-diarrheal medication, rule out other causes of diarrhea, including infectious agents. Reduce selinexor by one dose level until resolved to ≤ Grade 1, then re-start at the current dose level.<br>If diarrhea returns as Grade ≥ 2, then reduce selinexor dose by one dose level. If patient is stable and diarrhea resolves (Grade 0 or baseline with or without anti-diarrheals) for 4 weeks, then the patient's dose may be re-escalated |
| Grade 3 | Hold until ≤ Grade 1. Decrease ibrutinib to next lowest dose level. | If diarrhea is present despite maximal anti-diarrheal medication, rule out other causes of diarrhea, including infectious agents. Delay selinexor until |

| | | |
|---|---|---|
| | | resolved to Grade ≤2, then reinitiate selinexor at one dose level below. If patient is stable and diarrhea resolves (Grade 0 or baseline with or without anti-diarrheals) for 4 weeks, then the patient's dose may be re-escalated. |
| Recommendations:<br>-Full supportive care and antidiarrheal agents. See Section 4.4. | | |

| **Event Name** | **Fatigue** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| Grade 1 | No change in dose | Ensure adequate caloric intake and assess volume status. Recommend high calorie and/or energy drinks and/or foods. Adjust other medications. Rule out other causes of fatigue such as adrenal insufficiency, hypothyroidism, etc. |
| Grade 2 | No change in dose | Ensure adequate caloric and fluid intake and assess volume status. Add supportive care for fatigue, or reduce the dose of selinexor by one level. If patient's fatigue is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |
| Grade 3 | No change in dose | Ensure adequate caloric and fluid intake and assess volume status. Interrupt selinexor dosing until resolved to Grade ≤ 2, reduce dose of selinexor by 1 level. If patient's fatigue is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |
| Recommendations:<br>- Optimize supportive care including caloric and fluid intake. Add glucocorticoids when not contra-indicated. See Section 4.4. | | |

| **Event Name** | **Rash - Maculopapular** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib* | Management/Next Dose of Selinexor* |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume same dose. | No change in dose |

| | | |
|---|---|---|
| Grade 3 | Hold until toxicity ≤ Grade 1.<br>• 1st occurrence: Decrease ibrutinib to next lowest dose level.<br>• 2nd occurrence: Decrease ibrutinib to next lowest dose level. | Hold until toxicity ≤ Grade 1 or baseline.<br>• 1st occurrence: No change in dose.<br>• 2nd occurrence: Decrease selinexor to next lowest dose level. |
| *Dose reductions < ibrutinib 140 mg daily or selinexor 20 mg weekly are not permitted.<br>Recommendations:<br>- Review medication list and discontinue any medications that commonly cause rash if possible.<br>-Consider skin biopsy. | | |

| **Event Name** | **Thrombosis/Thromboembolic Event** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 or 3 | Hold until therapeutically anticoagulated and platelets are ≥ 50,000/$mm^3$. Resume at the same dose level. | Hold until therapeutically anticoagulated and platelets are ≥ 50,000/$mm^3$. Resume at the same dose level. |
| Recommendation: Anticoagulation (warfarin prohibited) | | |

| **Event Name** | **Hyponatremia** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| Grade 1 (Lower Limit of Normal to 130 nM) | No change in dose | Maintain selinexor dose and frequency level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, and consider salt supplementation 1-3 times per day. Correct sodium level for hyperglycemia (serum glucose >150 mg/dL). Rule out other causes of low sodium (e.g., SIADH, cardiac, hepatic, adrenal, renal, and thyroid diseases, Fanconi Syndrome, diuretic use, etc.). |
| Grade 3 (126-129 mmol/L) | No change in dose | Ensure patient is euvolemic and has sufficient fluid and electrolyte intake. Replace fluids orally or IV if patient is dehydrated. Correct sodium level for hyperglycemia. Rule out other causes of low sodium (see above for Grade 1).<br>Hold selinexor until hyponatremia |

| | | |
|---|---|---|
| | | resolves to Grade ≤1 (≥130 nM) and initiate aggressive salt supplementation 2-3 times per day. Restart at the same dose and frequency of selinexor and monitor serum sodium closely. If this recurs, measure urine sodium and creatinine levels to investigate for other causes of hyponatremia. |
| Grade 3 (120-125 mmol/L ) | No change in dose | Hold selinexor dose until sodium ≥ 125 mmol/L*. Decrease selinexor to the next lowest dose level for initial and each subsequent occurrence. |
| *If sodium does not recover to ≥ 125 mmol/L within 14 days of holding selinexor, selinexor should be permanently discontinued<br>• *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 = Measured sodium + 0.024 * (Serum glucose - 100).* | | |

| **Event Name** | **Anorexia** | |
|---|---|---|
| Grade of Event | Management/Next Dose Selinexor | |
| Grade 1 | | Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider an appetite stimulant(s) (see the NCCN Clinical Practice Guideline for anorexia). |
| Grade 2 | | Add high-calorie supplements (e.g., Ensure®). Add an appetite stimulant(s) (see the NCCN Clinical Practice Guideline for anorexia). Selinexor dosing may be interrupted intermittently while supportive medications are instituted, usually for <1 week. If Grade 2 anorexia does not resolve after institution of supportive medications, reduce selinexor dose by 1 level . If patient's anorexia is Grade |

| | | |
|---|---|---|
| | | ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |
| Grade 3 | | Interrupt dosing with selinexor until resolution to Grade ≤2. Add high calorie supplements. As described above, initiate supportive medications for anorexia. Restart selinexor at 1 dose level reduction . once anorexia resolves to Grade ≤ 2 and follow the guidelines above. If patient's anorexia is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |
| | | |

| **Event Name** | **Weight Loss** | |
|---|---|---|
| Grade of Event | | Management/Next Dose of Selinexor |
| Grade 1 | | Assess dietary options (e.g. try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). If fatigue or nausea also present, consider corticosteroids on day of and day after selinexor dosing. Consider an appetite stimulant(s) (see the NCCN Clinical Practice Guideline for anorexia and anti-emesis). |
| Grade 2 | | Add high-calorie supplements (e.g., Ensure®). Consider corticosteroids on day of and day after selinexor dosing. Consider an appetite stimulant(s) (see the NCCN Clinical Practice Guideline for anorexia and anti-emesis). Consider megesterol acetate 80-400mg daily. Consider anabolic steroids such as oxandrolone. Consider dronabinol (Marinol®). If Grade 2 weight loss does not resolve after institution of supportive medications, reduce selinexor dose by 1 level. |
| Grade 3 | | Interrupt dosing with selinexor. Add high calorie supplements. Use supportive medications from above alone or in combinations. Restart |

| | | |
|---|---|---|
| | | selinexor at 1 dose level reduction once weight loss resolves to Grade ≤2. If Grade 2 weight loss persists with supportive medications, reduce dose of selinexor by 2 levels. If patient's weight loss is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level. |

| **Event Name** | **Hypertension** | |
|---|---|---|
| Grade of Event | Management/Next Dose Ibrutinib | Management/Next Dose of Selinexor |
| Grade 1 | No change in dose | No change in dose |
| Grade 2 | No change in dose | No change in dose |
| Grade 3 | No change in dose if hypertension is medically managed. | No change in dose |
| Grade 4 | If possibly, probably, or definitely related to ibrutinib, consider holding dose until hypertension improves to baseline with medical management of hypertension. Ibrutinib can then be reinsituted at the same dose at first occurrence. At second occurrence, reduce dose to 280 mg daily. | No change in dose |

### 6.3 Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. If dialysis is implemented during selinexor treatment, then selinexor should always be given after dialysis. Selinexor tablets are to be taken with at least 120 mL (4 ounces) of fluids (water, juice, etc.) at approximately the same time each day.

