PROTOCOL NUMBER: 2016-0622

PROTOCOL TITLE: A phase 2, open-label, investigator sponsored study of selinexor (KPT-330) in patients with advanced thymic epithelial tumor (TET) progressing after primary chemotherapy (SELECT)

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Study Drug: **Selinexor (KPT-330)**
IND Number: *132625*
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***Drug Supplier/Partial Funding Source**:* *Karyopharm Therapeutics, Inc.*

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SYNOPSIS

Protocol no.	3.0
Protocol version (Date)	May 11, 2020
Title	Selinexor in patients with advanced thymoma
Detailed title	A phase II study of selinexor (KPT-330) in patients with advanced thymic epithelial tumour (TET) progressing after primary chemotherapy.
European Principal investigator	Gedske Daugaard, Department of Oncology, Rigshospitalet, Copenhagen, Denmark
Sponsor-Investigator	Chul Kim, MD, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC
Sponsor	Lombardi Comprehensive Cancer Center at Georgetown University
Study design	International, multicenter, open label phase II, Simons two stage design.
Anticipated start date	2018.01.01
Duration of study	24 month accrual and 6 months follow-up
Total number of sites	2 in the US
Study population	Adults with histologically confirmed, advanced, inoperable TETs who are progressing after treatment with at least one platinum containing chemotherapy regimen.
Objectives	
Primary objective	• To determine the efficacy of selinexor in adults with TETs determined by overall response rate (RECIST 1.1) in patients with advanced thymomas progressing after primary chemotherapy
Secondary objectives	• To determine the efficacy of Selinexor in adults with thymoma determined by overall response rate according to modified ITMIG response criteria • To determine six months PFS of patients with thymoma treated with selinexor • To determine overall survival of patients with thymoma treated with selinexor • To evaluate exploratory biomarkers for prediction of response to selinexor in patients with thymoma • To determine progression free survival in patients with advanced, inoperable thymoma treated with selinexor • To evaluate safety and tolerability of Selinexor
Planned sample size	This study is comprised of 2 similar phase II trials, one running in US (25 patients) and one running in EU (25 patients): Arm A: Thymoma • Stage 1: 15 patients • Stage 2: 10 patients (across all EU and US sites) Arm B: Thymic carcinoma (closed due to interim analysis) • Stage 1: 15 patients • Stage 2: 10 patients
Inclusion criteria	• Histologically confirmed advanced TET (thymoma) • Progression after Primary Chemotherapy

	• No more than two previous lines (Neoadjuvant or chemoradiotherapy will count as one line if disease progression has occurred within 6 months) • Inoperable per local Investigator (Masaoka Stage III or IV) • Progression after treatment with least one platinum containing chemotherapy regimen • Measurable disease (RECIST 1.1) • Age ≥18 years • ECOG PS $\leq$2 • Patients must have recovered from the toxic effects of prior therapy at the time of initiation of the study drug unless toxicity is stable. • A 4 weeks or five half lives interval from any investigational agents or cytotoxic chemotherapy to start of study is required (whichever is shorter) • Signed informed consent • Adequate bone marrow function and organ function: - Hematopoietic function: total white blood cell count (WBC) ≥ 3000/mm³, absolute neutrophil count (ANC) ≥ 1500/mm³, platelet count ≥ 100,000/mm²; Hemoglobin $\geq$ 9.0 gm/dL - Hepatic function: bilirubin < 1.5 times the upper limit of normal (ULN), ALT < 2.5 times ULN or ALT < 5.0 times ULN in the presence of liver metastases - Creatinine clearance > 30 ml/min according to Cockcroft-Gault • Patients of childbearing potential must agree to use adequate birth control during and for 7 months after participation in this study
Exclusion criteria	• No significant medical illness that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy, including - Unstable cardiovascular function - Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface *antigen*) - Markedly decreased visual acuity - Active infection requiring intravenous antibiotics • Pregnancy or breast-feeding • Symptomatic brain metastasis requiring corticosteroids • Uncontrolled autoimmune disorders. Patients with autoimmune disorders under control on medication may be included. Patients with pure red cell aplasia may be included if haemoglobin levels are relatively stable on transfusions or medication • Significantly diseased or obstructed gastrointestinal tract, malabsorption, uncontrolled vomiting or diarrhea or inability to swallow oral medications • No dehydration of NCI-CTCAE grade ≥ 1 • Serious psychiatric or medical conditions that could interfere with treatment.

	• No history of organ allograft • No concurrent therapy with approved or investigational anticancer therapeutics
Treatment schema	Patients will receive oral Selinexor 40 mg twice weekly (Monday/ Wednesday, Tuesday/ Thursday, or Wednesday/Friday). One cycle is 28 days. Patients will be dosed 3 weeks on and one week off in 4 week-cycles (6 doses/cycle). Treatment will continue until disease progression or the development of unacceptable toxicities or until deemed without benefit to the patient.
Primary parameter	• Overall response rate according to RECIST 1.1
Secondary parameters	• Overall response rate according to modified ITMIG response criteria • Six months PFS • Overall survival • Common Terminology Criteria for Adverse Events (CTCAEs) version 4.03
Exploratory parameters	• Exploratory biomarkers in archived tissue samples (TBD)
Study procedures	• CT scans after every 2 cycles of Selinexor • Physical examination every 2 weeks for the first 2 cycles, then every 4 weeks
Randomisation procedure	N/A
Sample size calculation	Simon's minimax design will be used. The following assumptions are used in each of the two arms: • A response rate of 10 % is considered clinically irrelevant • A response rate of 30 % is considered promising and clinically relevant • Type one error rate: 0.05 • Power: 0.80 In stage 1, 15 evaluable patients are to be included. If response according to RECIST 1.1 and/or ITMIG criteria is observed in 2/15 patients in stage 1, accrual of 10 evaluable patients will continue in stage 2. If responses are observed in 5 out of 25 patients, the alternative hypothesis is accepted and Selinexor is considered active and appropriate for further evaluation. This is not an intention to treat (ITT) study and included patients who are not evaluable for response will be replaced.
Planned interim analysis	An interim analysis is planned after stage 1. Decision to go to stage 2 will be made by a consortium with representatives from both EU study and US study and Karyopharm. In case 2 patients out of 15 patients derive clear clinical benefit according to a unanimous agreement among members of the consortium, a decision can be made to proceed to stage 2. Clear clinical benefit is defined as: non-progressive disease with improvement in tumor related symptoms and treatment is well tolerated.

FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY

	Screening		Cycle 1- 2	Cycle ≥3	EOT Visit	EOS Visit
Visit window [days]	< 28 days prior to start of therapy	< 7 days prior to start of therapy	Day 1 & 15 ± 3 days	Day 1 ± 3 days	Off treat-ment	30 days ± 7 days
Informed consent[1]	x					
Inclusion and exclusion criteria		x				
Demographics	x					
Medical History[2]	x					
Pregnancy test (if applicable)[3]		x			x	
Body height and weight[4]		x	x	x	x	x
Vital signs[5]		x	x	x	x	x
Physical examination and ECOG[6]	X		x	x	x	x
12-lead ECG	x					
Hematology (CBC)[7, 8]		x	x	x	x	x
Complete Serum chemistry[7,9]		x	x		x	x
Limited Serum chemistry[10]				x		
Assessment of disease status[12]	x			x	x	
Selinexor Dispensing			x[16]	x		
Adverse events	x	x	x	x	x	x
Concomitant Medication	x	x	x	x	x	x
Obtain Archive Tumour biopsy tissue[13]		x				
Ophthalmic exam[14]	X					
Nutritional consultation[15]	x					

Notes

[1] Prior to the first study-specific measures

[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Applicable for women of childbearing potential. Serum β-HCG test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window

[4] Body height will be measured at screening only

[5] Vital signs: blood pressure, pulse and temperature

[6] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed.

[7] Laboratory assessments do not need to be repeated on Day 1 if they were completed within the previous 7 days.

[8] Hematology: hemoglobin, hematocrit, mean corpuscular volume, white blood cell (WBC) count, WBC differential, neutrophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated. Hematology will be repeated twice a week in case of severe (grade 3-4) neutropenia or thrombocytopenia.

[9] Complete Serum Chemistry for baseline, cycles 1&2 and end of study/treatment visit include Sodium, Potassium, Creatinine, Glucose, Calcium ion, Magnesium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, LDH, Albumin, TSH.

[10] Limited Chemistry including: Sodium, Potassium, Creatinine, Glucose, ALT, AST, Alkaline Phosphatase, Total Bilirubin

[12] Disease status will be measured once every two cycles with CT scan of chest and abdomen.

[13] Tumour tissue will be obtained pre-dose provided that the patient has available archival biopsy tissue.

[14] Full ophthalmic examination is required at Screening, and, if clinically indicated, during the study. Prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; fundoscopy and slit lamp to document lens clarity – if a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system.

[15] Nurse/research nurse can provide this in person or via phone call.

[16] Dispensing only occurs at Day 1 of Cycle 1 and 2.

1 Background and Rationale

1.1 Background

1.1.1 Thymic Epithelial Malignancies

Thymomas and thymic carcinomas (TC) are rare epithelial tumours of the thymus. Based on cancer registry data, the overall incidence of thymoma in the US is 0.13 per 100,000 person-years. Thymoma is exceedingly uncommon in children and young adults, rises in incidence in middle age, and peaks in the seventh decade of life.

Although most thymomas have organo- typic features (i.e., resemble the normal thymus), TC are morphologically indistinguishable from carcinomas in other organs. Apart from their different morphology, TC and thymomas differ also in functional terms (TC, in contrast to thymomas, have lost the capacity to promote the maturation of intratumourous lymphocytes), have different genetic features, a different immunoprofile (most TC overexpress c-KIT, whereas thymomas usually do not), and different clinical features (TC, in contrast to thymomas, are usually not associated with myasthenia gravis or other autoimmune phenomena). Thus, although all the data suggest that the biology of thymomas and TC is different, in clinical practice, their therapeutic management up to now is similar [1]. However, thymic carcinoma are more often diagnosed at a later stage, are less often radically resectable and respond less well to standard chemotherapy. Overall survival of TC is inferior even in advanced stages.

