INVESTIGATOR-INITIATED PHASE I/II CLINICAL TRIAL OF SELINEXOR (KPT-330) AND LIPOSOMAL DOXORUBICIN FOR RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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TITLE: INVESTIGATOR-INITIATED PHASE I/II CLINICAL TRIAL OF SELINEXOR (KPT-330) AND LIPOSOMAL DOXORUBICIN FOR RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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SPONSOR: H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE

DRUG PRODUCT SUPPLIER: KARYOPHARM THERAPEUTICS

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Synopsis

Study Title	Investigator-initiated Phase I/II Clinical Trial of Selinexor (KPT-330) and liposomal doxorubicin for relapsed and refractory multiple myeloma
Study Rationale	Multiple myeloma accounts for 10% of all hematologic neoplasms, and approximately 20,000 patients were diagnosed with multiple myeloma in the United States in 2012[1]. Advances in therapy have resulted in the availability of novel immunomodulatory agents and proteasome inhibitors with a resultant improved survival of patients[2-7]. Despite those advances, the disease remains uniformly fatal. The outcomes of patients with multiple myeloma who have failed lenalidomide and bortezomib remains poor and the development of new active therapies for this group of patients represents an unmet medical need. There is extensive experience with the use of doxorubicin and liposomal doxorubicin (LD) for the treatment of multiple myeloma. Historically, patients with multiple myeloma received infusion doxorubicin in a regimen called VAD (vincristine, doxorubicin, and dexamethasone). Because LD is associated with shorter infusion times and less cardiotoxicity, it was incorporated into the induction regimen instead of doxorubicin resulting in the DVD regimen. Outpatient DVD has been compared to VAD and resulted in similar response rates to VAD—with less alopecia, neutropenia and obviating the need for hospitalization[8]. However, it was associated with greater incidence of palmar plantar erythrodysesthesias or hand-foot syndrome (HFS). More recently, LD in combination with bortezomib was found to be superior to bortezomib alone—showing a significant increased time to progression, 15-month survival rate, and duration of response for the LD/bortezomib arm[2]. This led to the approval by the US Food and Drug Administration of LD for patients with relapsed and refractory multiple myeloma in 2007. We have previously evaluated the addition of LD to thalidomide and lenalidomide in patients with relapsed and refractory myeloma as well as in the newly diagnosed setting with evidence of clinical synergy[9-11]. Selinexor, a Selective Inhibitor of Nuclear Export / SINE™ Compound, forces multiple tumor suppressor proteins to accumulate in the cell nucleus where they perform their growth inhibiting function. Selinexor has shown potent broad anti-cancer cytotoxicity *in vitro* and robust anti-cancer activity against multiple tumors in preclinical animal models. Selinexor is being evaluated in several Phase I studies, including patients with advanced hematological

	malignancies (NCT01607892), advanced metastatic solid tumors (NCT01607905), and in a food effect study in patients with sarcomas (NCT01607905). Initial results have shown that selinexor has acceptable tolerability with clear anti-tumor activity in these studies. The laboratory of Dr. Sullivan has demonstrated that high-density human myeloma cell lines and patient myeloma cells export DNA topoisomerase IIα from the nucleus to the cytoplasm, thus rendering the myeloma cells resistant to the cytotoxic effects of topoisomerase II inhibitors—for example, doxorubicin[12]. The export of human topoisomerase IIα has been shown to be mediated by two CRM1 (XPO1)-dependent nuclear export signals[13]. More recently, the same lab has shown that XPO1 inhibitors (leptomycin B and ratjadones) and XPO1 siRNA block the nuclear export of topoisomerase IIα and re-sensitize these cells to doxorubicin[14]. Finally, this lab has demonstrated that selinexor (and other SINE™ XPO1 antagonists) sensitize high-density human myeloma cell lines and patient myeloma cells to doxorubicin and have little effect on normal PBMN's and bone marrow cells[15]. These recent results also demonstrated that optimal myeloma cell kill occurs when the administration of selinexor precedes that of doxorubicin. Thus, the present study aims to evaluate the safety and efficacy of selinexor in combination with LD and dexamethasone in patients with relapsed and refractory multiple myeloma.
Primary Objective	For the phase I portion, the primary objective is to determine the safety and recommended phase II dose of selinexor in combination with LD and dexamethasone in patients with relapsed and refractory myeloma. In the phase II portion, the primary objective is to evaluate the efficacy (overall response rate—partial response and better) of selinexor, LD, and dexamethasone in patients with relapsed and refractory myeloma.
Secondary Objectives	To estimate the progression-free (PFS) and overall survival (OS) in patients with relapsed and refractory myeloma treated with this combination. To estimate the clinical benefit rate (minimal response and better) of the combination in relapsed and refractory myeloma.