### 6.4 Dose Adjustment for Infection

Patients with active uncontrolled serious or suspected serious infections (i.e. Grade 3 or higher, or Grade 2 or higher at the discretion of the treating physician) should have selinexor and ibrutinib treatment withheld until infection has clinically resolved or stabilized. Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. After the infection has resolved clinically, or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics or other anti-microbial agents for prolonged periods while re-initiating

their selinexor regimen at the discretion of the investigator. Note: selinexor has not been associated with opportunistic infections in approximately 400 patients treated as of 1 August 2014.

### 6.5 Conditions not Requiring Dose Reduction

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

- Alopecia of any grade
- Electrolytes abnormalities that are reversible with standard interventions

### 6.6 Missed or Vomited Doses

Selinexor missed doses- If the dose was missed for more than 48 hours, the dose will be skipped and the next dose will be taken as per schedule. If the dose was missed within 48 hours, then it will be replaced.

If a patient missed a full week of dosing for non-study drug related events (eg. a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced. For example, if patient missed C2D7 to C2D14, then patient will start on C2D15.

Ibrutinib missed doses- If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be reported at the next scheduled visit.

Selinexor or ibrutinib vomited doses- If a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

### 6.7 Delays, Modifications and Reintroduction

All delays, modifications, and reintroductions of selinexor or ibrutinib dosing will be made in consultation with the principal investigator.

## 7. ADVERSE EVENTS (AES): LIST AND REPORTING REQUIREMENTS

All patients must be carefully monitored for AEs, including clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug. For consistency, events are to be graded using the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If CTCAE criterion does not exist for a particular AE, the investigator should use the grade or adjectives as described below:

- Grade 1=Mild=Does not interfere with patient's usual function
- Grade 2=Moderate=Interferes to some extent with patient's usual function
- Grade 3=Severe=Interferes significantly with patient's usual function
- Grade 4=Life-Threatening=Results in a threat to life or in an incapacitating disability.

## 7.1 Definition of an Adverse Event

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

## 7.2 Recording of Adverse Events

All AE will be reported and recorded from the time of the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.
AE monitoring should be continued for at least 30 days following the last dose of study treatment (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator). AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

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

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

## 7.3 Laboratory Test Abnormalities

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

separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be recorded as an AE. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE. A Grade 3 or 4 event (severity per the current version of NCI CTCAE) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 5.11 and/or as per the Investigator's discretion.

## 7.4 Adverse Events of Special Interest

AESIs for selinexor include cataracts and acute cerebellar syndrome. All cases of cerebellar toxicity, Grade 3 or higher must be reported.

**All cases of Grade 3 or higher cerebellar toxicities** occurring in patients enrolled in the study from the informed consent signature and up to 30 days after the last drug administration, or after if related to study drug, **must be immediately reported as SAE** (even if not meeting the definition of a SAE) to the Sponsor by the investigator **within 24 hours of first knowledge of the event by study personnel**, using the SAE form provided by the Sponsor (follow reporting rules for SAE in section 13.3).

### Reporting of Cataracts

Sponsor is closely monitoring the occurrence of cataracts during treatment with selinexor as adverse events of special interest. Ophthalmic examinations are planned on regular basis to identify cataracts or worsening of existing cataracts. Any cataracts or worsening of existing cataracts has to be reported as an AE irrespectively of grade.

## 7.5 Adverse Event Severity Assessments

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

- If NCI CTCAE grading does not exist for an AE, the severity should be characterized as 'mild,' 'moderate,' 'severe,' 'life-threatening', or 'fatal' (corresponding to Grades 1 to 5) according to the following definitions:
- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.
- Life-threatening
- Fatal event.

*Severity ≠ Seriousness: The term 'severe' is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as a 'serious' AE. Grades do not define seriousness.

## 7.6 Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in Table 1.

Table 1: Classification of Adverse Events by Causality

| | |
|---|---|
| Not related | The lack of a temporal relationship of the event to the study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions |
| Related | The temporal relationship of the event to the study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions. |

## 7.7 Adverse Event Reporting

The Investigator will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance twice per year in the form of line-listings. Karyopharm will supply the cut-off dates. The line listings will contain the following information: study ID, unique subject ID, adverse event term, serious event (yes or no), onset date (complete or partial), end date (complete or partial), action taken with selinexor, causality to selinexor, event ongoing (yes or no), outcome of AE, severity CTCAE Grade (1-5), subject dosed with selinexor (yes or no), date of first dose of selinexor, preferred term (optional, system organ class (optional)

## 7.8 Serious Adverse Events

An AE is considered an SAE if at least one of the following conditions applies:

- Death was an outcome of an adverse event;
- Life threatening AE (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- A new cancer diagnosed during the study (histopathologically different from the cancer under study; and

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

abuse. Hospitalizations for elective surgery or other medical procedures that are not due to an AE are not considered SAEs. A hospitalization meeting the regulatory definition for 'serious' is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital.

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

### 7.9 Recording of Serious Adverse Events

Per the Good Clinical Practices, it is recommended that Investigator has the responsibility to record and document all SAEs occurring from the signing of the Informed Consent Form until at least 30 days after the patient has stopped study treatment.

### 7.10 Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the Karyopharm medications, occurring after the patient has signed informed consent until 30 days after the patient has stopped study treatment must be reported to the Karyopharm Pharmacovigilance within 24 hours of awareness. A Karyopharm SAE Report Form template is provided for this purpose (Appendix D). For reporting any SAE to Karyopharm Pharmacovigilance Department, a completed and signed (by the Investigator) SAE Report Form will be submitted to Karyopharm Pharmacovigilance:

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

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617 (USA)

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

An SAE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. New information, recurrences, complications, or progression of the initial SAE must be reported as follow-up to the initial report within 24 hours of the Investigator receiving the follow-up information.

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

accordance with local regulations.

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

## 7.11 Suspected Unexpected Serious Adverse Reactions

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

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

## 7.12 Procedures for Handling Special Situations

### 7.12.1 Pregnancy

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

To ensure patient safety, a pregnancy occurring while the patient is on study treatment must be reported to Karyopharm Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided Karyopharm Therapeutics Inc.

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

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence.

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

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

## 7.13 Abuse, Misuse, Medication Errors, Overdose, and Occupational Exposure

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

### 7.13.1 Overdose

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

### 7.13.2 Abuse, Misuse, or Medication Error

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

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

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

### 7.13.3 Occupational Exposure

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

All occurrences of occupational exposure with Karyopharm drug are to be reported on an SAE report form to Karyopharm pharmacovigilance regardless of whether or not an AE or SAE has

occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE report form must be submitted to Karyopharm pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible.