Histology

Based on available current knowledge about the biology of these tumours, the World Health Organization (WHO) classification of thymic epithelial tumours separates thymomas from thymic carcinomas [1]. Thymomas are defined as neoplasms arising from or exhibiting differentiation toward thymic epithelial cells, usually with a variable component of non-neoplastic lymphocytes. All types of thymomas have the potential of metastasising and are hence malignant [2].

From a morphologic point of view, there are two major types of thymoma: in type A, the neoplastic epithelial cells have a spindle- or oval-shaped nucleus with a uniform bland cytology. In type B, the tumour cells have a predominantly round or polygonal appearance. Type B thymomas are further subdivided depending on the degree of atypia and the size of the lymphocyte component into B1 (richest in lymphocytes), B2, and B3 (richest in epithelial cells). Thymomas combining type A with type B features are designated AB [2, 3].

Apart from their different morphology, type A, AB, and B thymomas also show differences with respect to molecular genetics, expression of immunohistochemical markers, such as MHC class II or AIRE (autoimmune regulator)[2-4], a different capacity to promote maturation of intratumoural lymphocytes, and different association with clinical autoimmune syndromes, such as myasthenia gravis (MG). Together with gene expression data, these findings have led to the unifying hypothesis that the different histologic thymoma subtypes may reflect different maturational stages of a thymic epithelial progenitor cell.

In most published series, the predominant histologic subtypes are B2 and AB thymomas (each 20–35% of all cases), whereas type B1 and type A thymomas are more rare types (5–10% in most studies). For clinical purposes, thymomas can be stratified into two different risk groups: type A, AB and B1 thymomas in most retrospective studies pursued an indolent course with 5- and 10-year overall survival rates between 80 and 100%. By contrast, type B2 and B3 thymomas are potentially aggressive tumours with a potential for distant metastases (approximately 15% of cases), usually to lung, liver, bone, and soft tissues. More frequently (up to 25% of cases in some series), these tumours show pleural dissemination. Lymph node metastases are rare.

Thymic carcinomas by definition are malignant epithelial tumours with overt cytologic atypia, almost invariably invasiveness and lack the “organotypic” (thymus-like) features of thymomas. They are further subclassified into squamous cell, basaloid, lymphoepithelioma-like, neuroendocrine, and many other types. Squamous cell carcinoma is the most frequent subtype with a higher incidence in Asia than in western countries. The typical autoimmune phenomena seen in thymoma (e.g. MG, pure red cell aplasia) are usually not found in thymic carcinoma, although other paraneoplastic syndromes such as polymyositis can occur. In contrast to thymomas, thymic carcinomas may show metastasis to regional lymph nodes (mediastinal, cervical, and axillary). They frequently express CD117 (c-KIT), a helpful immunohistochemical feature, to differentiate thymic carcinomas from mediastinal metastases of carcinomas located elsewhere.

Staging

Thymomas are staged according to the Masaoka-Koga classification system according to involvement of adjacent structures and spread. Tumour extent is defined as follows [4]:

- Stage I: completely encapsulated
- Stage II: invasion by the second layer surrounding the tumour
- Stage III: direct invasion beyond the second layer
- Stage IV: Discontinuous progression

Invasion into the pleural cavity is preceded by breaching of anatomic barriers in the following sequence: capsule, mediastinal pleura, visceral pleura, and finally lung. On the other hand, when the tumour invades the mediastinum, it invades through the capsule, mediastinal adipose tissue, pericardium or great vessels, and finally heart. Accordingly, the second layer surrounding the tumour is either the mediastinal pleura or mediastinal adipose tissue. Stage IV disease is divided into two categories IVa and IVb. Stage IVa consists of serosal dissemination, i.e., involvement of the pleura and pericardium. Stage IVb consists of metastasis via lymphogenous and hematogenous routes. Accordingly, stage IVb includes cases with lymph node metastasis at any station.

Patients with a high Masaoka-Koga stage have a worse prognosis [4]. A new WHO staging stystem is anticipated in 2016 [5].

Treatment

Although the treatment of malignant thymomas and thymic carcinomas in daily clinical practice is similar, the available data suggest that their biology is different and that in fact they may also require different therapeutic approaches. Advanced thymomas and TC that cannot be completely resected require neoadjuvant or adjuvant systemic treatment, often in combination with radiotherapy. Cisplatin-based regimens, such as the PAC scheme (cisplatin, adriamycin, and cyclophosphamide) are most often used with response rates as first line therapy of 50%-80% [6-8]. Relapses or progressive disease can be expected to occur in 10 to 30% of all patients. In 20 to 30% of these patients, objective remissions can be achieved by cisplatin-based regimens after relapse-free intervals. Approximately 50% of patients with an advanced malignant thymoma or thymic carcinoma will be candidates for a—so far undefined— second-line treatment [1].

Initial studies of targeted treatment in thymoma have demonstrated disappointing results [9]. In thymic carcinoma, the multikinase inhibitor sunitinib achieved a response rate of 25% in a recently reported phase II trial [10]. Other targeted agents investigated in patents with TETs include EGFR targeted agents, HDAC inhibitor, antiangiogenic agents, IGFR targeted therapies and studies investigating PD-1/PD-L1 targeted agents are under development.

1.1.2 Nuclear Export

Over 10 major tumour suppressor pathways have evolved in order to prevent the development and progression of neoplasia. The majority of the tumour suppressor (TSP) and growth regulatory proteins (GRP) mediating these pathways act in the cell nucleus downstream of signaling pathways. Accumulating data suggest that in order to maintain their malignant behaviour, neoplastic cells must inactivate most or all of

the known TSP and GRP pathways. Active nuclear export of TSP/GRP is one very efficient and rapid means of overcoming the normal cell cycle and genomic instability checkpoints mediated by these proteins.

The majority of proteins > 40 kD and many RNAs require specific transporters in order to enter and exit the nucleus through the nuclear pore complex (NPC), and these transporters are known as importins or exportins, depending on their specific activity. There are seven known nuclear export proteins, exportins 1-7. Exportin 1 (XPO1), also called chromosome region maintenance protein 1 (CRM1), is the major nuclear export protein in the cell and has found to be overexpressed in many types of cancer.

XPO1 is the sole exportin responsible for the transport of most of the TSP and GRP out of the nucleus into the cell.

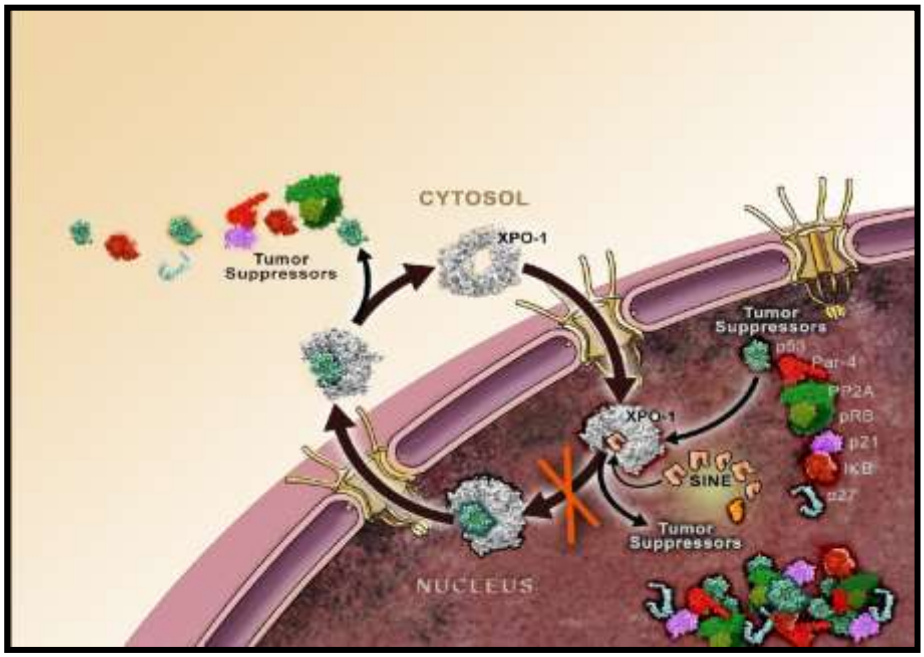


Figure 1: XPO1 nuclear export cycle

The regulation of TSP and GRP is normally tightly regulated by the cell in response to environmental signals. In order for cells to divide efficiently, ordered activation and inactivation of cell cycle control proteins is required. One of the most efficient means of altering a protein's functions is simply to change the protein's location. Because TSP and GRP mediate the majority of their control functions in the nucleus, the nuclear export of these molecules is an efficient means of inactivating them. Emerging data suggest that tumour cells take advantage of this by increasing XPO1 levels.

XPO1 can be inhibited by the Selective Inhibitor of Nuclear Export (SINE) selinexor (see Section 1.1.3). Thereby, the nuclear retention of key TSP/GRP is forced and multiple TSPs/GRPs are enhanced, as shown in Table 1.