Endpoints	Primary Endpoints: 1. Phase I: determine the MTD and RP2D of the combination 2. Phase II: determine the overall response according to the uniform criteria of the IMWG (partial response and better) Secondary Endpoints: 1. Clinical benefit rate (minimal response and better) 2. Progression-free survival of the combination 3. Duration of response 4. Overall survival 5. Adverse event profile as assessed by the NCI CTC version 4. Exploratory correlative analyses (see below)
Correlative / Exploratory studies	Patients will have a bone marrow aspirate and biopsy performed on screening, within the loading phase (day -7) at least 2 hours after the selinexor administration, and at the time of disease progression. The bone marrow biopsies will be used to construct a tumor microarray for the analyses below. Bone marrow aspirates will be aliquoted and a portion will be CD138 selected. If a patient has <5% involvement plasma cells in the bone marrow in screening, a repeat bone marrow biopsy is not needed on day -7 (loading). <u>Myeloma Patient Bone Marrow Biopsy Microarrays</u> Plasma cells in tumor microarrays (produced from patient bone marrow biopsies) will be identified by lambda or kappa light-chain staining and examined for the expression and intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, topoisomerase IIβ, p53, XPO1, IkB, NF-kB, and possibly other biomarker of relevance before and after in vivo treatment with selinexor and at the time of disease progression. <u>Myeloma Patient Bone Marrow Aspirates</u> Patient bone marrow aspirates collected during screening will be used to evaluate the predictive value of baseline *ex vivo* sensitivity testing with selinexor and LD. The lymphocyte fraction of patient bone marrow aspirates will be isolated by ficoll-gradient centrifugation and incubated overnight in the presence of selinexor (0, 0.156, 0.625, 2.5, 10 and 40 μM), +/- doxorubicin (2μM), and if adequate sample is available, KPT8602 (0, 0.156, 0.625, 2.5, 10 and 40 μM) +/- dexamethasone (10μM) . . *Ex vivo* sensitivity to will be assayed in CD-138/light chain double positive myeloma

	cells by flow cytometry and activated caspase 3 apoptosis assay for EC50 analysis. A portion of the lymphocyte fraction will be incubated overnight in the presence of selinexor (100 nM and 300 nM) and cytospin slides made to assay the intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, topoisomerase IIβ, p53, XPO1, IkB and NF-kB and possibly other biomarker of relevance with or without treatment with selinexor.The intracellular location of topoisomerase IIα, topoisomerase IIβ, p53, XPO1, IkB and NF-kB seen in plasma cells from the aspirates will be compared to that seen in the biopsy tissue arrays. A portion of the cells from the lymphocyte fraction of the bone marrow aspirate will be isolated using CD-138 magnetic bead selection. In the future, DNA from CD-138 positive myeloma cells will be isolated and interrogated for specific mutations by targeted exome sequencing. In addition, gene expression of RNA isolated from CD-138 positive myeloma cells will be assayed by microarray analysis. <u>Myeloma Patient Blood Samples for PK Analyses (Appendix C)</u> Patients enrolled on the phase I and phase II parts of this study will also have peripheral blood collected for limited PK analyses of selinexor and LD. Samples will be collected after administration of selinexor (to measure peak plasma concentrations) and at the time of bone marrow aspirates. Blood samples will also be collected post-LD administration to measure free doxorubicin to estimate overall patient exposure to free doxorubicin. We will correlate blood levels of selinexor and LD with the expression and intracellular location of the proteins described above. <u>Myeloma Patient Blood Samples for PD Analyses (Appendix C)</u> 1. XPO1 Inhibition. Leukocytes will be isolated from patient blood samples collected pre- and post-dosing (≥4hr) and total RNA will be isolated to study changes in gene expression before and after exposure to selinexor. Inhibition of XPO1(selinexor target) will be assessed by qRT-PCR of XPO1 and other genes, which are upregulated once XPO1 is inactivated (based on Karyopharm gene chip studies)(e.g., ARRDC3, NGFR, SLC family, PCLO). 2. Cytokines. Blood samples (1 ml) will be collected pre- and post-dosing and analyzed for plasma cytokine concentrations. Cytokines include: IL1α,