### 7.14 Data Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in minutes. For each dose level, the Principal Investigator, study coordinator, and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments. The Principal Investigator of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the Principal Investigator and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator will also submit a biannual progress report that will be reviewed by the committee per the DSMC plan. All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present every month to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each monthly teleconference. The minutes will be stored in the MCTP protocol files.

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with selinexor and ibrutinib can be found in Sections 7.1 and 7.2, respectively.

### 8.1 Selinexor Description/Availability

Selinexor is 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.

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 drug order forms will also be used for re-supply of study medication. Instructions for re-orders are included on the form. Requests should

be made to allow for 5-7 days for delivery. The investigator (or designee) will verify and acknowledge receipt of all study drug shipment by signing and returning all required forms.

### 8.1.1 Selinexor Composition and Preparation

Selinexor will be supplied in 20 mg tablets in wallet-sized blister packs (12 tablets per blister pack). Each wallet-size blister package of selinexor tablets will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada, EMA, etc. Blister packages for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws.

### 8.1.2 Selinexor Administration

Each dose will consist of selinexor tablet(s) for oral administration on a fixed dose basis. Selinexor oral doses are given Days 1, 8, and 15 of each 28 day cycle.

Selinexor tablets are to be taken with at least 120 mL (4 ounces) of fluids (water, juice, etc.) at approximately the same time each day. Selinexor tablets should not be crushed because of increased risk of dermatologic toxicity if the powder comes in contact with skin.

Selinexor for the study are provided by Karyopharm Therapeutics and will be labeled as per the applicable regulations. Study drug must be requested 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.

Selinexor accountability records will be maintained at each participating institution and must be available for review when requested for auditing purposes and at time of study close out.

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).

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

### 8.1.3 Drug Storage

Selinexor tablets will be stored at or below 30 ˚C (86 ˚F) in white high-density polyethylene (HDPE) bottles or in blister packs, in a locked and secured area with restricted access. Selinexor tablets can be stored at room temperature (recommended) or refrigerated, but should not be stored frozen or at freezer temperatures. Selinexor tablets are currently in on-going stability studies. The current expiry is 24 months from date of manufacture, and will be extended when further stability data becomes available. 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).

8.1.4 Accountability and Destruction of Investigational Medicinal Product

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

8.1.5 Safety Considerations

**Anorexia/Weight Loss**

Selinexor treatment can cause reduced food (caloric) intake and concomitant weight loss. Patients should be advised to monitor their weight carefully, and to try different foods in order to maintain a healthy caloric intake. See Section 4.4 and 4.5 for detailed supportive care recommendations for anorexia.

**Fatigue**

Fatigue may be related to underlying malignancy, selinexor side effects, side effects of other agents, or concurrent morbidities. Fatigue may also be related to anorexia and/or dehydration, so caloric and fluid intake should be optimized in all patients. See Section 4.5 for detailed supportive care recommendations for anorexia and fatigue.

**Nausea/Vomiting**

Supportive care for nausea and vomiting should be given promptly. Prophylactic treatment can be considered in case of previous side effect of nausea and vomiting with prior anti-cancer therapy. The treatment should start with the first sign of nausea. Standard anti-emetics are allowed and strongly recommended. See Section 4.4 and 4.5 for detailed supportive care recommendations for emesis.

**Thrombocytopenia**

The etiology of thrombocytopenia in patients treated with selinexor is unclear, but has been experienced by patients on the phase I study. See Section 5.1 for dose adjustments related to thrombocytopenia.

**Infection**

Selinexor may lead to neutropenia. Patients should report any symptoms or signs of infection such as fever, pain, sweating, redness to their physician immediately. Section 5.4 for dose adjustments related to infection.

**Liver Function Abnormalities**

In some species such as dogs (but not rodents or monkeys), selinexor can cause increases in liver function tests and these should be followed carefully. Patients should minimize their use of acetaminophen on dosing days as these drugs can cause liver toxicity.

## 8.2 Ibrutinib Description/Availability

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase. The compound is manufactured by Pharmacyclics, Inc (Sunnyvale, CA) using methods in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of antineoplastic agents for human use.

### 8.2.1 Ibrutinib Composition and Preparation

Ibrutinib for oral administration is supplied as either capsules or tablets. The capsules are hard gelatin capsules containing micronized ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are manufactured as 140mg in a size 0, gray, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 capsules. Ibrutinib capsules are to be dispensed in their original containers. The tablet formulation is manufactured as 140, 280, or 420 mg and is dispensed as a blister pack.

### 8.2.2 Ibrutinib Administration

Ibrutinib should be taken with 8 ounces (approximately 240 mL) of water (avoid grapefruit or Seville orange juice due to CYP450 3A4 inhibition). Each dose of ibrutinib should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. The capsules or tablets should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be reported at the next scheduled visit.

Ibrutinib should be held for any procedure using the following guidelines:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage

tubes.
- For minor procedures (i.e. such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Ibrutinib will be provided as standard of care through individual patient insurance authorization.

Ibrutinib accountability records will be maintained at each participating institution and must be available for review when requested for auditing purposes and at time of study close out.

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).

8.2.3 Ibrutinib Safety Considerations

**Nausea/Vomiting**

Supportive care for nausea and vomiting should be given promptly. The treatment should start with the first sign of nausea. Standard anti-emetics are allowed and strongly recommended. See Section 4.4 for detailed supportive care recommendations for emesis.

**Diarrhea**

Supportive care for diarrhea should be given promptly. See Section 4.4 for detailed supportive care recommendations for diarrhea.

**Bleeding**

Life-threatening bleeding adverse events were recorded in patients who were concurrently taking ibrutinib and warfarin. If a patient requires warfarin therapy, they are ineligible for this trial.

**Atrial fibrillation**

Ibrutinib has been noted to lower the heart rate and patients taking this drug have a slightly increased risk of atrial fibrillation. ECG is required prior to initiation of ibrutinib.

## 9. CORRELATIVE STUDIES

### 9.1 Ibrutinib Steady State Plasma Levels (Cohorts 1 and 2 only)

9.1.1 Objective: To measure steady-state levels of ibrutinib for comparison with historical data to assess for significant drug-drug interactions with selinexor.

9.1.2 Collection of Specimen(s): Two plasma samples will be collected predose on Cycle 1, days 15 and 16. Each sample must be drawn prior to the ibrutinib dose that day.

9.1.3 Handling of Specimens(s) Approximately 5 mL of blood will be collected in sodium heparin (green top) tubes, placed on ice and immediately centrifuged at 1,200 x g for 10 minutes to isolate plasma. Plasma will be frozen in two separate vials and stored in a -70°C (or less) freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained, and date and time the sample was placed in the -70°C freezer.

9.1.4 Shipping of Specimen(s):
Samples will be retained until a batch of samples is available for each subject. Samples will then be shipped in batches on dry ice via FedEx Monday through Thursday to:
The OSU Pharmacoanalytical Shared Resource (PhASR)
Attn: Jiang Wang, PhD
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, Ohio 43210
Phone: (614) 688-0578
Fax: (614) 292-7766
Email: PhASR@osumc.edu

8.2.5 Sites Performing Correlative Study: OSU PhASR

**9.2 Pharmacodynamic (PD) properties of Selinexor**

9.2.1 Objectives:
To evaluate the inhibition of the B-cell receptor signaling pathway in patients with relapsed or refractory CLL who receive the combination of selinexor and ibrutinib.
To evaluate the change in localization of tumor suppressor proteins (such as P53, p73, Bcl-2, c-myc, Bcl-6, NFκB/IκB, FOXO3a and FOXO1) in patients with relapsed or refractory CLL following treatment with selinexor and ibrutinib.