Table 1: XPO1 inhibition enhances multiple TSPs/GRPs

Oncogenic Pathway	TSP/GRP Enhanced by XPO1 inhibition	Oncogenic Pathway	TSP/GRP Enhanced by XPO1 inhibition
AKT↑, PI3K↑, PTEN↓	FOXO, p27	CDK2-CyclinE-E2F1	pRb, p27, $p21^{CIP1}$
deletion p53, MDM2↑	$p21^{CIP1}$, p53, $p14^{ARF}$	NPM1 Mutation	p53, $p14^{ARF}$
HER2, EGF-R	FOXO, pRB	c-Myc ↑	PP2A, $p21^{CIP1}$
$p16^{INK4A}$↓ or $p14^{ARF}$↓	pRB, p53	Bcr-Abl	PP2A, Abl
mTOR↑	p53, p27, FOXO	Bcl2 ↑, Bcl-xL ↑	p53, $p16^{INK4A}$
Wnt / ß-Catenin ↑	APC, HMGBP1	Notch ↑	FOXO
deletion pRb	p27	NF-êB ↑	I-κB

For each of the major growth and tumour stimulating pathways found across the various cancers, XPO1 appears to stimulate at least one counteracting pathway. This may explain the broad activity of XPO1 inhibitors in vitro and in animal models. Similar data are now emerging in the ongoing clinical trials of Selinexor (KPT-330) in both solid tumours and hematologic malignancies. By activating a genome survey, TSP/GRP can "distinguish" between cancerous and normal cells, inducing apoptosis in the former, and maintain cell cycle arrest in the latter (until the XPO1 export block is released, see Figure 2):

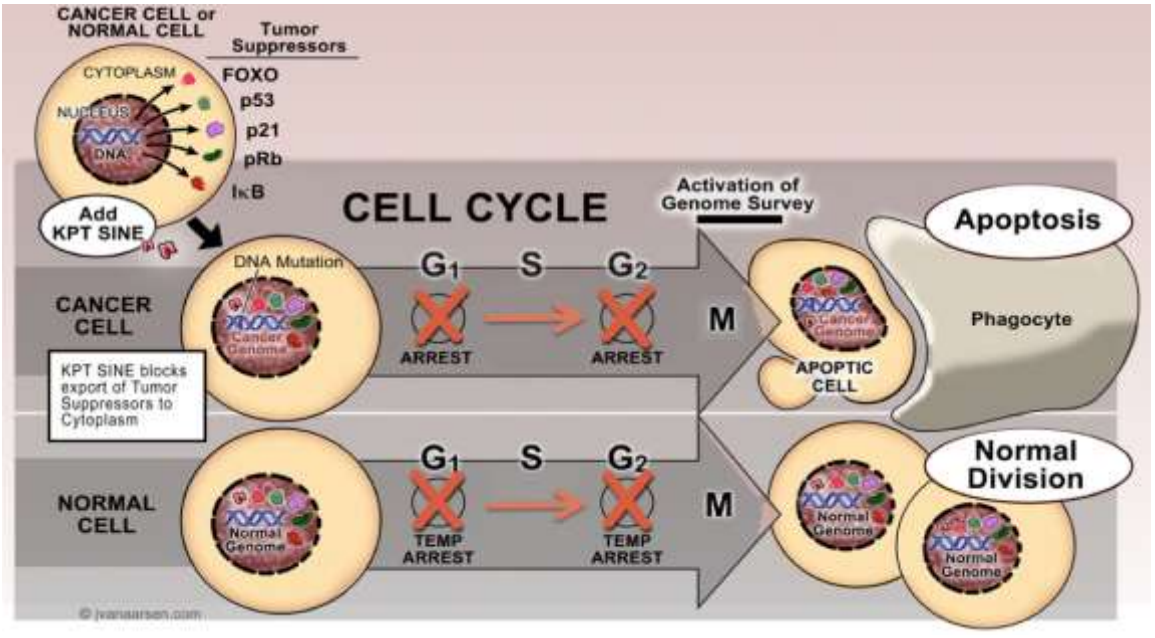


Figure 2: KPT-SINE (XPO1 inhibitors) induce distinct outcomes in normal and malignant cells

1.1.3 Selinexor: Mechanism of Action

A brief summary of key aspects of the preclinical evaluation of selinexor is presented below. Further detailed information is provided in the Investigator's Brochure.

Selinexor is an oral, first in class, potent, slowly reversible, covalent Selective Inhibitor of Nuclear Export (SINE™) that specifically blocks the karyopherin protein Exportin 1 (XPO1/Exportin 1), also called chromosome region maintenance 1 (CRM1).

XPO1 is overexpressed 2-4 fold in all cancers studied to date. XPO1 is an exclusive nuclear transporter for shuttling the major Tumour Suppressor Proteins (TSPs) and other growth regulators out of the nucleus. Since TSPs require nuclear localization to mediate their deoxyribonucleic acid (DNA) damage assessment/tumour suppressing functions, nuclear export leads to their functional inactivation. In addition, many TSPs are degraded by the proteasome when they are transported to the cytoplasm.

Blockade of XPO1 leads to marked accumulation of TSPs in the nucleus of all cells, leading to cell cycle arrest at the G1±G2 checkpoints. Cells with damaged genomes – *i.e.*, cancer cells – undergo apoptosis, whereas undamaged normal cells remain in cell cycle arrest until the XPO1 block is released. Consistent with its activation of multiple TSPs, selinexor has shown broad anti-cancer activity in nonclinical murine xenograft, orthotopic, primagraft, and leukemograft models, largely independent of the resistance profile of the cancer cell line being investigated.

A related SINE™ compound, KPT-335 (INN "verdinexor"), has shown potent oral single agent activity in dogs with spontaneous newly diagnosed or chemotherapy refractory Non-Hodgkin's lymphomas (NHL, primarily diffuse large B-cell lymphoma (DLBCL) and some T-cell lymphomas) with a response rate of 31% at doses of 25-30 mg/m^2 (1.25-1.5 mg/kg) orally 2-3 times per week.

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

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumour-derived cell lines and patient samples in culture including resistant cancers due to multiple factors, with the majority of 50% inhibitory concentration (IC_{50}) values for cytotoxicity <800 nM and most hematologic tumour lines having IC_{50} values of 20 – 400 nM for selinexor. Moreover, selinexor demonstrated cytotoxicity in multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) cells in the absence or presence of bone marrow stroma cells (BMSC). In contrast, normal

cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC_{50} values were typically >5 µM.

As noted above, selinexor had little effect on normal (nonmalignant) lymphocytes or other nontransformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction.

1.1.4 Selinexor: Clinical Summary

1.1.4.1 Clinical Pharmacokinetics and Pharmacodynamics

Selinexor is orally bioavailable and exhibits dose-proportional exposure with moderate- to –high inter-patient variability across a wide dose range of doses in patients with advanced hematologic malignancies or solid tumors. The elimination (terminal) half-life (t½) of selinexor is approximately 6 to 8 hours.

Clinical pharmacodynamics (PDn) of selinexor have been studied in patients with advanced neoplasms, showing that XPO1 inhibition by selinexor leads XPO1 mRNA induction and nuclear retention of TSPs. Selinexor-induced nuclear localization of TSPs, including p53, p27, FOXO-1, and FOXO-3A, was evident in-patient biopsies. Reduction in the proliferation marker Ki67, with increases in apoptotic markers, was also observed.

1.1.4.2 Clinical Efficacy and Safety

Results from ongoing clinical studies have shown that selinexor induces durable antitumor responses across a broad range of relapsed/refractory (R/R) hematologic and solid tumor cancers, which is consistent with its proposed mechanism of action. In general, these effects appear to be independent of tumor type or prior treatment(s).

In Part 2 of the STORM study (KCP-330-012), a total of 123 patients with RRMM were treated with selinexor 80 mg in combination with dexamethasone 20 mg. The ORR of the 122 patients in the efficacy population was 26.2%, which included 2 sCRs (both assessed as MRD negative), 6 VGPRs, and 24 PRs assessed by the IRC using IMWG criteria. The median time to first response was 4 weeks (range: 1 to 10 weeks). The median OS was 8.6 months overall, with patients who had ≥PR or ≥MR having a median OS of 15.6 months (both groups), compared with 1.7 months for patients with PD or NE).

In the SADAL study (KCP-330-009), as of the cutoff date for the IB of 31 March 2019, the overall ORR was 28.3%, with 13 CRs and 23 PRs, and the ORR was 33.9% and 20.6% for patients with the GCB or non-GCB

subtypes, respectively. The median DOR was 9.2 months. The median OS for all patients was 9.0 months, but median OS was not reached in responding (≥PR) patients.

As of 31 March 2019, 3111 patients with hematologic or solid-tumor malignancies had received at least 1 dose of selinexor; in addition, 115 patients received at least 1 dose of selinexor or blinded study treatment (ie, selinexor or placebo) to a total of 3226 patients. These 3226 patients include 2076 patients from Company-sponsored trials (CSTs; 1961 who received selinexor and 115 who received blinded study treatment), 1016 patients from ISTs who received selinexor, and 130 patients from the selinexor expanded access program (EAP) who received selinexor; and 4 patients who received selinexor through clinical trials sponsored by Ono Pharmaceutical Co., Ltd. Safety data from all CSTs, ISTs and the EAP are reviewed at least monthly by the Sponsor.