	TNFα, IL-6, MCP1, IFNγ, VEGFα, IL-8, IFNα, IL-10
Sample Size	Approximately 6-24 adult patients will be enrolled in the phase I portion and 7 to 23 patients (excluding patients treated at the RP2D in the phase I) will be enrolled in the phase II portion. Overall, up to 47 patients may be enrolled.
Study Design	A Phase I/II Study of oral selinexor in combination with LD and dexamethasone in patients with relapsed and refractory multiple myeloma. **Phase I:** The phase I portion will be a standard 3+3 dose escalation design. Briefly, 3 patients will be enrolled on each dose level. • If no patient develops a dose limiting toxicity (DLT), the next 3 patients are enrolled at a higher dose level. • If 1/3 develops a DLT, the cohort is expanded and 3 additional patients are enrolled to that dose level. If 0 of 3 (total 1/6) patients experience DLT, proceed to the next higher dose level. If >1 patient suffers a DLT (≥2/6), then the dose will be de-escalated to the previous lower level. Three additional patients will be enrolled to that lower dose cohort unless 6 patients had been treated at that lower dose. If ≤1 of 6 patients experience DLT, this lower dose level will be declared the maximum tolerated dose (MTD). • If 2 or more patients (≥2/3) develop a DLT, 3 additional patients will be enrolled at a lower dose cohort unless 6 patients had been treated at that lower dose. **Loading phase** Selinexor will be administered orally at 80 mg on day, -7 during a loading phase and then once weekly on days 1, 8, and 15 (twice weekly for cohort 3m and 4m). Dexamethasone will be administered at 40 mg weekly (or 20 mg in case of intolerance or in patients 75 years or older). **Treatment phase and dose escalation:** Patients will received liposomal doxorubicin (20-30 mg/m^2 IVPB on D1) at least 2 hours but less than 4hours after selinexor administration, and dexamethasone (40 mg PO weekly). Cycle 1 is the cycle when all 3 drugs are given. A cycle is 21 days Dexamethasone will be given at 40 mg weekly during the

	treatment phase. The dose escalation for the phase I will be as follow: Dose level -1: 40mg on days 1,8, 15 in combination with 20 mg/m² LD Dose level 1: 40 mg/m² (~68 mg) on days 1,8, 15 in combination with 20 mg/m² LD includes a 2 week loading phase (4 total doses in loading) Dose level 2: 80 mg on days 1, 8, 15 in combination with 20 mg/m² LD (includes a 2 week loading phase (4 total doses in loading) Dose level 1m: 60 mg on days 1, 8, 15 in combination with 20 mg/m² LD (Includes a single loading dose on day -7) Dose level 2m: 80 mg on days 1, 8, 15 in combination with 20 mg/m² LD (Includes a single loading dose on day -7) Dose level 3m: 80 mg on days 1,3,8, 10 in combination with 20 mg/m² LD (Includes a single loading dose on day -7) Dose level 4m: 80 mg on days 1,3,8, 10 in combination with 30 mg/m² LD (Includes a single loading dose on day -7) After amendment 5, patients will start dosing on dose level 2m **Intra-patient dose escalation** Intra-patient dose escalation of selinexor will be allowed at the discretion of the principal investigator and treating physician, provided that dose level has been found to be well tolerated(cleared DLT with 6 patients treated at that dose level). Intrapatient dose escalation would only occur after patients have completed the first cycle and can also occur in the maintenance setting. **Maintenance phase:** After 8 cycles of therapy with selinexor, LD, and dexamethasone, patients will be eligible to proceed on maintenance with the tolerated dose of weekly selinexor and dexamethasone until disease progression. In maintenance, cycles are 28 days. **Definition of dose limiting toxicity (DLT)** DLT is defined as any of the following occurring in the first cycle (excluding the selinexor loading period from D-14 to D-