9.2.2 Collection of Specimen(s): Markers of B-cell receptor signaling pathway activation (such as phosphorylation of BTK, Plc$_\gamma$, AKT, and ERK) will be assessed via immunoblot. Localization of tumor suppressor proteins will be assessed with confocal microscopy. Expression of targets regulated by these proteins (NFκB, Mcl1, Tcl1, BTK, p21, BCLxL, cMyc) will be assessed by real time PCR and immunoblot. Four 8.5-mL ACD yellow top tubes and two 6-mL purple (EDTA) topped Vacutainer tubes of whole blood will be collected pretreatment and 4 hours post-treatment on Cycle 1 Day 1, pretreatment on Cycle 1 Day 2, Cycle 1 Day 8, and Cycle 2 Day1. For cohort 3, samples will be collected C1D1, C2D1, C6D1, and C14D1

9.2.3 Handling of Specimens(s): Specimens should be stored at room temperature until sent to the laboratory for processing.

9.2.4 Shipping of Specimen(s): Ship to:
OSU CLL Experimental Therapeutics Laboratory
410 W 12th Avenue
4th Floor CCC Building
Columbus, OH 43210
Phone (614) 292-8824

9.2.5 Site(s) Performing Correlative Study: Ohio State University

**9.3 Pharmacogenomics (PGx) (Cohorts 1 and 2 only)**

9.3.1 Collection of Specimen(s): A single whole blood sample will be collected in a 6 mL lavender top (K2EDTA) collection tube prior to treatment on day 1 of cycle 1.

9.3.2 Handling of Specimens(s): The tube should be inverted 8-10 times then whole blood immediately separated into two equal volumes into cryo-storage tubes and immediately stored in a freezer maintained at or less than -70°C. DNA will later be extracted, and PGx analysis will be conducted using multiplexed or gene-specific methods to assess polymorphisms in drug metabolizing enzymes, transporters, target genes and/or genes relevant in the targeted BTK or XPO1 pathways.

9.3.3 Shipping of Specimen(s):
The OSU Pharmacoanalytical Shared Resource
Attn: Ming Poi, PhD
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, Ohio 43210
Phone: (614) 688-0578
Fax: (614) 292-7766
Email: PhASR@osumc.edu

9.3.4 Site Performing Correlative Study: OSUCCC, Pharmacoanalytical Shared Resource

**9.4 Primary and Secondary Resistance Studies**

9.4.1 To preliminarily assess potential causes for primary and secondary resistance to selinexor and ibrutinib.

9.4.2 Collection of Specimen(s): Buccal swab will be obtained at baseline for germline DNA and SNP filtering. Subjects relapsing during ibrutinib will be examined for baseline characteristics and will potentially be subjected to extensive molecular

characterization to determine the reason for drug resistance. This could include genomic, transcriptome, proteomic, biochemical, plasma (including exosomes) or epigenetic studies of baseline and serial samples. Additionally, as common mutations of ibrutinib resistance have been characterized by our group, we will monitor serially (Q 3m) from blood/plasma mRNA of C381S BTK and PLCγ2 and XPO1 by ion torrent analysis. Four 8.5 mL yellow ACD tubes and one 6-mL lavender EDTA tubes will be obtained every 3 months and transported to the OSU CLL Experimental therapeutics laboratory. Additionally, five 8.5-mL yellow ACD tubes and one 6-mL lavender EDTA tube at time of relapse should be drawn and transported to the OSU CLL Experimental Therapeutics laboratory. Lymph node material in excess to that required for clinical diagnosis (pre-treatment or at relapse) may also be used for these studies. This will be obtained from pathology and fresh tissue preferred. Excess material from samples may be used for additional studies related to mechanism action and toxicity of these two drugs or biology of CLL. These samples may be shared with other investigators working collaboratively with OSU.

9.4.3 Handling of Specimens(s): Material should be transported or shipped to the OSU CLL Experimental Therapeutics Laboratory.

9.4.4 Shipping of Specimen(s): Ship to:
OSU CLL Experimental Therapeutics Laboratory
410 W 12th Avenue
4th Floor CCC Building
Columbus, OH 43210
Phone (614) 292-8824

9.4.5 Site Performing Correlative Study: OSU CLL Experimental Therapeutics Laboratory

## 10. STUDY CALENDAR

Pre-study evaluations must be completed within 2 weeks of study registration, unless otherwise noted. Karyotype, FISH, bone marrow biopsy, peripheral blood immunophenotyping, and CT scans must be performed within 45 days of study registration. Informed consent must be obtained within the time frame specified by local policy. IgVH mutational status does not need to be repeated if performed previously. It is acceptable for individual cycles to begin ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of therapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. New cycles of ibrutinib can be started up to 7 days before the protocol-defined date for major life events. Documentation to justify a delay or advance of a cycle should be provided. Additionally, all tests and observations associated with the beginning of a cycle may be performed up to 48 hours prior to beginning the cycle of therapy.

Calendar for dose escalation and expansion cohorts

| General Study Calendar | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cycle | Pre-Study | 1 | | | | 2-3 | | 4-6 | 7+[k] | Off Treatment | Follow-up[l] |
| Day | | 1 | 8 | 15 | 22 | 1 | 15 | 1 | 1 | | |
| Eligibility checklist | X | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | |
| History[a] | X | | | | | | | | | | |
| Progress note[b] | | X | X | X | X | X | X | X | X | X | X[l] |
| Physical exam | X | X | X | X | X | X | X | X | X | X | X[l] |
| Ophthalmologic exam[c] | X | | | | | | | | | X | |
| Concurrent meds | X | X | X | X | X | X | X | X | X | | |
| Vital signs/weight/ height/BSA | X | X | X | X | X | X | X | X | X | X | |
| ECOG[d] | X | X | X | X | X | X | X | X | X | X | |
| CBC, dif, platelets | X | X | X | X | X | X | X | X | X | X | |
| Coagulation[e] | X | X | X | X | X | X | X | X | X | X | |
| Chemistry[f], Ca, Mg, Phos | X | X | X | X | X | X | X | X | X | X | |
| Liver function tests[g] | X | X | X | X | X | X | X | X | X | X | |
| LDH | X | X | | | | X | | | | | |
| Uric acid | X | X | | | | | | | | | |
| Peripheral blood immunophenotyping | X | | | | | X[m] | | X[n] | X[o] | X | X[l] |
| Quant immunoglobulins | X | | | | | | | | | | |
| SPEP with | X | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| immunofixation | | | | | | | | | | | |
| CLL karyotype, FISH panel[h] & IgVH mutational analysis | X[i] | | | | | | | | | | |
| Pregnancy test[j] | X | | | | | | | | | | |
| HIV/Hep | X | | | | | | | | | | |
| Buccal swab | X | | | | | | | | | | |
| ECG | X | | | | | | | | | | |
| Dispense KPT-330 | | X | | | | X | | X | X | | |
| Adverse event evaluation | X | X | X | X | X | X | X | X | X | X | X[h] |
| PET/CT or CT scans | X | | | | | X[m] | | X[n] | X[o] | X | X[h] |
| Bone marrow biopsy and aspirate | X[p] | | | | | | | X[q] | X[q] | | X[q] |
| Histologic review | X[r] | | | | | | | | | | |
| Correlative studies | See Correlative Study Calendar | | | | | | | | | | |