Serious adverse events (SAEs) from all patients (CSTs, ISTs and the EAP) are collected in the Sponsor global safety database; cumulative summaries of SAEs through 31 March 2019 for all patients have been reviewed and quantified in Appendix 12 of the IB v 9. Summaries of clinical safety data including SAEs and adverse events (AEs) are provided in Section 5.4 in IB v 9. The most commonly reported treatment-emergent adverse events (TEAEs) in CSTs were nausea (65.1%), fatigue (57.9%), thrombocytopenia (52.1%), anorexia (includes MedDRA “decreased appetite”; 51.0%), anemia (42.3%), vomiting (38.2%), and diarrhea (36.0%), that were generally low-grade and reversible (Section 5.4.2 and Table 39 in IB v 9). TEAEs of thrombocytopenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies. In addition to safety results, efficacy (response and duration of disease control) results from ongoing clinical studies are included by cancer type in this IB update. An overview of ongoing

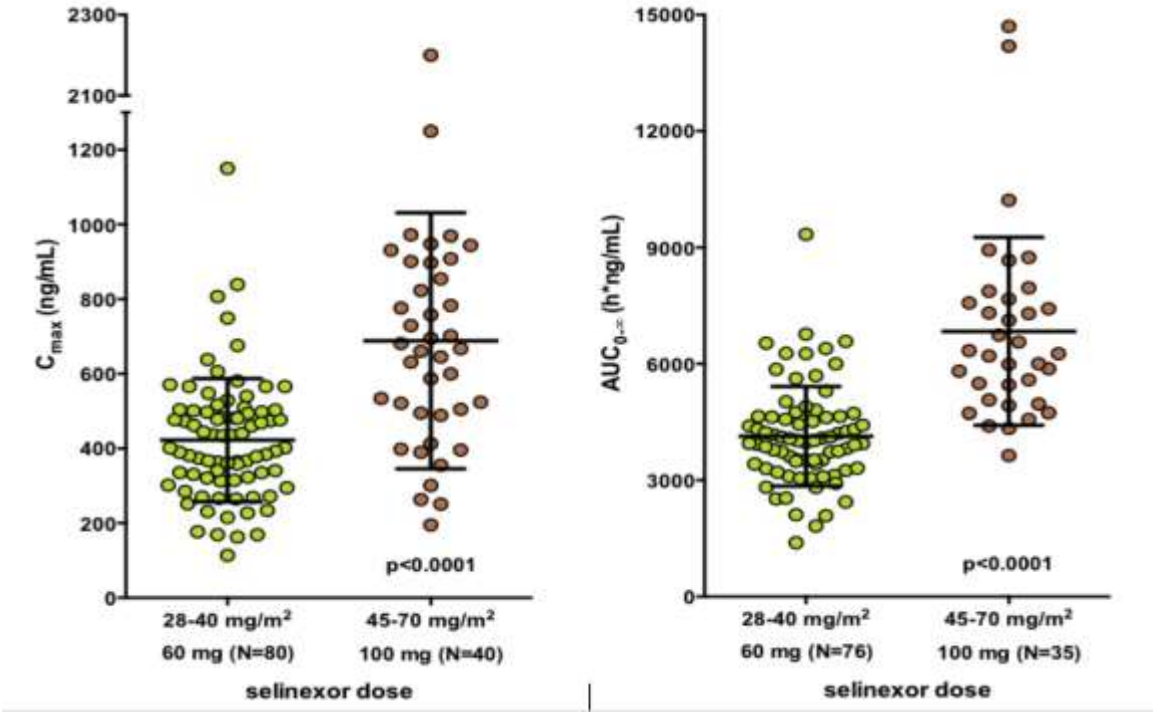
CSTs (as of 31 March 2019, except where noted) is provided in Appendix 1 of IB v 9. Additional ISTs are ongoing and efficacy results from these studies are not discussed in this IB. Based on these preliminary efficacy and safety data, the Sponsor plans to continue the development of selinexor to treat a wide variety of malignancies, including diseases that are not currently mentioned in this IB.

1.1.5 Dosing rationale

An analysis of Phase 1 patient data showed that patients receiving doses ≤60 mg stayed on study longer than patients receiving doses ≥65 mg (120 days vs 90 days). In addition, a higher percentage of patients receiving 60 mg stayed on study ≥4 months as compared to patients receiving doses ≥65 mg (27% vs 19%). The 60 mg dose was associated with maximal responses (CR, PR, SD). These data supported 60 mg as the RP2D when the current study originally was designed. However, tolerability seems poorer than expected among the first 16 patients included in total in the EU and US studies. Either dose reductions or discontinuation of treatment due to toxicity have been necessary in ten out of 16 patients and

consequently most patients have been treated at 40 mg twice weekly for three weeks in a four week schedule. In general, toxicities resulting in dose reductions were typically nausea, vomiting, loss of appetite and fatigue followed by grade 4 thrombocytopenia (n=1) and severe pneumonia. Based on these data, the starting dose going forward will be 40 mg twice weekly.

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 5th and 95th 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 (Cmax and AUC(0-∞)) for a given flat (fixed) dose of selinexor were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA.



Currently the dosing schedule for selinexor in phase II trials is twice weekly (Day 1 and 3) during each week. This schedule is supported by pharmacodynamics studies showing selinexor binding to its XPO1 target persisted for at least 48 hours. A dosing regimen of 10 doses per Cycle (3 doses during weeks 1 and 3, 2 doses during weeks 2 and 4) was evaluated in Phase 1 studies and found to be less tolerated than the twice weekly (8 doses per Cycle) regimen, supporting the use of the twice weekly dosing regimen as the preferred regimen (Chen C et al, ASH 2015).

1.1.6 XPO1 and Selinexor in Thymic Epithelial Tumours

XPO1/CRM1 is overexpressed in many tumour cells including pancreas, prostate and gastric cancers, glioma, osteosarcoma, myeloma, AML and lymphoma. Expression of XPO1/CRM1 in TETs are not well characterised. However, both *RB* and $P16^{INK4}$ have been implicated in TETs [11]. Selinexor enhances the nuclear presence of these proteins, where phosphorylated *RB* lead to G1→S block.

Furthermore, TETs seems to be largely dependent on alterations in the BCL-2 family (BCL-1 and BCL-xl), and FOXC1. Copy number variations in the BCL-2 family and FOXC1 seems to be frequent and correlated with poor prognosis [12-14].

1.2 Study Rationale

So far, four patients with advanced TETs have been treated with selinexor in phase I trials. Metabolic response was noted in a patient with squamous thymic carcinoma previously treated with two lines of chemotherapy and radiotherapy. Structural tumour shrinkage and metabolic responses were seen in two patients. A patient with recurrent type B2 thymoma achieved a 15 % reduction in tumour measurements that was sustained for 20 months. A partial response of 44 % was achieved in a patient with type B1 thymoma who had progressed after multiple surgery, radiotherapy and two lines of chemotherapy. The fourth patient remains on study for 10 months with stable disease.

Available data suggest that TETs may be dependent on the activity of only few oncogenic pathways including BCL-2 family and inactivation of few tumour suppressors including FOXC1 and RB. TETs are usually described as tumours with few genetic alterations and therefore little redundancy. This makes them theoretically very susceptible to activation of tumour suppressors and more unlikely to develop resistance. Selinexor has shown retention of tumour suppressors to the nucleus, which are capable of reverting the malignant phenotype of cells harbouring these alterations, making selinexor a possible active drug in these tumours. Furthermore, studies in cell lines have shown activity of selinexor in TETs (unpublished data).

2 Study Objectives

2.1 Primary Objectives

The aim of the study is to determine the efficacy of selinexor in adults with TETs determined by overall response rate (RECIST 1.1) in two parallel cohorts of patients with advanced thymomas progressing after primary chemotherapy.

2.2 Secondary Objectives

Secondary objectives of the study are

- To determine the efficacy of Selinexor in adults with TETs determined by overall response rate according to modified ITMIG response criteria.
- To determine the overall response rate of selinexor in patients with advanced thymomas.
- To determine six months PFS of patients with TET treated with selinexor.
- To determine overall survival of patients with TET treated with selinexor.
- To evaluate exploratory biomarkers for prediction of response to selinexor in patients with TET.
- To determine progression free survival in patients with advanced, inoperable TETs treated with selinexor
- To evaluate safety and tolerability of Selinexor.

3 Investigational Plan

3.1 Study Design and Dosing Regimen

3.1.1 Definition of Treatment Cycle

One cycle is defined as 28 days. Selinexor 40 mg oral tablets will be administered twice weekly, either on Monday/Wednesday, Tuesday/Thursday, Wednesday/Friday, Thursday/Saturday, or Friday/Sunday in a 3-weeks-on and 1-week-off schedule. Patients will receive a supply of selinexor tablets for at-home dosing.

Study drug administration may be delayed for toxicity according to protocol Section 6.3.

3.1.2 Treatment Duration

Patients will discontinue treatment with selinexor if one of the following events should occur

- Progression of disease demonstrated by CT scan according to RECIST 1.1
- Clinical progression in the opinion of the investigator
- Unacceptable toxicities
- Patient’s request to discontinue
- The investigator considers it in the patient’s best interest to discontinue treatment.

Details of the study schedule are illustrated in the study flow chart.

3.1.3 End of Treatment Visit

Patients who discontinue treatment will be encouraged to undergo an end-of-treatment visit unless they have withdrawn consent to participate in the trial.

3.1.4 Follow-Up Phase

Patients who discontinued for reasons other than progression of disease (and withdrawal of consent for participation in the trial) should be encouraged to attend an End-of-Study visit 30 days after discontinuation of treatment and to visit the clinic for clinical evaluation of their disease every 4 weeks and assessment by CT scan every 12 weeks until disease progression. If the patient is in follow-up and/or treated post-study, the clinical evaluation can be done by the treating physician and the patient need not to visit the site. After disease progression all patients will be evaluated for survival and further therapy by reviewing their medical charts regularly.

4 Study population

4.1 Target Population

Adults with histologically confirmed, advanced, inoperable TETs who are progressing after primary chemotherapy.

4.2 Inclusion Criteria

Please refer to the synopsis.

4.3 Exclusion Criteria

Please refer to the synopsis.

5 Schedule of Assessments and Procedures

Please refer to the Schedule of Assessments at the end of the synopsis for an overview.

Data will be collected via the completion of a Case Report Form (CRF) for each enrolled patient. The investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study. Written Informed Consent must be obtained before any study specific assessment is performed. A study specific assessment is defined as a procedure that is not part of the routine assessments performed for diagnostic purposes or standard care. Screening assessments should occur within 28 days of the first administration of study drug. Patients who do not meet the eligibility criteria will not be enrolled in the study. Patients should receive their first dose of study treatment as soon as possible after registration, but not later than 7 days after registration.