	1) that is *not* due to an a cause other than study drug toxicity • ≥ 1 missed doses (out of 3 doses) in 21 days at the target dose due to study drug toxicity • Discontinuation of a patient due to a toxicity that is not due to a cause other than drug toxicity before completing cycle 1 • Grade ≥ 3 nausea/vomiting, diarrhea or dehydration while taking optimal supportive medications • Any other Grade ≥3 non-hematological toxicity except alopecia, steroid induced hyperglycemia or electrolyte abnormalities correctable with supportive therapy • Grade ≥ 3 AST or ALT elevation • Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm3] lasting ≥7 days • Febrile neutropenia (ANC<1000/mm3 with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour); • Grade ≥3 thrombocytopenia associated with clinically significant bleeding **Determination of maximum tolerated dose (MTD) and recommended phase II dose (RP2D)** The MTD is defined as the highest dose level in which ≤ 1 of 6 patients experience a DLT. In general, we anticipate that the MTD will be the RP2D. However, based on evaluation with co-investigators, and a focus on those patients tolerating longer-term treatment, the RP2D dose may be less than the MTD. **Phase II:** Simon Two stage phase II. Thirteen eligible patients will be enrolled in the first stage (including the 6 patients from the phase I treated at the RP2D). If 3 or more partial responses are noted, another 16 patients will be enrolled. If 8 or more patients achieve a partial response or better among the 29 subjects, the combination is deemed active. Under this two-stage

	optimum design, there would be a 90.7% chance of detecting a tumor response rate of at least 40% and a response rate of 15% or less would lead to the conclusion that the regimen lacks antitumor activity at a 0.05 significance level. The probability of early stopping (in stage I) is 0.058 if the true response rate of the combination is 40%. **Dose Schedule** Loading phase: Patients will receive selinexor at 80 mg on D-7 orally. This dose was shown to be tolerable in a study of patients with chronic hematologic malignancies including myeloma (NCT01607892). In addition, patients will receive dexamethasone 40 mg on day -7. The loading phase lasts 1 week. Induction phase: Patients will be treated initially with selinexor at the RP2D PO weekly dose (on days 1, 8, 15) (or twice weekly dosing on cohort 3m and 4m), liposomal doxorubicin at the RP2D IVPB on D1 (at least 2 hours (and no longer than 4 hours) after the selinexor dose), and dexamethasone 40 mg PO weekly (on days 1, 8, 15). Cycles are repeated every 3 weeks (21 days) and patients will receive a maximum of 8 cycles of therapy with this combination. For patients with prior doxorubicin exposure, after a total dose of 450 mg/m2, patients will be required to have cardiac assessments (echocardiograms or MUGA) every 2 cycles. Any patient with a decrease in ejection fraction of ≥ 20% from baseline will have LD discontinued. Maintenance phase: After 8 cycles of therapy with selinexor, LD and dexamethasone, patients will be eligible to proceed on maintenance with the tolerated dose of selinexor and dexamethasone until disease progression. Cycles are repeated every 28 days **Discontinuation Criteria**: At the discretion of the Investigator, the investigator may remove a patient from the study for the following reasons: • Due to disease progression • Noncompliance with study procedures • Patient no longer consents to participate in the study • Intercurrent illness that interferes with study assessments • Investigator discretion • Incidence or severity of AEs in this study indicates a potential health hazard to the patient • Termination of the study by the sponsor