a. Initial medical history should include: baseline symptoms; a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness; family and social history; calculation of Rai Stage (for CLL patients), MIPI (for MCL patients), or IPI (NHL patients other than MCL; see Appendix C).
b. Progress notes should include: new symptoms or adverse events, ECOG performance status (Appendix A), documentation of physical exam, status of disease.
c. Ophthalmologic exam: required at screening, if clinically indicated during study, and at final visit. Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, and color vision test. Dilated fundoscopy and slit lamp exam including anterior segment photos to document lens clarity.
d. For ECOG performance status, see Appendix A
e. Prothrombin time, international normalization ratio, and activated partial thromboplastin time
f. Sodium, potassium, bicarbonate, BUN, calcium, chloride, creatinine
g. Albumin, alkaline phosphatase, total bilirubin, total protein, SGOT [AST], SGPT [ALT]
h. FISH panel will use probes to detect for abnormalities in chomosomes 13q, 12, 11q, and 17p.
i. For CLL patients only.
j. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Female of childbearing potential must have a negative serum β-Hcg pregnancy

test result within 3 days of first study dose.

k. For cycles 7 and higher, patient will be required to return for evaluation and to receive KPT-330 every 3rd month (eg. Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1….)
l. Reassessment off therapy will occur 4 weeks from the last dose of study therapy. For patients removed from study for reasons other than disease progression, reassessment will then occur then every 6 months until progression or an alternative therapy is started.
m. Cycle 2 Day 1 only.
n. Cycle 4 Day 1 only.
o. Restaging scans and immunophenotyping will be performed every 3 cycles for the first year and then every 6 months thereafter.
p. Bilateral bone marrow biopsies are preferred for lymphoma patients.
q. A bone marrow biopsy and aspirate should be performed to confirm a complete response if there was bone marrow involvement at diagnosis, clinical MRD flow should be performed in this case.
r. For patients with DLBCL only: Paraffin block must be submitted for immunohistochemistry evaluation of CD10, bcl-6, and MUM-1 to determine ABC vs GCB subtype. Biopsy to confirm histologic review does not need to be repeated for pre-study requirements, so long as previously obtained tissue confirms patient meets histologic eligibility criteria prior to study registration.

Cohort 3 Study

Calendar

| Cycle | Pre-Study | Day 1, Cycles 1-3 | Day 1, Cycles 6, 9, 12 | Cycle 14 Day 1 | Day 1, every 3 cycles following cycle 14 (continue ibrutinib) C17, 20, 23, 26, etc. | Day 1, every 3 cycles following cycle 14 (off therapy) | Follow-up (off therapy)[j] |
|---|---|---|---|---|---|---|---|
| Eligibility checklist | X | | | | | | |
| Informed consent | X | | | | | | |
| History[a] | X | | | | | | |
| Progress note[b] | | X | X | X | X | X | X |
| Physical exam | X | X | X | X | X | X | X |
| Ophthalmologic exam[c] | X | | | | | | |
| Concurrent meds | X | X | X | | X | | |
| Vital signs/weight/ height/BSA | X | X | X | | X | X | |
| ECOG[d] | X | X | X | | X | X | |
| CBC, dif, platelets | X | X | X | | X | X | |
| Coagulation[e] | X | X | X | | X | | |
| Chemistry[f], Ca, Mg, Phos | X | X | X | | X | X | |
| Liver function tests[g] | X | X | X | | X | | |
| LDH | X | | | | | | |
| Uric acid | X | | | | | | |
| Peripheral blood immunophenotyping | X | | X | | | X | X |
| Quant immunoglobulins | X | | X | | | | |
| SPEP with immunofixation | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CLL karyotype, FISH panel[h] & IgVH mutational analysis[h] | X | | | | | | |
| Pregnancy test[i] | X | | | | | | |
| HIV/Hep | X | | | | | | |
| Buccal swab | X | | | | | | |
| ECG | X | | | | | | |
| Adverse event evaluation | X | X | | | X | | |
| PET/CT or CT scans | X | | | | | X[k] | X |
| Bone marrow biopsy and aspirate | X | | | X | | | |
| Correlative studies | X | X | X | X | X | X | |

a. Initial medical history should include: baseline symptoms; a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness; family and social history; calculation of Rai Stage (for CLL patients)
b. Progress notes should include: new symptoms or adverse events, ECOG performance status (Appendix A), documentation of physical exam, status of disease.
c. Ophthalmologic exam: required at screening and if clinically indicated during study. Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, and color vision test. Dilated fundoscopy and slit lamp exam including anterior segment photos to document lens clarity.
d. For ECOG performance status, see Appendix A
e. Prothrombin time, international normalization ratio, and activated partial thromboplastin time
f. Sodium, potassium, bicarbonate, BUN, calcium, chloride, creatinine
g. Albumin, alkaline phosphatase, total bilirubin, total protein, SGOT [AST], SGPT [ALT]
h. Only if not done prior to initiation of ibrutinib
i. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Female of childbearing potential must have a negative serum β-

Hcg pregnancy test result within 3 days of first study dose.

j. Reassessment off therapy will occur 4-6 weeks from the last dose of study therapy. For patients removed from study for reasons other than disease progression, reassessment will then occur then every 6 months until progression or an alternative therapy is started.
k. Restaging scans and immunophenotyping will be performed every 3 cycles for the first year and then every 6 months thereafter.

Bilateral bone marrow biopsies are preferred for lymphoma patients.

l. A bone marrow biopsy and aspirate should be performed to confirm a complete response if there was bone marrow involvement at diagnosis, clinical MRD flow should be performed in this case.

| Cycle | 1 | | | | | | | | | | | | | | | 2 | Q3 Cycles | Relapse |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | 1 | | | | | | 2 | 8 | 15 | | | | | | 16 | 1 | 1 | |
| Time* | Pre-dose[1] | 30-min post dose[2] | 1-hr post dose[1] | 2-hr post dose[1] | 4-hr post dose[3] | 8-hr post dose[4] | 24-hr post dose[5] | Pre-dose[1] | Pre-dose[1] | 30-min post dose[2] | 1-hr post dose[1] | 2-hr post dose[1] | 4-hr post dose[3] | 8-hr post dose[4] | 24-hr post dose[5] | Pre-dose[1] | | Any |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| Ibrutinib PK (Section 9.2) | | | | | | | | | A | | | | | | A | | | |
| PD B-cell Receptor Signaling Pathway and tumor suppressor localization (Section 9.3)[$] | B | | | | C | | C | C | | | | | | | | C | | |
| Pharmaco-genomics (PGx) (Section 9.5) | D | | | | | | | | | | | | | | | | | |
| Resistance Studies (Section 9.6) | | | | | | | | | | | | | | | | | E | F |