5.1 Study Assessments

5.1.1 Tumour Assessment

The disease status will be measured by CT scans and response will be assessed according to RECIST 1.1. Only patients with measurable disease will be enrolled. Furthermore, disease status will be evaluated according to ITMIG response criteria.

The baseline CT scan must be recorded and measured within 28 days prior to treatment start. A CT scan performed as part of standard of care can be used as the baseline CT scan provided study treatment will start within the 28-day window.

Patients are evaluated for surgery as per institutional standards.

5.1.2 Translational and pharmacodynamics (PDn) analyses

Tumour Biopsies

Archived Tumour tissue may be obtained from before the first dose. Tissue may be tested for levels of expression and cellular localization (nuclear/ cytoplasm) of biomarkers of response including XPO1; representative XPO1 cargos such as: P53, SURVIVIN, FOXO1; markers of direct-tumour response such as the proliferation marker Ki-67 and the apoptotic marker Cl. Casp3 and potential predictive biomarkers by immunohistochemistry.

Tumour tissue obtained before treatment should be available as paraffin embedded-formalin fixed sample. Tumour samples may be stained by OHC for XPO-1 antibody and protein expression will be quantified. XPO-1 expression will be correlated with response to treatment.

Samples collected may be sequenced using NEXTGEN technology on our recently acquired Miseq sequencer (Georgetown University). Patients who have no available tissue will be eligible for the trial. A custom-designed cancer-associated gene panel which includes all the identified recurrent mutations in thymic carcinomas, published cancer driver genes and COSMIC cancer gene census (http://cancer.sanger.ac.uk/cosmic/census) will be used for targeted sequencing [15-17]. Comparative sequencing analysis of the tumour/blood pairs will allow us to identify specific somatic mutations and the number of somatic mutations in a given tumour. In addition, samples may be sequenced for the identification of mutations in DNA damage repair genes such: ATM, ATR, BRCA1, BRCA2, CHEK1, CHEK2, FAM175A, GEN1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51, ERCC1, MLH1. The data will be employed to evaluate the correlation between the type/number of mutations and patients' response to Selinexor therapy.

All biopsy-related studies will be performed at Georgetown Lombardi Comprehensive Cancer Center.

5.1.3 Safety and Tolerability Assessments

Safety will be monitored by assessing physical examinations including vital signs and weight, performance status, concomitant medication use, and laboratory parameters. Information regarding AEs will be collected and each AE will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v 4.03) beginning at day of first administration of study drug, throughout the treatment period and to the extent possible until 30 days after last dose of study drug.

5.1.4 Laboratory Assessments

The standard clinical laboratory analysis is to be performed by the study site's local laboratories according to the Schedule of Assessments. More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded on the eCRFs. At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g. interruption or delay of study treatment or require therapeutic intervention) must be recorded in the CRF. When abnormal laboratory values or test results constitute an adverse event, they must be recorded on the CRF Adverse Events page. Every effort must be made to follow the schedule outlined in the Schedule of Assessments.

5.2 Study Procedures

5.2.1 Screening Procedures

All patients will be screened and screening procedures must be performed within 28 days prior to the start of study treatment unless otherwise stated in *FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY*.

Please refer to *FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY* in the end of the synopsis for details on screening procedures.

5.2.2 Treatment Phase

Please refer to *FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY* in the end of the synopsis.

5.2.3 End of Treatment and End of Study

Patients who discontinue therapy for any reason other than withdrawal of consent will be encouraged to have an End of Treatment (EOT) and End of Study (EOS) visit at the day they are withdrawn from study and 30 day after EOT, respectively. At the EOT and EOS visits, the patients will undergo safety assessments according to the *FLOW CHART: SCHEDULE OF ASSESSMENTS DURING THE STUDY* in the end of the synopsis.

5.2.4 Follow-up before progression of disease

For patients who discontinued for reasons other than progression of should be encouraged to visit the clinic for clinical evaluation and CT evaluation every three months for the first year, then every 6 months until progression of disease is determined.

5.2.5 Survival Follow-up

After disease progression all patients will be evaluated for survival and document subsequent anticancer therapy by reviewing their medical charts every 3 months. Patients who have not expired by the data analysis cut-off date will be censored at their last date known to be alive.

5.2.6 Completion of Study

The study will be completed when the last patient has died or all patients have completed EOT and have been followed for at least 6 months after their last dose of study drug, or have been lost to follow-up, or withdrew consent, whichever occurs first.

5.3 Planned Treatment of the Patients after End of Treatment Phase

After completion of the End of Treatment visit, patients will be treated at the discretion of the investigator according to standard medical routine.

5.4 Removal of Patients from Treatment

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients will be removed from further treatment for the following reasons:

- Disease progression
- Non-compliance
- Patient no longer consents to participate in the study
- Illness that interferes with study assessments
- The patient undergoes radical surgery
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion for any reason
- Pregnancy
- Termination of the study by the sponsor

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the safety evaluation for the EOT should be performed, if possible. The CRF section entitled “End of Treatment” must be completed in all cases. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient’s withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

5.5 Study Discontinuation

The study may be discontinued at the discretion of the sponsor in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

6 Investigational medicinal product (IMP)

The IMP in this study is selinexor.

6.1 Preparation and Administration of Selinexor

6.1.1 Preparation and Administration of Selinexor

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol.

Tablets, including instructions for administration, are dispensed by study personnel on an outpatient basis. Patients will be provided with an adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

6.1.1.1 Drug Name, Formulation and Storage

Drug name: Selinexor (KPT-330)

Formulation: Tablets. Selinexor will be supplied and administered as coated, immediate-release oral tablets in a strength of 20 mg tablets in wallet-sized blister packs.

Storage: Do not store above 30°C. Do not freeze. Store in a locked and secured area with access restricted to the site staff pharmacist or designee(s). Selinexor tablets are currently in on-going stability studies. The

expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

Handling

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

Availability

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

Preparation

No special preparation required.

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

Administration

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

Ordering

Drug order forms with all the needed contact information will be provided at the start of the trial, along with recommended initial and resupply stock orders. Orders submitted via e-mail will be filled within 7-10 business days of receipt.

Accountability

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

Destruction and Return

At the end of the study, unused supplies of selinexor should be destroyed and documented according to institutional policies. Copies of drug accountability records must be sent to Karyopharm Therapeutics, Inc. upon request and at the end of the trial.

6.1.1.2 Route of Administration

Selinexor tablets will be taken orally twice weekly, either on Monday and Wednesday or on Tuesday and Thursday or Wednesday and Friday in a 4-weeks cycle with dosing in weeks 1-3. Selinexor is to be taken with a solid food consumption together with a glass of water. Each dose will consist of flat dose 40 mg selinexor for oral administration.

6.1.1.3 Compliance

The investigator should ensure that the investigational product is used only in accordance with the protocol. The investigator/ designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.

6.2 Supportive Care and Dose Reduction Guidelines

6.2.1 Clinical Supportive Care Recommendations

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 2500 adult patients treated with selinexor as of 31 Mar 2018, the main side effects are primarily related to anorexia with poor caloric and fluid intake, weight loss, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.

Besides 5-HT3 antagonists, supportive care including anti-nausea / anti-emetic therapy, per institutional guidelines and/or National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN CPGO) should be utilized as clinically indicated at the discretion of the treating physician.

Required 5-HT3 Antagonists

Prophylactic therapy with 5-HT3 antagonists is required for all patients initiating selinexor treatment on day of selinexor q 8 hours and for 2 days post selinexor (see Nausea and Vomiting guidance in Section 6.1.2 for additional details). In addition all patient should receive a second anti-emetic of olazepine 5 mg daily qhs.

Particular attention should be paid to anorexia with poor caloric and fluid intake which can lead to weight loss, dehydration and fatigue. Supportive care per institutional guidelines and/or National Comprehensive

Cancer Network® Clinical Practice Guidelines in Oncology (NCCN) should be utilized as clinically indicated at the discretion of the treating physician.

Supportive care recommendations based on the cumulative clinical experience with selinexor to date are presented in the following sections. Dose reduction guidance, including specific supportive care recommendations by AE grade, to address selinexor-related adverse events is provided in **Table 3**.

Gastrointestinal and Constitutional Effects

Nausea and Vomiting

Nausea and vomiting are very common, occurring in the majority of patients who do not receive supportive care. All patients are required to receive prophylactic anti-emetics. Note: Patients are required to receive ondansetron 8 mg (or similar 5-HT3 antagonist) before their first dose of selinexor and continued 2 or 3 times daily. Additionally, olanzapine are required to be given prior to the first dose of selinexor and continued qhs per NCCN Guidelines. Neurokinin-1 receptor antagonists (e.g., aprepitant) should also be considered in the event of uncontrolled emesis with standard treatments. Patients with severe nausea and vomiting early in their course may be experiencing significant anti-tumor response, and early response assessment should be considered.

Anorexia (Decreased Appetite)

In patients with problematic food/liquid/caloric intake secondary to anorexia, a patient log of food and drink should be considered and monitored by site staff. Maintaining adequate fluid intake is also of paramount importance, particularly in older patients whose thirst reflex may be attenuated. Fresh juices, simple carbohydrates, as well as ginger-containing foods and beverages can improve appetite; ginger containing foods may also improve dysgeusia.

Patients should also receive dietary counselling and monitor both their caloric and fluid intake carefully. Dysguesia may contribute to the anorexia, and dietary adjustments can be helpful. It is strongly recommended that patients receive ongoing weight assessment and nutritional consultation. Administration of high caloric beverages (e.g., Boost®, Ensure®) and appetite stimulating agent(s) should be considered in patients who develop early signs of anorexia despite the required prophylactic therapy.

A combination of appetite stimulating agents and anti-emetics is usually effective in managing selinexor associated anorexia that does not respond to the above interventions. Appetite stimulating medications can be tapered in many patients in Cycle 1, but prevention of anorexia is much more effective than treatment once problems begin. Additional information on the management of anorexia is provided in the NCCN Guidelines.