	• Pregnancy
Duration of Treatment	After 8 cycles of the combination of LD, dexamethasone, and selinexor, patients may continue to receive selinexor and dexamethasone until disease progression or occurrence of an unacceptable toxicity in the phase I and II.
Inclusion /Exclusion Criteria	**Inclusions:** 1. Written informed consent in accordance with federal, local, and institutional guidelines 2. Age ≥ 18 years 3. Patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies which must include lenalidomide and a proteasome inhibitor. Patients must have disease refractory to the most recent therapy. Refractory myeloma is defined as progressive disease during or within 60 days of last therapy. Patients must have previously received or be ineligible for (or refused) autologous stem cell transplant. 4. Patients must have measurable myeloma paraprotein levels in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour urine collection sample) or by free light chain (involved free light chain greater than 100 mg/L). 5. ECOG performance status of 0-1. ECOG 2 allowed if due to bone disease. 6. Must have an echocardiogram or MUGA indicating LVEF ≥ 50% within 42 days prior to first dose of study drug. 7. Adequate hematological function: a. In the phase I portion: absolute neutrophil count (ANC) ≥1000/mm³, platelet count ≥50,000mm³. GCSF is not allowed during screening or during the first cycle for phase I patients. b. In the phase II portion, if the patient has significant bone marrow involvement (BM plasma cells ≥ 50%), platelet count ≥30,000mm³ and (ANC) ≥ 1000/mm³ are required. GCSF is allowed during screening and therapy for all phase II patients. Alternatively, with less BM involvement, an absolute neutrophil count (ANC) ≥ 1000/mm³, and platelet count ≥50,000mm³ are required. 8. Adequate hepatic function within 14 days prior to loading phase (day -14): total bilirubin <2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of

< 3 times ULN), and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <2.5 times ULN.

9. Adequate renal function within 14 days prior to loading phase (day-14): measured or estimated creatinine clearance of ≥ 30 mL/min, (Cockroft and Gault)
10. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

Exclusions:

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

1. Patients who are pregnant or lactating
2. Radiation, chemotherapy, or immunotherapy or any other approved anticancer therapy ≤2 weeks prior to loading phase (day -7)
3. Major surgery within four weeks before loading phase (day -7)
4. Myocardial infarct within 6 months before enrollment, New York Heart Association (NYHA) Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
5. Prior cumulative exposure to doxorubicin (including liposomal preparation) > 350mg/m2
6. Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose; patients with controlled infection or on prophylactic antibiotics are permitted in the study
7. Known to be HIV seropositive
8. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg

	(HBV surface antigen) 9. Any underlying condition that would significantly interfere with the absorption of an oral medication 10. Grade >2 peripheral neuropathy at baseline (within 14 days prior to loading phase (day -7)) 11. Serious psychiatric or medical conditions that could interfere with treatment 12. Participation in an investigational anti-cancer study within 3 weeks prior to loading phase (day -7) 13. Concurrent therapy with approved or investigational anticancer therapeutic. Patients are allowed to receive corticosteroids for the treatment of non-malignant disorders in doses not to exceed the equivalent of prednisone 20 mg/day 14. Patients with coagulation problems and active bleeding in the last month (peptic ulcer, epistaxis, spontaneous bleeding) 15. Patients who have had a previous allogeneic transplant for treatment of multiple myeloma within the past 6 months or have evidence of clinically significant GVHD
Screening Assessments	Signed written informed consent Demographics and medical history (prior therapy) Pregnancy test (if applicable) (within a week of loading phase) Physical examination and vital signs (within 2 weeks of loading phase) Ophthalmologic exam (within 4 weeks of loading phase) Cardiac evaluation: echocardiogram or MUGA(within 6 weeks of loading phase), ECG Hematology (CBC) (within 2 weeks of loading phase) Clinical chemistry (with LDH, b2microglobulin,) (within 2 weeks of loading phase) Urinalysis (within 4 weeks of loading phase) Coagulation (within 2 weeks of loading phase) Assessment of disease status (within 4 weeks of loading phase) (SPEP, 24h UPEP, serum free light chain) Bone marrow aspiration and biopsy with cytogenetics, FISH, MyPRS (gene expression profile) and correlative endpoints described above (within 4 weeks of loading phase) Chest radiograph (within 4 weeks of loading phase) Skeletal survey (within 4 weeks of loading phase) Concomitant medication