A. *For Ibrutinib PK plasma:* Approximately 5 mL of blood will be collected in sodium heparin (green top) tubes, placed on ice and immediately centrifuged at 1,200 x g for 10 minutes to isolate plasma. Plasma will be frozen in two separate vials and stored in a -70°C (or less) freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained.
B. Correlative study samples (4 x 8.5-mL ACD yellow top tube, and 6-mL potassium EDTA [lavender-top vacutainer] from blood) should be drawn at baseline.
C. Correlative study samples (2 x 8.5-mL ACD yellow top tube and 6-mL potassium EDTA) should be drawn on Cycle 1 Day 1; 4 hours post-treatment and Cycle 1 Day 8 and Cycle 2 Day 1 pretreatment. Cohorts 1 and 2 only
D. A PGx blood sample (1 x 6-mL EDTA lavender top) should be collected prior to dosing on Cycle 1 Day 1. Cohorts 1 and 2 only
E. *To monitor for resistance:* Four x 8.5 mL ACD yellow top tubes and 1 x 6-mL EDTA lavender tubes will be obtained every 3 cycles and transported or shipped to the OSU Experimental Therapeutics Laboratory. This will start at cycle 4. Lymph node material in excess to that required for clinical diagnosis (pre-treatment or at relapse) may also be used for these studies. Cohorts 1 and 2 only
F. *To evaluate resistant samples:* Five x 8.5-mL ACD yellow top tubes and 1 x 6-mL EDTA lavender top tube at time of relapse should be drawn and transported shipped to the OSU Experimental Therapeutics Laboratory. Lymph node material in excess to that required for clinical diagnosis (pre-treatment or at relapse) may also be used for these studies. Cohorts 1 and 2 only

## 11. MEASUREMENT OF EFFECT

### 11.1 Response Criteria

Response will be assessed by the International Working Group (IWG) Response Criteria for NHL patients[42] and the International Workshop on CLL (IWCLL) criteria[14] for CLL patients after 1 and 3 months of therapy, then every 3 months for 1 year, and then every 6 months thereafter until disease progression with no maximum treatment length.

#### 11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with selinexor.

Evaluable for response. Only those patients who have received at least four weeks of therapy and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of 4 weeks will also be considered evaluable.)

#### 11.1.2 Response Criteria for NHL

**Definition of Response for NHL Patients:** Criteria for response will utilize the IWG Response Criteria for NHL patients[42].

**Complete Response (CR):**
Complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy.

- In patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET-negative.
- The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but that demonstrates a small population of clonal lymphocytes by flow cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

**Partial Response (PR):**

- At least a 50% decrease in the sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected prior to initiation of therapy according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by ≤ 50% in their SPD, or, for single nodules, in the greatest transverse diameter.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- If performed, the post-treatment PET should be positive in at least one previously involved site.

**Stable Disease (SD):**
Patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). If performed, the PET should be positive at prior sites of disease, with no new areas of involvement on the post-treatment CT or PET.

**Progression (PD) or Relapse:**

- Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 by ≤ 1.0 will not be considered as abnormal for relapse or progressive disease.
- Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of <

1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.

- At least a 50% increase in the longest diameter of any single previously identified node > 1.0 cm in its short axis.
  Lesions should be PET-positive if a typical FDG-avid lymphoma or the lesion was PET- positive prior to therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

11.1.3 Response Criteria for CLL Patients

**Definition of Response for CLL Patients:** Criteria for response will utilize the IWCLL Response criteria[14].

**Complete response (CR):**
CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x $10^9$/L (4000/μL). The presence of minimal residual disease (MRD) after therapy should be assessed. The sensitivity of the method used to evaluate for MRD should be reported.
- Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by CT scan of the abdomen, pelvis, and thorax.
- No hepatomegaly or splenomegaly by physical examination.
- Absence of constitutional symptoms.
- Blood counts above the following values:
  - Neutrophils more than 1.5 x $10^9$/L (1500/μL) without need for exogenous growth factors.
  - Platelets more than 100 x $10^9$/L (100 000/μL).
  - Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.
- A marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results as above demonstrate that a CR has been achieved.
  - To define a CR, the marrow sample must normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If lymphoid nodules are present then these nodules should be recorded as nodular PR. However, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. The quality of the CR should be assessed for MRD by flow cytometry or by immunohistochemistry (IHC).

**CR with incomplete marrow recovery (CRi):**
All the criteria for a CR (including the marrow examination) have been met though there is persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity.

**Partial response (PR)** PR is defined as follows:

- A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.
- Reduction in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
- No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan.
- The blood count should show one of the following results:
- Neutrophils more than 1.5 x $10^9$/L (1500/μL) without need for exogenous growth factors.
- Platelet counts greater than 100 x $10^9$/L (100 000/μL) or 50% improvement over baseline.
- Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

**Progressive Disease:**
Characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B-lymphocytes per microliter.
- Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL. During therapy, cytopenias cannot be used to define disease progression.
- The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x $10^9$/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

**Stable Disease:**
Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

11.1.4 Duration of Response

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

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

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

11.1.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 6.0 (Adverse Events: List and Reporting Requirements).

### 12.1 Patient Protection

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines. The Principal Investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical practice (GCP) and applicable local regulatory requirements.

### 12.2 Patient Information

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

### 12.3 Informed Consent

Patient / legally acceptable representative (as applicable) written consent must be obtained according to local Institutional Review Board requirements and must conform to the ICH guidelines for Good Clinical Practice, prior to any study-specific screening procedures and trial entry. The written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Investigator at each participating site and available for inspection by regulatory authority at any time. A copy of all external participating site consents must also be sent to the OSU Multi-Institution Program Coordinator to be filed in the OSU multi-institution regulatory files.

### 12.4 Data Submission

The study will be managed per the Multi-Center Trial Program (MCTP) policies. Subsite data must be submitted to the MCTP as outlined in the protocol-specific monitoring plan, which will be provided to external participating sites. Data will be submitted using case report forms and the Data Submission Form cover sheet (refer to Supplemental Forms Document) supplied by the MCTP. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design

Cohorts 1 and 2 of this study represent a prospective, multi-center, phase I dose escalation study in two diseases: CLL and NHL. Dose-finding will proceed using a modified continual reassessment method and targeting a probability of DLT<0.30. To ensure safety, the starting dose level will be the lowest dose level and dose escalation will proceed by increasing only one dose level at a time. Groups of 2-3 patients will be treated until convergence on an MTD, defined as 10-12 patients treated at a particular dose level which is also a subsequently suggested dose level by the model *or* a maximum of 36 evaluable patients, whichever occurs first. At the MTD, up to 10 CLL patients and 10 NHL patients will be accrued.

### 13.2 Sample Size/Accrual Rate

For cohort 1 and 2, with groups of 2-3 patients per month enrolled in the dose finding study, it is expected that approximately 9 groups of patients will be treated over 18-30 months. Expansion at the MTD is expected to accrue over 6-12 months. Thus, the total study duration is estimated to be 24-42 months. On average, we expect 32 patients to be enrolled, but the total sample size could be as many as 50 patients and will depend on the dose escalation and composition of CLL and NHL patients treated at the estimated MTD as part of the dose-finding portion of the study.