Diarrhea

Diarrhea associated with selinexor is typically low grade and usually responds to treatment with standard anti-diarrheal agents (e.g., loperamide) and/or dose modification. Careful assessment of the patient's volume status is essential. Fluid replacement is important to prevent dehydration, fatigue and electrolyte abnormalities (e.g., hyponatremia).

Fatigue

Prevention of anorexia, vomiting, and dehydration may reduce fatigue. Hemoglobin levels must be optimized as anemia appears to contribute substantially to fatigue, particularly in patients with heavily pretreated hematologic malignancies. Please see the NCCN Guidelines for more information. In patients with adequate anti-tumor control on selinexor, once-weekly dosing is often associated with improvement in fatigue and other side effects.

Renal

Maintenance of adequate volume status is essential to prevent creatinine increases and other renal effects observed in patients treated with selinexor. Patients with acute increases in creatinine (usually accompanied by disproportionately higher elevations of BUN) should be evaluated for volume status and fluid intake as well as electrolyte levels. Fluid repletion usually leads to resolution of creatinine increases in patients with dehydration associated with selinexor.

Hematologic Effects

Thrombocytopenia

Selinexor may induce reductions in platelet counts, with minimal effects on numbers of megakaryocytes. The effects of selinexor on platelet generation are related to a slowing of maturation of megakaryocytes and a reduction in their average ploidy. There is no known effect on platelet function, and bleeding associated with low platelets has been uncommon.

Interruption or dose reduction of selinexor therapy, when appropriate, may lead to return of platelet counts in 1-3 weeks. See **Table 3** for specific guidance for managing Grades 1-4 thrombocytopenia.

Neutropenia

Standard granulocyte growth factors are highly effective for the treatment of neutropenia seen during treatment with selinexor and should be used early in patients whose neutrophil counts decline during

treatment. Patients should be instructed to report any symptoms or signs of infection such as fever, pain, sweating, and redness to their physician immediately.

Anemia

Selinexor-induced anemia may contibute to dizziness, confusion, syncope and/or fatigue, particularly in elderly patients and patients who are at greater risk of cognitive sequellae. Per NCCN Guidelines, treatment with RBC transfusions and/or growth factors, per institutional guidelines, should be considered for patients with symptomatic anemia.

Other Adverse Events Observed during Studies

Vision Blurred and Cataracts

Patients reporting blurry vision or other visual changes should be evaluated by an ophthalmologist. Nearly all cases of treatment emergent visual changes have not been associated with objective findings. Changes in lens prescriptions and/or wetting drops may improve vision. Blurred vision associated with selinexor use is typically self-limited, and dosing can usually be maintained at the same level and frequency.

Patients who are at risk of cataract formation, or have cataracts present at baseline, should be monitored for changes in lens opacity. If changes in lens opacity are observed, the patient should be evaluated by an ophthalmologist. In selinexor clinical studies, several patients have undergone cataract surgery with minimal to no interruption of selinexor dosing and without complications.

Hyponatremia

Investigators should rule out the possibility of pseudo-hyponatremia due to elevated glucose (or monoclonal protein) levels. Abnormal serum sodium levels should be corrected. Adequate fluid and caloric intake, including electrolyte-rich beverages instead of plain water, has led to reversal of hyponatremia. Diuretic use should be addressed and possibly stopped, and salt supplements should be considered. If hyponatremia persists, cardiac, hepatic, adrenal, renal and thyroid disorders, along with the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), and Fanconi syndrome should be ruled out.

Infection

Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended in any patient with Grade 4 infection or sepsis (even in the absence of documented infection) until the patient's clinical condition is stabilized. Selinexor can then be re-started at the same dose once the patient's clinical status has stabilized, even in the setting of continued intravenous antibacterial or other anti-microbial

agents (see section 6.1.3). Selinexor is not known to have any drug interactions with standard antimicrobials.

Dose Reduction Guidelines

Dose reductions and/or schedule modifications are allowed in order to optimize the antitumor activity and tolerability of selinexor. For some AEs, dose interruption and/or reduction is recommended. See **table 2** for pre-specified dose modifications for AEs related to study treatment and see **table 3** for dose reduction and interruption recommendations. Please note, however, that investigators should refer to specific dose reduction and interruption guidance within each protocol for the most up-to-date recommendations for each study.

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

The CTCAE v 4.03 is used for grading the severity of AEs; the therapy modifications described in Table 3 below are applied according to this severity grading. Toxicity will be documented as described in Section 7. If more than 1 type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay, as well as the reason, must be documented.

Tumour lysis syndrome

As of 31 March 2019, selinexor treatment-emergent TLS has been reported in a total of 8 patients including 6 SAEs. Four were from selinexor CSTs, 2 from IST, and 2 from EAP.

These 8 cases of tumor lysis syndrome occurred in patients with heavily pretreated malignancies (including 5 patients with MM, 2 patients with ALL, and 1 patient with AML). The intensity was reported as Grade 3 in 5 cases and as Grade 4 in 3 cases. The outcome was reported as recovered in 4 patients and not recovered in 2 patients; and was not reported in 2 patients. Total selinexor dosage prior to the event onset ranged from 20 mg to 320 mg (median 160 mg) and event onset latency ranged from 3 to 8 days (median 4 days). Out of 4 cases of TLS reported in 4 CSTs, 2 patients (Studies KCP 330-001 and KCP-330-008) received selinexor only, 1 patient (Study KCP-330-012) received selinexor plus dexamethasone, and 1 patient (Study

KCP-330-017) received selinexor, dexamethasone, and pomalidomide. In the selinexor EAP, 1 patient received selinexor plus dexamethasone and the other patient received selinexor plus bortezomib and dexamethasone (administration dates for bortezomib and dexamethasone were not reported).

Two patients from ISTs were reported receiving only selinexor. Treatment with selinexor was stopped prior to the event in 2 cases, withdrawn in 1 case, temporarily interrupted in 3 cases, and dose not changed in 2 cases.

Of the 8 cases summarized above, there were 3 cases with fatal events reported. The cause of death in each of these cases was reported as:

• Grade 5 Respiratory failure secondary to advanced MM

• Grade 5 Sepsis

• Grade 5 Respiratory failure, chemotherapy (non-selinexor) induced cardiomyopathy, and ALL

No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing selinexor EAP.

As a causal relationship between selinexor treatment and the onset of TLS cannot be completed excluded, it was determined that TLS should be considered as an important potential risk for selinexor.

Early recognition of signs and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are most relevant.

Table 2. Pre-specified Dose/Schedule Modifications for Adverse Events Related to Study Drug

Dose Level	Dose of Selinexor
Dose level 0 (starting dose)	40 mg twice weekly, 3 weeks on/1 week off
Dose level -1	20 mg day 1 plus 40 mg day 2, 3 weeks on/1 week off
Dose level -2	40 mg once weekly , 3 weeks on/1 week off
Dose level -3	20 mg once weekly, 3 weeks on/1 week off
Dose level -4	Discontinue Dosing

6.2.2 Dose Adjustment Guidelines for Selinexor Related Toxicities

All selinexor related non-hematological toxicities except those mentioned in the table below should be handled as follows:

Interrupt selinexor dosing in case of grade ≥ 3 non-hematological toxicity and resume dosing when resolved to grade 1 or less. Reduce selinexor dose by one dose level.

Table 3. Suggested Supportive Care and Dose Adjustment Guidelines for AEs Related to Selinexor (according to IB v 9)

Adverse Event	Occurrence	Action
Hematologic Adverse Events		
Thrombocytopenia		
Platelet count 25 × 109/L to <75 × 109/L	Any	• Reduce selinexor by 1 dose level (see Table 2) • Consider additional supportive care and discuss with Sponsor-Investigator
Platelet count 25 × 109/L to <75 × 109/L with concurrent bleeding	Any	• Interrupt selinexor • Restart selinexor at 1 dose level lower after bleeding has resolved (see Table 2) • Consider additional supportive care and discuss with Sponsor-Investigator
Platelet count <25 × 109/L	Any	• Interrupt selinexor • Monitor until platelet count returns to at least 50 × 109/L • Restart selinexor at 1 dose level lower (see Table 2) • Consider additional supportive care and discuss with Sponsor-Investigator
Neutropenia		

ANC 0.5 to 1.0 × 109/L without fever	Any	• Initiate growth factor support
ANC <0.5 × 109/L OR febrile neutropenia	Any	• Interrupt selinexor • Monitor until ANC returns to ≥1.0 × 109/L • Restart selinexor at 1 dose level lower (see Table 2) • Initiate growth factor support
Anemia		
Hb <8.0 g/dL	Any	• Administer blood transfusions and/or other treatments per clinical guidelines

Adverse Event	Occurrence	Action
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt selinexor • Monitor until Hb returns to ≥8.0 g/dL • Restart selinexor at 1 dose level lower (see Table 2) • Administer blood transfusions and/or other treatments per clinical guidelines
Nonhematologic Adverse Events		
Hyponatremia		
Sodium ≤130 mmol/L	First	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at same dose
	Second	• Interrupt selinexor and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at 1 dose lower (see Table 2)
Fatigue		
Grade 2 lasting >7 days OR Grade 3	Any	• Interrupt selinexor and provide appropriate supportive care • Add methylphenidate • Monitor until fatigue resolves to Grade 1 or baseline • Restart selinexor at 1 dose level lower (see Table 2)
Nausea and Vomiting		

Grade 1 or 2 nausea OR Grade 1 or 2 vomiting	Any	• Maintain selinexor and initiate additional anti-nausea medications
Grade 3 nausea OR Grade ≥3 vomiting	Any	• Interrupt selinexor • Monitor until nausea or vomiting has resolved to ≤Grade 2 or baseline. • Initiate additional anti-nausea medications • Restart selinexor at 1 dose level lower (see Table 2)
Adverse Event	**Occurrence**	**Action**
Diarrhea		
Grade 2	First	•Maintain selinexor and institute supportive care
	Second and subsequent	•Reduce selinexor by 1 dose level (see Table 2) •Institute supportive care
Grade ≥3	Any	• Interrupt selinexor and institute supportive care • Monitor until diarrhea resolves to Grade ≤2 • Restart selinexor at 1 dose level lower (see Table 2)
Weight Loss and Anorexia		
Weight loss of 10% to <20% OR anorexia associated with significant weight loss or malnutrition	Any	• Interrupt selinexor and institute supportive care • Monitor until weight returns to >90% of baseline weight • Restart selinexor at 1 dose level lower (see Table 2)
Other Nonhematologic Adverse Events		
Grade 3 or 4	Any	• Interrupt selinexor and institute supportive care • Monitor until resolved to ≤Grade 2 • Restart selinexor at 1 dose level lower (see Table 2)

Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be held for alopecia of any grade, or forelectrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

Selinexor Dose Adjustment in the Setting of Infection

In patients who develop fever or other signs of systemic infection, appropriate antimicrobial should be initiated immediately. Selinexor should be withheld in any patient with active uncontrolled infection, any Grade 4 infection or sepsis (even in the absence of documented infection) until the patient is clinically stable. After the infection has stabilized clinically or resolved, Selinexor treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics for prolonged periods while re-initiating their Selinexor regimen at the discretion of the investigator. Selinexor is not known to have any drug interactions with standard antimicrobials.