Treatment and Post-Treatment Assessments	**Loading Phase** Physical examination and vital signs (includes weight and ECOG performance status) (on day -7 only) Hematology (on day -7 only) Clinical chemistry (on day -7 only) Assessment of disease status (Day -7) (SPEP, 24h UPEP, serum free light chain) PK of selinexor (appendix C) Adverse events and concomitant medication Pregnancy test (if applicable) Bone Marrow aspiration and biopsy at least 2 hours post selinexor dosing on day -7 **Cycle 1** Physical examination and vital signs (includes weight and ECOG performance status) Hematology Complete clinical chemistry (weekly in cycle 1) Assessment of disease status (SPEP, 24h UPEP, serum free light chain) PK of doxorubicin, and selinexor and PD (appendix C) Adverse events and concomitant medication Pregnancy test (if applicable) **Cycle 2 and Beyond** Physical examination and vital signs (on day 1) (includes weight and ECOG performance status) Cardiac evaluation (echocardiogram or MUGA every 2 cycles if patient has prior anthracycline exposure with greater than 450 mg/m2) Hematology (on day 1) Complete clinical chemistry (on day 1) Assessment of disease status (SPEP, 24h UPEP, serum free light chain) (on day 1) Adverse events and concomitant medication Pregnancy test (if applicable) PK of doxorubicin, and elinexor and PD (appendix C) **Final Visit (end of study)** Physical examination and vital signs (includes weight and ECOG performance status) Pregnancy test (if applicable) Cardiac evaluation (echocardiogram or MUGA) Hematology

	Complete clinical chemistry Assessment of disease status (SPEP, 24h UPEP, serum free light chain) Bone marrow aspiration and biopsy (in the event of discontinuation due to disease progression) Adverse events and concomitant medication Pregnancy test (if applicable)
Response	Response will be assessed per the uniform response criteria of the IMWG incorporating minimal response (≥25% decrease in serum M protein and ≥50% decrease in the 24h urine m spike).
Safety Variables & Analysis	The safety and tolerability of the combination of selinexor, LD and dexamethasone will be evaluated by means of drug related DLT, AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) V 4.03 will be used for grading of AEs. Investigators will provide their assessment of causality as 1) unrelated, 2) unlikely related 3) possibly related, or 4) probably or 5) definitely related for all AEs to one of or all three study drugs.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRM1	Chromosome region maintenance protein 1
CTCAE	Common terminology criteria for adverse events
CT Scan	Computed Tomography Scan
CYP450	Cytochrom P450
D	Day
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good laboratory practice
H	Hour
HFS	Hand foot syndrome
HR	Hazard ratio
ICH	International Conference on Harmonization
IMWG	International myeloma working group
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
LDH	Lactate dehydrogenase
m^2	Square metre (body surface area)
Mg	Milligram
Min	Minute
MyPRS	Myeloma Prognostic Risk Signature
MCRN	Moffitt Clinical Research Network
Ml	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

NCI	National Cancer Institute
NES	Nuclear export signal
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
LD	liposomal Doxorubicin
PO	Per oral
PR	Partial response
PTT	Partial thromboplastin time
RP2D	Recommended phase II dose
Topo II	Topoisomerase II
SAE	Serious adverse event
SD	Stable disease
SINE	Selective inhibitor of nuclear export
SUSAR	Suspected unexpected serious adverse reaction
TSH	Thyroid stimulating hormone
TSP	Tumor suppressor protein
TTP	Time to progression
UNL	Upper normal limit
WBC	White blood cell count
XPO1	Exportin 1

1 Introduction

1.1 Overview

Multiple myeloma accounts for 10% of hematologic malignancies and about 2% of all cancer death in the United States[1]. The United States Food and Drug Administration recently approved 6 agents for the treatment of myeloma including immunomodulators (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib), and an anthracycline (liposomal doxorubicin)[2, 4-7, 16, 17]. Despite advances in therapy the disease remains uniformly fatal and finding novel agents to overcome drug resistance represents an unmet medical need.