Cohort 3 will be a pilot study to gain data on the ability of selinexor to deepen responses with ibrutinib. Ten patients who have been treated with ibrutinib as their frontline therapy for CLL/SLL for at least 12 cycles and have obtained PR will be accrued to this cohort, and selinexor will be added to ibrutinib for 14 more cycles. The deepening of response rate is defined as the percentage of patients who convert to a MRD negative complete response (MRD- CR) from PR at the end of 14 cycles of selinexor plus ibrutinib among this cohort. If we observe 3 or more patients out of 10 who achieve the conversion from PR to MRD-CR, we will consider this regimen promising and move it forward for further study. For various true deepening of response rates, the table below shows the probability of observing at least 3 MRD-CRs in 10 patients. For example, if the true deepening response rate is 30%, then the probability of declaring the regimen promising is 61.7% with 10 patients.

| True Deepening of Response Rate | Probability of Observing 3 or More MRD-CR in 10 Patients |
|---|---|
| 0.1 | 0.070 |
| 0.2 | 0.322 |
| 0.25 | 0.474 |
| 0.3 | 0.617 |
| 0.35 | 0.738 |
| 0.4 | 0.833 |

With an accrual rate of 2 patients per month, we expect accrual to be complete in 5 months.

### 13.3 Evaluability

Any patient who is eligible for the trial and has received at least one dose each of the selexinor and ibrutinib will be evaluated for toxicity (descriptive summary as well as dose escalation determination in the first two cohorts) and for response. Patients who are not evaluable for toxicity at a given dose level will be replaced.

### 13.4 Definition of Primary Endpoint

The primary endpoint is DLT. DLT has been defined in Section 4.2 above.

### 13.5 Definition of Secondary Endpoints

13.5.1 Toxicity will be graded by CTCAEv4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

13.5.2 Clinical response and survival will be measured by:

- International Working Group Criteria for NHL patients.
- IWCLL 2008 Guidelines for CLL patients.

Response criteria are detailed in Section 10.

Responders will be defined as those with complete response (CR) or partial response (PR). Overall response rate (ORR) will be calculated as the number of evaluable responders divided by the total number of evaluable patients and will be analyzed by cohort. All patients who receive at least one dose of study medication will be included in the ORR and progression free survival.

Progression Free Survival (PFS): PFS will be calculated from the date of study enrollment to disease progression or death, whichever occurs first. Patients who do not progress or die will be censored at the time of last contact with response assessment by physical exam and laboratory studies.

Overall Survival (OS): OS will be calculated from the date of study enrollment to death. Patients who do not die will be censored at the time of last contact. This will be analyzed in each cohort independently.

13.5.3 Response as related to chronic lymphocytic leukemia (CLL) karyotype and IgVH mutational status. Response criteria are detailed in Section 10.

13.5.4 For Cohort 3, the rate of deepening of response is defined as the percentage of patients who attain a MRD negative complete response (MRD- CR) at the end of 14 cycles of selinexor plus ibrutinib.

### 13.6 Definition of Exploratory Endpoints

13.6.1 Pharmacodynamic endpoints for patients with CLL include:

- Markers of downmodulation or inhibition of the B-cell receptor pathway including BTK expression and phosphorylation of SYK, AKT, and ERK will be assessed pretreatment and post-treatment where feasible, and reported as a continuous measure.
- Change in localization of tumor suppressor and oncogene proteins and mRNAs (P53, p73, Bcl-2, c-myc, Bcl-6, NFκB/IκB, FOXO3a and FOXO1) will be will be assessed pretreatment and post-treatment where feasibile. Change in localization will be measured through blood sample collection, analyzed by immunoblot, and reported as percentage of protein fragments observed in the nucleus at each time point.
- Potential predictive biomarkers will be assessed before and after in vitro treatment of patients' pretreatment leukocytes via qRT-PCR and results will be reported as fold change from baseline.

### 13.7 Analytic Plan for Primary Objective

The primary objective is to identify the highest dose level of selinexor administered with ibrutinib that corresponds to an acceptable probability of DLT, defined as <0.30, in relapsed/refractory CLL and NHL patients. We do not expect that toxicity will be different between CLL and NHL, thereby justifying the use of both groups in dose escalation. Dosing

decisions will be made throughout the course of the trial based on a modified continual reassessment method (MRCM),[43-45] combining information assumed *a priori* with observed data to update the estimate of the true dose-toxicity curve. *A priori*, it is assumed that the dose toxicity curve is monotonically increasing and belongs to the family of two-parameter logistic models, allowing the scale and slope to vary as described by Piantadosi et al.[45] To implement the model, including input of prior assumptions, data collection, and estimation of the dose-toxicity curve, software developed by Piantadosi (Modified Continual Reassessment Method, version 4.0) will be used. For model initiation, the *a priori* curve has been defined using three coordinates elicited from the clinical investigators to represent a "safe", "moderately risky" and "risky" weekly dose level of selinexor when combined with the standard dose of ibrutinib in this patient population (Figure 2). The information represented in the *a priori* curve is equivalent to that of only 1.5 subjects, and hence, observed data accumulated throughout the trial is expected to outweigh any pseudo-data pre-specified when making dosing decisions. The target dose for each cohort will be identified by the software, but the starting dose and dose escalation will be constrained by design to ensure safety, as suggested in Garrett-Mayer's 2006 tutorial, using the following rules: 1) the starting dose level will be the lowest dose level, 2) the dose level assigned for each successive cohort will be the highest dose level less than or equal to the target dose identified by the software provided there is not escalation by more than one dose level; otherwise, the target dose identified by the software will be disregarded and an increase in only one dose level at a time will be permitted, and 3) in the absence of DLT, decisions will be made following cohorts of 2 or 3 patients, cohort sizes that have been shown to balance accurate MTD information and safety.[46] We will only escalate dosing when $\leq$33% of patients at a dose level experience DLT, and patients will not be assigned to an escalated dose level if there is a high probability that the DLT rate at that dose level is >30%. It is planned that groups of 2 patients will be treated at lower dose levels of selinexor and groups of 3 patients will be treated beginning with dose level 3 in order to expedite the dose finding process. The trial will stop when the MCRM is deemed to have adequately converged on an MTD. Specifically, the trial will stop when 10-12 patients (depending on cohort size) are treated at a particular dose level which is also subsequently a suggested dose level by the model *or* a maximum of 36 evaluable patients have been treated, whichever occurs first (approximately 6-14 cohorts). At the time the trial terminates, the MTD will correspond to the highest dose level with probability of DLT<0.30. The MCRM process will be summarized, including number of DLTs observed in each cohort and the recommended dose at the end of each cohort. Using the parameter and covariance estimates from the model, and assuming parameters are from a bivariate normal distribution, repeated sampling will be used to construct an empirical distribution of the probability of DLT at the selected dose level to obtain 95% confidence intervals. At the MTD, we will accrue up to 10 CLL patients and 10 NHL patients in an expansion.

## 13.8 Analytic Plan for Secondary Objectives

### 13.8.1 Toxicity

Toxicities will be tabulated by type and grade and displayed in summary form. In addition, the number of cycles started/completed, number of patients requiring dose reductions, and the reason for going off treatment may be summarized to assess treatment tolerability.