Prophylactic antibiotics are permitted concurrently with Selinexor treatment, but are not recommended for most patients. Patients with a history of recurrent infections or those at high risk for specific infections may continue their prophylactic antimicrobial regimens without modification when initiating selinexor therapy. In a randomised study in old patients with acute myeloid leukemia (AML), sepsis occurred more frequently in patients receiving Selinexor compared with patients receiving physician's choice of therapy.

6.2.3 Dose reduction for decreased glomerular filtration rate (GFR)

Selinexor is not significantly eliminated by the kidney, therefore, no dose alteration of selinexor is required in patients with renal dysfunction.

However, creatinine increase and other renal effects have been observed in patients treated with selinexor. For their prevention, maintenance of adequate volume status is essential. Acute increases in creatinine are usually accompanied by disproportionately higher elevations of BUN. Therefore, all patients with renal dysfunction should be evaluated for volume status and fluid intake as well as electrolyte levels. Fluid repletion usually leads to resolution of creatinine increases in patients with dehydration associated with selinexor.

6.2.4 Missed or vomited doses

Missed Doses

Missed doses should be managed as follows:

If a dose was missed, the schedule of that week should be altered to accommodate two doses in that week with at least 36 hours between two consecutive doses.

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

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

Vomited Doses

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

6.2.5 Concomitant Medication and Treatment

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

Permitted Concomitant Medication

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

Restrictions and Prohibited Medications

Concurrent

Therapies: Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the sponsor-investigator.

Alcohol: Ethanol should be avoided on selinexor dosing days as it may compete for glutathione (GSH)-mediated metabolism.

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

Medications:

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

Given the theoretical potential for GSH depletion, the total dose of acetaminophen should be ≤1 gram per day on days of selinexor dosing.

6.2.6 Use of Blood Products

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

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

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

6.2.7 Contraception Requirements

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential must agree to use two methods of contraception (one highly effective and one effective) 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 childbearing potential.

Highly effective methods include:

Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)

Intrauterine device or intrauterine system

Vasectomy or tubal ligation

Effective methods include:

Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)

Notes:

- *No barrier method by itself achieves a highly effective standard of contraception*
- *The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.*
- *The cervical cap and contraceptive sponge are less effective in parous women.*
- *The use of spermicide alone is not considered a suitable barrier method for contraception.*
- *When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above.*
- *Male and female condoms should not be used together as they can tear or become damaged.*

Alternatively, the following fulfill the contraception requirements:

A sexual partner who is surgically sterilized or post-menopausal.

Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The method of acceptable contraception must be explained to both male and female potential patients. In order to be eligible for the study, patients must agree to use the methods of birth control described above throughout the study and for 3 months following the last dose of study treatment at the time of consent for the study.

Please see Section 7.12.1 for additional safety information related to pregnancy.

6.2.8 Radiation Treatment

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

7 Assessment of Safety

7.1 Adverse Events

7.1.1 Definitions

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

7.1.2 Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent should be recorded by the Investigator, regardless of relationship to study treatment. AE monitoring should be continued for at least 30 days following the last dose of study treatment (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator). AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

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

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

7.2 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 1.1.1 and/or as per the Investigator's discretion.

7.3 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

AESIs for selinexor include cataracts and acute cerebellar syndrome. All cases of cerebellar toxicity, Grade 3 or higher must be reported (see Section 7.8).

7.4 Adverse Event Severity Assessments

The severity* of the AE should be graded by the Investigator according to the NCI CTCAE Grading Scale, utilizing NCI CTCAE (version 4.03: June 14, 2010). 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 is not the same as 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.

7.5 Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in Table 7.

7.6 Table 7: Classification of Adverse Events by Causality

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

Related: The temporal relationship of the event to the study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

7.7 Adverse Event Reporting

The Investigator will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance every 6 months in the form of line-listings. The line listings will include the following information: subject number, study drug information (start/stop date, dosage, and frequency), adverse event (onset/stop date, event intensity, event outcome and action taken), seriousness (serious with applicable criteria, or non-serious), and the Investigator's causality assessment. Karyopharm Therapeutics will provide the preferred template.

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 (see Section 6.9.2.2). 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. Karyopharm Therapeutics, Inc. will provide the required SAE Report Form.. 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 to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

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 (per the current version of the IB) 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 by 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 Pharmacovigilance within 24 hours of learning of its occurrence.

Pregnancies must be reported to Karyopharm Pharmacovigilance, 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.

7.12.2 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 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 Pharmacovigilance should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be recorded. 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 report must be submitted as soon as possible.

7.14 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.

7.15 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.

8 Statistical Considerations

8.1 Trial Design

This is a non-randomised, open label two armed phase II trial. Arm A includes patients with thymoma and arm B include patients with thymic carcinoma.

The primary objective of the trial is to determine the effect of selinexor in patients with inoperable thymoma and in patients with thymic carcinomas, previously treated with with at least one platinum containing chemotherapy regimen as determined by overall response rate according to RECIST 1.1.

The study is composed of two similar phase II trials conducted in the US and Europe. The final analysis will be performed on data pooled from both trials. The calculation of the total sample size is based on the pooling of data from both trials.

The following assumptions are the basis for the sample size:

- Simon's minimax design will be used
- A response rate of 10 % is considered clinical irrelevant.
- A response rate of 30 % is considered undesirable to overlook.
- Type one error rate: 0.05
- Power: 0.80
- Stage 1: 15 evaluable patients in each arm
- Stage 2: 10 evaluable patients in each arm
- For each arm: If response is observed in 2/15 patients in stage 1, accrual will continue in stage 2.
- For each arm: If response in 5 out of 25 patients, the alternative hypothesis is accepted and the drug is considered active and appropriate for further evaluation.

Included patients who are not evaluable for response will be replaced.

All patients receiving at least one dose of selinexor will be included in the final analysis of primary and secondary endpoints. However this is not an intention to treat (ITT) study.

8.1.1 Interim analysis

Patient inclusion is reported to the sponsor and shared between US and EU sponsor. EU sponsor has the responsibility to monitor the inclusion rate and in collaboration with the US sponsor announce when inclusion should be halted for interim analysis. After inclusion of 15 evaluable patients in each arm (comprising both US and EU trial), an interim analysis will be performed. A decision to continue in stage 2 will be based on pooled data of stage 1 in both the US and European trial. Each study arm may be closed separately after stage 1, if it does not reach the pre-specified responses. Decision to go to stage 2 will be made by a consortium consisting of US sponsor, EU sponsor, one investigator from each site in US and EU, and 1-2 Karyopharm representatives. In case 2 patients out of 15 patients derive clear clinical benefit according to a unanimous agreement among members of the consortium, a decision can be made to proceed to stage 2. Clear clinical benefit is defined as: non-progressive disease with improvement in tumor related symptoms and treatment is well tolerated.

The results of the interim analysis showed three responses out of fifteen patients in the thymoma cohort (3 according to ITMIC and 2 according RECSIST). Therefore, the thymoma cohort will be continued and additional 10 patients will be included across all EU and US sites.

No response was observed in the thymic carcinoma group. This cohort will be closed.

8.2 Statistical plan

8.2.1 Study populations

Thymoma

This population consists of all patients with thymoma who have received at least one dose of study drug on trial.

Thymic carcinoma

This population consists of all patients with thymic carcinoma who have received at least one dose of study drug on trial. This arm was closed as no response was observed within the fifteen patients.

Safety population

This population consists of all patients who have received at least one dose of study drug on trial.

8.2.2 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized separately for each cohort and will include at a minimum age, gender, diagnosis, performance status, and number of prior lines of therapy.

8.2.3 Analysis of primary endpoint

Analysis of ORR according to RECIST 1.1 will be reported with 95% CI. Each arm will be analysed separately.

8.2.4 Analysis of secondary endpoints

Analysis of time to event endpoints will be done using the Kaplan-Meier method. Median time and 95% CI will be reported.

8.2.5 Analysis of exploratory endpoints

Data from biomarker analysis will be treated as continuous or discrete variables as appropriate and correlated to response, time to event endpoints and safety endpoints using univariate and multivariate analysis. Biomarker data will be transformed prior to analysis as appropriate.

9 Administrative Matters

9.1 Data Safety Monitoring Plan

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study Phase II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI, Karyopharm Therapeutics, Inc. (drug supplier) and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Deputy Director must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC Deputy Director will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the LCCC Deputy Director. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the LCCC Deputy Director.