Cancer cells must inactivate their tumor suppressor proteins (TSPs) in order to perpetuate their neoplastic phenotype. TSPs require nuclear localization in order to function. Like most proteins, TSPs are shuttled into the nucleus by carrier proteins called importins, and they are carried out of the nucleus by exportins. Exportin 1 (XPO1), also called CRM1, is one of seven major nuclear exporters responsible for carrying ~220 cargo proteins out of the nucleus into the cytoplasm[18]. Nearly all TSPs are transported out of the nucleus exclusively by XPO1. Furthermore, XPO1 is overexpressed by 2-4 fold in nearly all cancer cells, and its levels correlate with poor prognosis and/or chemotherapy resistance[19]. Current research suggests that cancer cells have co-opted XPO1 in order to neutralize their TSPs. In addition, DNA topoisomerase II is a substrate for XPO1[19]. Topoisomerase II alpha is located in the cytoplasm of high density myeloma cells consistent with XPO1 activity and lack of response to doxorubicin[14].

Selinexor is a small molecule, drug-like, orally available Selective Inhibitor of Nuclear Export / SINE™ compound that is a slowly reversible covalent antagonist of XPO1. By blocking XPO1, selinexor induces the accumulation of TSPs in the cell nucleus, leading to activation of their tumor suppressing function. Cells with marked genomic (DNA) damage, including cancer cells, undergo apoptotic cell death; normal cells, with little or no genomic damage, undergo transient, reversible cell cycle arrest. Consistent with its novel mechanism of broadly inducing TSP function, selinexor has shown broad anti-tumor in preclinical mouse models and spontaneous canine cancers. Selinexor is currently being studied in three Phase 1 clinical trials in patients with advanced hematologic or solid tumor malignancies, and in patients with treatment refractory sarcomas. Preliminary evidence of anti-tumor activity in humans with a diverse set of cancers formed the basis for studying the effect of selinexor on patients with myeloma. In addition, we have shown that selinexor and other XPO1 inhibitors are able to restore topoisomerase II alpha location into the nucleus and hence susceptibility to doxorubicin, forming the basis of this clinical trial.

1.2 Selinexor: Mechanism of Action and Preclinical Summary

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

Selinexor is an orally available, irreversible, potent and Selective Inhibitor of Nuclear Export / SINE™ compound that specifically blocks XPO1. Selinexor restores many of the TSP and other growth regulatory proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. All cell types exposed to SINE™ compounds in vitro undergo G1 ± G2 cell cycle arrest, followed by a 'genomic fidelity' review, and cells with significant genomic (DNA) damage are induced to undergo apoptosis. Normal cells, with minimal or no DNA

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

Preclinical Safety

Sprague-Dawley rats and cynomolgus monkeys were chosen as the toxicology species for the selinexor nonclinical safety program. In both species, the primary effects of oral selinexor were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs. At high repeated doses of selinexor associated with marked weight loss, there were changes in cerebellar granular layer neurons in both rats (≥300 mg/m^2) and monkeys (≥72 mg/m^2), but only monkeys showed any CNS symptoms. No central nervous system (CNS)-related adverse side effects were observed in the GLP, rat and monkey 4-cycle toxicity studies. A GLP, rat neurofunctional study (Irwin test) has also been performed at dose levels of 12, 60, or 300 mg/m2 (2, 10, and 50 mg/kg). No behavioral changes were observed at all doses tested.

In the pivotal, GLP, 4-week monkey study, there was no evidence of a direct or indirect effect of selinexor on the morphology and intervals of the ECG at up to 36 mg/m2 (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for selinexor.

In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

Preclinical Efficacy

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, including multiply-resistant cancers, with the majority of IC50s for cytotoxicity <800 nM and most hematologic tumor lines having IC50s of 20-400 nM for selinexor. In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC50s 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 GI dysfunction.