### 13.8.2 Clinical Response an Survival

The degree of response will be summarized within each disease group and at each dose level. ORR will be presented for those patients treated at the MTD with an exact 95 % confidence interval. Also among patients who are treated at the MTD, PFS and OS will be described using Kaplan-Meier curves for each disease group. In cohort 3, the deepening of response rate will be calculated as percentage of patients who achieve MRD-CR, and will be provided with an exact 95% confidence interval.

### 13.8.3 Correlative endpoints

Formal statistical tests of hypotheses will not be performed given the nature of early clinical trials. Descriptive statistics such as mean, standard deviation, median, range, etc, for continuous variables and proportions for discrete variables will be used to summarize correlative endpoints in each of the defined strata. Graphical summaries will also be used extensively to visualize the data.

Pharmacokinetic (PK) and pharmacodynamics (PD) properties of selinexor in patients with relapsed and refractory CLL and aggressive NHL will be assessed (See Section 12.4-5). PK endpoints will be computed using non-compartmental and compartmental methods and summarized with descriptive statistics.

For expression data collected serially over time (i.e. tumor suppressor proteins and phosphoproteins), changes in expression will be explored graphically using boxplots and/or individual line plots, as well as analytically with repeated measures models.

Relationships between PK and PD endpoints with response will be largely exploratory, but may identify particular patterns of interest.

Potential predictive Biomarker qRT-PCR fold change data will be correlated to patients' clinical response once it becomes available. Predictive power of NGFR and other potential marker will be statistically tested when data of at least 100 patients will be collected from all clinical trials.

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## APPENDIX A PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX B INDUCERS AND INHIBITORS CYP3A4/5

A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. **Strong inducers and inhibitors are in bold.**

| CYP3A4/5 INDUCERS | CYP3A4/5 INHIBITORS |
|---|---|
| | |
| **Efavirenz** | **Cyclosporine** |
| **Nevirapine** | **Indinavir** |
| | **Miconazole** |
| Barbiturates | **Nelfinavir** |
| Carbamazepine | **Poscanazole** |
| Modafinil | **Ritonavir** |
| Oxcarbazepine | **Clarithromycin** |
| Phenobarbital | **Itraconazole** |
| Phenytoin | **Ketoconazole** |
| Pioglitazone | **Nefazodone** |
| Rifabutin | **Saquinavir** |
| Rifampin | **Telithromycin** |
| St. John's wort | **Voriconazole** |
| Troglitazone | |
| | Aprepitant |
| | Atazanavir |
| | Clotrimazole |
| | Conivaptan |
| | Cimetidine |
| | Delavirdine |
| | Desipramine |
| | Diltiazem |
| | Efavirenz |
| | Erythromycin |
| | Fluconazole |
| | Fosaprepitant |
| | Grapefruit juice |
| | Haloperidol |
| | Isoniazid |
| | Metronidazole |
| | Nicardipine |
| | Norfloxin |
| | Quinidine |
| | Tetracycline |

## APPENDIX C STAGING SYSTEMS

| **Rai Stage – CLL Patients Only*** (Rai, 1975)** | |
|---|---|
| Stage | Definition |
| 0 | Lymphocytosis |
| I | Lymphocytosis and lymphadenopathy |
| II | Lymphocytosis with splenomegaly or hepatomegaly |
| III | Lymphocytosis with anemia (hemoglobin < 11g/dL) |
| IV | Lymphocytosis with thrombocytopenia (platelets < 100,000/$mm^3$) |

| **International Prognostic Index – NHL Patients (Except MCL)** |
|---|
| Patients will receive one point for each of the following characteristics: |
| Age greater than 60 years<br>Stage III or IV disease<br>Elevated serum LDH<br>ECOG performance status of 2, 3, or 4<br>More than 1 extranodal site |

| **Mantle Cell Lymphoma International Prognostic Index – MCL Patients Only (Hoster, Blood 2008)** | | | | |
|---|---|---|---|---|
| **Point(s)** | **Age (years)** | **ECOG PS** | **LDH** | **WBC (/$mm^3$)** |
| 0 | < 50 | 0-1 | < 0.67 x ULN | < 6,700 |
| 1 | 50-59 | | 0.67-0.99 x ULN | 6,700-9,999 |
| 2 | 60-69 | 2-4 | 1.00-1.49 x ULN | 10,000-14,999 |
| 3 | ≥ 70 | | ≥ 1.50 x ULN | ≥ 15,000 |
| LDH = lactate dehydrogenase, MCL = mantle cell lymphoma, PS = performance status, ULN = upper limit of normal, WBC = white blood cell | | | | |

## APPENDIX D KARYOPHARM SAE REPORT FORM

Karyopharm Therapeutics

FRM-PV-0001 v. 6.0

**Serious Adverse Event Report Form** | **Effective:** 30 Nov 2017

| **Protocol Number:** | | Initial Report: ☐ | Follow-up Report Number: |
|---|---|---|---|
| Investigator: | Site ID#: | Country of Incidence: | |

**PATIENT INFORMATION**

| Patient ID#: | Weight (kg): | Height (cm): |
|---|---|---|
| Date of birth *(DD-MMM-YYYY)*: | ☐ Male | ☐ Female |
| Baseline Diagnosis: | Date of Baseline Diagnosis *(DD-MMM-YYYY)*: | |

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

**Please select the most applicable Medication Error category below:**

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

**Associated with Serious Adverse Event?**

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

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

**ADVERSE EVENT INFORMATION**

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

**Please complete the following sections, as applicable:**

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

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

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

| **Protocol Number:** | |
|---|---|
| Patient ID#: | Site ID#: |
| **STUDY DRUG INFORMATION** | |
| Study Drug(s): | |
| Therapy Dates *(DD-MMM-YYYY)*: | Medication Dosage and Frequency |
| Date of First Dose: | First dose: mg *or* mg/m² |
| Date of Last Dose Prior to Event: | Frequency: |
| **ACTION TAKEN WITH STUDY DRUG** | |
| ☐ Dose unchanged | |
| ☐ Dose reduced<br>Date of dose reduction *(DD-MMM-YYYY)*:<br>Dose reduced to: mg *or* mg/m² | Did event abate or improve after stopping/reducing medication?<br>☐ Yes ☐ No ☐ N/A |
| ☐ Temporarily interrupted *Date (DD-MMM-YYYY)*: | |
| ☐ Date of re-initiation *(DD-MMM-YYYY)*:<br>Re-initiation dose: mg *or* mg/m² | Did event reappear after re-administration?<br>☐ Yes ☐ No ☐ N/A |
| ☐ Permanent withdrawal Date *(DD-MMM-YYYY)*: | |
| ☐ Not Applicable (Please explain): | |

| **RELEVANT PAST MEDICAL HISTORY AND/OR RELEVANT CONCURRENT CONDITIONS** | | | |
|---|---|---|---|
| Medical condition(s) | Ongoing Condition? | Start date *(DD-MMM-YYYY)* | End date *(DD-MMM-YYYY)* |
| | ☐ Ongoing | | |
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| Karyopharm Therapeutics | FRM-PV-0001 v. 6.0 |
|---|---|
| **Serious Adverse Event Report Form** | **Effective:** 30 Nov 2017 |

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

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