9.2 **Collaboration with Other Institutions (in the US and EU)**

This study (US) will be conducted in collaboration with Hackensack University Medical Center. Dr. Chul Kim is the US Principal Investigator for the study and will oversee the study including the data gathering, safety and reporting. Dr. Martin E. Gutierrez will be the main study contact at Hackensack University Medical Center. Patients will be recruited at all institutions for the study.

Monthly conference calls will be conducted between all institutions to follow up on the progress of the trial. Dr. Kim will be responsible for coordination of the trial between all institutions. Study coordinators will notify Dr. Kim upon the accrual of any patients in any institution.

Monthly teleconferences will also be conducted between the centers in the US and those in Europe. An update of each center will be provided in writing and detailed in terms of US and EU participation. Accrual, safety and activity will be discussed in detail during these teleconferences.

9.2.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, at Lombardi-Georgetown, there will be a dedicated “multi-institutional” research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for Dr. Kim and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including “remote” screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) Reviewing and confirming all study-related adverse events; 2) Submitting all SAE reports to the Georgetown IRB (The research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the “multi-institutional” coordinator will submit the final report); 3) Gathering and preparing primary source data for review/audit.

9.2.2 Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 - 48 hours containing the subject number, to the PI, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator. Patients should not start therapy until both PI and the multi-institutional coordinator have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

9.2.3 Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

9.3 Data Management

Patient data will be entered into the on-line accessible Oracle Clinical database. This database is housed at Georgetown, but is accessible anywhere there is internet access. All research coordinators and data managers will attend an on-line training session to learn how to accurately enter any data into the Oracle database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit. The LCCC QA Manager will be reviewing all online data on a regular basis to ensure compliance.

9.4 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), Division 5 of the Health Canada Food and Drug Regulations - Drugs For Clinical Trials Involving Human Subjects, and with the ethical principles laid down in the Declaration of Helsinki.

9.5 Institutional Review Boards/Ethics Committees

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board (IRB) before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to

give access to all relevant data and records to the Sponsor, Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs/REBs and regulatory authorities as required.

9.6 Regulatory Authority Approval

Before implementing this study, the protocol must be approved by the FDA.

9.7 Protocol Adherence

Investigators attest they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the final clinical study report (CSR).

9.8 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment, and approved by the FDA where required, and the IRB. Only amendments that are required for patient safety may be implemented prior to IRB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the PI should be notified of this action and the IRB at the study site should be informed according to local regulations but not later than 10 working days.

9.9 Informed Consent

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

Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in this protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be recorded in their CRFs.

Additionally, consent will be requested to obtain/retain a blood sample for future analysis as warranted by our rapidly-advancing understanding in this field. Each patient's ICF will reflect that samples collected may be used for pharmacogenomic investigations.

9.10 Patient Confidentiality and Disclosure

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

9.11 Collection, Auditing Study Documentation, and Data Storage

9.11.1 Study Documentation, Record Keeping and Retention of Documents

The Georgetown Lombardi Clinical Research Management Office will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Authorized representatives of the Sponsor and regulatory agencies will be permitted to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs, an audit trail will be maintained by the system.

The Investigator/Institution should maintain trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial.

9.11.2 Auditing Procedure

The drug supplier or the regulatory authority may conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

The Sponsor-Investigator agrees that representatives of the drug supplier and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

In the event that a major compliance or regulatory issues arises, the drug supplier may conduct an audit without prior notice.

9.12 Disclosure of Information

All information provided to the Investigator by the Sponsor, or its designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the Investigator in the Clinical Trial Agreement.

No information about this study or its progress will be provided to anyone not involved in the study other than to the Sponsor, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

9.13 Discontinuation of the Study

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

9.14 Study Report and Publication Policy

The PI assures that the key design elements of this protocol will be posted in a publicly accessible database such as *www.clinicaltrials.gov*. In addition, upon study completion the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

10 Appendices

Appendix A: KPTI SAE form

Appendix B: Ophthalmic Exam

Appendix C: 6 m AE LL spreadsheet template

References:

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3. den Bakker MA, Roden AC, Marx A, Marino M. Histologic Classification of Thymoma: A Practical Guide for Routine Cases. Journal of Thoracic Oncology 2014; 9: S125-S130.
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7. Loehrer PJ, Sr., Chen M, Kim K et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: an intergroup trial. J Clin Oncol 1997; 15: 3093-3099.
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13. Petrini I, Meltzer PS, Zucali PA et al. Copy number aberrations of BCL2 and CDKN2A/B identified by array-CGH in thymic epithelial tumors. Cell Death Dis 2012; 3: e351.
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17. Wang Y, Thomas A, Lau C et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. Sci Rep 2014; 4: 7336.

Appendix A: KPTI SAE form

Serious Adverse Event Report Form

Protocol Number:

Investigator: ☐ Initial Report Follow up Report Number:

Patient Information				
Patient ID# / initials	ID#	Initials:	Weight (kg):	Height (cm):
Date of birth			Male ☐	Female ☐

Adverse Event	
ADVERSE EVENT TERM *(verbatim)*:	
ONSET DATE:	
CTCAE/SEVERITY*	**OUTCOME TO DATE OF THIS REPORT**
☐ Grade 1/ mild	☐ Death
☐ Grade 2/ moderate	☐ Not recovered/Not resolved
☐ Grade 3/ severe	☐ Recovered with Sequelae On date: Time:
☐ Grade 4	☐ Recovered/Resolved On date: Time:
☐ Grade 5	☐ Other:

RELATIONSHIP TO STUDY MEDICATION	**OTHER POSSIBLE CAUSES FOR THE OCCURRENCE OF EVENT**
☐ Related	☐ Underlying disease
☐ Possibly related	☐ Pre-existing condition:
☐ Not related	☐ Other:

SERIOUS CRITERIA	
☐ Death	Date of Death:
☐ Life threatening	*Hospitalization:*
☐ Hospitalization/Prolonged hospitalization	Admission Date:
☐ Persistent / significant disability / incapacity	Discharge Date:
☐ Congenital anomaly / birth defect	
☐ Important medical event	

Serious Adverse Event Report Form – Page 2

Protocol Number:

Site ID/Patient ID: /

Study Medication

MEDICATION NAME:

THERAPY DATES *(dd/mmm/yyyy)*	**MEDICATION DOSAGE and FREQUENCY**
Date first dose:	First dose: mg /
Date dose changed:	Dose reduced to: mg /
Date last dose prior to event:	
Last dose administered: mg	
ACTION TAKEN WITH STUDY MEDICATION	**Did event abate after stopping/reducing medication?**
☐ Dose unchanged	☐ Yes
☐ Dose reduced	☐ No ☐ NA
☐ Medication withdrawn	
☐ Medication temporarily withdrawn	**Did event reappear after re-administration?**
☐ Date of withdrawal:	☐ Yes
☐ Date of re-initiation:	☐ No ☐ NA

Baseline Condition(s)

Condition	**Diagnosis date**

Past Medical History

Medical condition	**From date**	**To date *(dd/mm/yyyy)***

Serious Adverse Event Report Form – Page 3

Protocol Number:

Site ID/Patient ID: /

Relevant Concomitant Medication

MEDICATION NAME AND INDICATION	DATES AND DOSE/FREQUENCY OF ADMINISTRATION
1 Name: Indication:	From: To: Dose/frequency: mg/
2 Name: Indication:	From: To: Dose/frequency: mg/
3 Name: Indication:	From: To: Dose/frequency: mg/
4 Name: Indication:	From: To: Dose/frequency: mg/
5 Name: Indication:	From: To: Dose/frequency: mg/

Other Relevant Medical Conditions

Additional Details of SAE *(include medication/other measures administered to the patient to treat the event, etc.)*

Reporter Contact Details

Report completed by:	Telephone:
	Email:
INVESTIGATOR'S SIGNATURE	DATE OF THIS REPORT:

Appendix B: Ophthalmic Exam

An ophthalmic examination by an optometrist or ophthalmologist is required at screening and if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances). The examination is to include the following:

Prior to dilation:

- best corrected visual acuity
- slit lamp examination
- tonometry

Following dilation:

- fundoscopy
- slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org).

Grading of Cataracts*				
Cataract Type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nuclear Yellowing and sclerosis of the lens nucleus	Mild	Moderate	Pronounced	Severe
Cortical Measured as aggregate percentage of the intrapupillary space occupied by the opacity	Obscures 10% of intrapupillary space	Obscures 10% -50% of intra-pupillary space	Obscures 50% -90% of intra-pupillary space	Obscures >90% of intrapupillary space
Posterior subcapsular Measured as the aggregate percentage of the posterior capsular area occupied by the opacitiy	Obscures 10% of the area of the posterior capsule	Obscures 30% of the area of the posterior capsule	Obscures 50% of the area of the posterior capsule	Obscures >50% of the area of the posterior capsule
*Designation of cataract severity that falls between grade levels can be made by addition of a + sign (e.g., 1+, 2+). Grading of cataracts is usually done when pupil is dilated.				

Appendix C: 6 m AE LL spreadsheet template

Study ID	Unique Subject ID	Adverse Event Term	Serious Event? (Yes/No)	Onset Date (complete or partial)	End Data (complete or partial)	Action Taken with Study Treatment	Causality to Study Treatment	Ongoing (Yes/No)	Outcome of Adverse Event	Severity CTCAE Grade (1-5)	Date of First Dose	Preferred Term	System Organ Class

Notes:
1. For AE term (Columns C), it would be perferred to report the verbatim name of the event instead of a derived code.
2. For AE onset date and end date (column E and F), please provide a partial date to the best of your knowledge if the exact date is unknown.
3. If the AE was still ongoing at the time of data cut, please mark the "Ongoing" column (column I) as "Yes" and leave the end date (column F) blank.
4. Preferred Term and System Organ Class (Column M and N) are optional. Please report them if available as well as the MedDRA version.