Selinexor and other SINE™ compound analogs have been administered in efficacy studies to mice and dogs and in toxicology studies to rats and monkeys. Efficacy was demonstrated in mouse models of myeloma, mantle cell lymphoma, and T-cell acute lymphocytic leukemia xenografts. Moreover, efficacy, including significant survival advantages, was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)] [20, 21] and chronic lymphocytic leukemia (TCL-1) leukemografts. Efficacy was also demonstrated in solid tumor xenografts including prostate, breast, liver, glioblastoma, kidney, and colon cancers.

1.3 Selinexor: Clinical Summary

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

Study Designs

Karyopharm Therapeutics is currently conducting three open-label Phase I clinical trials to assess the safety, tolerability, and efficacy of selinexor given orally 2-3 times per week. The first study (KCP-330-001) is in patients with advanced hematological malignancies, the second (KCP-330-002) is in patients with advanced or metastatic solid tumor malignancies, and the third (KCP-330-003), a food effect study, is in patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. All patients entering these single-agent phase I studies have relapsed after available therapies and have objectively progressing tumors at time of study drug initiation. To date selinexor has been administered to over 200 patients.

KCP-330-001 is a dose escalation study in patients with advanced hematologic malignancies. KCP-330-002 is a dose escalation study in patients with advanced metastatic solid tumors. Dose escalation began at 3mg/m^2 given at 10 doses per cycle (Monday/Wednesday/Friday on weeks 1 and 3; Monday/Wednesday on weeks 2 and 4). The dose limiting toxicities (DLTs) were anorexia/nausea and fatigue at 40mg/m^2 (10 times per 4-week cycle) in KCP-330-002 and the maximum tolerated dose (MTD) was 30mg/m^2. Based on similar adverse events in KCP-330-001, escalation beyond 30mg/m^2 (10 times per cycle) was not performed. The recommended phase II dose (RP2D) for 10 times per cycle dosing is 30mg/m^2. Reduced intensity dosing at twice weekly (8 times per cycle, Days 1 & 3 of each week) has shown improved tolerability. Dose escalation on this schedule in KCP-330-002 is currently proceeding at 50mg/m^2; 40mg/m^2 cleared DLT. Escalation on this twice-weekly schedule in KCP-330-001 is currently proceeding at 35mg/m^2 and is anticipated to increase to 40mg/m^2 in patients with non-AML hematologic malignancies. In patients with relapsed AML, escalation is currently ongoing at 40mg/m^2 on the twice weekly (Day 1, 3) schedule.

KCP-330-003 (OZM-050) is an open label Phase Ib trial to evaluate the effects of food and formulation on pharmacokinetics of selinexor in patients with advanced soft-tissue or bone sarcoma.

Clinical Safety

In ongoing clinical trials, the most common AEs suspected to be related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and weight loss. Most of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. Overall, the most frequently observed laboratory abnormalities include mild/moderate thrombocytopenia, hyponatremia, and a decrease in red blood cells (RBC).

Less common adverse events include: changes in taste, changes in vision including blurred vision, low platelets, decrease in red blood cells, low sodium without symptoms and rare side effects include worsening of pre-existing cataracts, elevated levels of bilirubin, elevated liver enzyme levels (ALT and AST), and acute cerebellar syndrome.

In a previous study, one patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 4 doses of selinexor at 85 mg/m2 BSA twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to

walk. Since the date of the initial reported event, this patient is recovering, with both speech and mobility recovered to near baseline over ~6 weeks. No other patients have reported similar symptoms to date.

Patients should avoid alcohol consumption or any products containing ethanol (such as certain cough suppressant medications) on days that selinexor is administered. Alcohol and ethanol may interfere with the breakdown of selinexor in the body; therefore, alcohol consumption, particularly on days of selinexor therapy, should be minimized. Acetaminophen use on the days of selinexor dosing should be limited. Selinexor should be taken within 30 minutes of eating.

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

Please see the selinexor Investigator's Brochure for additional information.

Clinical Evidence of Anti-Cancer Activity

Hematological Malignancies In the dose escalation phase of study KCP-330-001, tumor load reductions and disease stabilization have been noted across many tumor types, consistent with the broad anti-tumor mechanism and results observed in preclinical studies. Responses have been documented in patients with multiple myeloma (MM), mantle cell and diffuse large B cell (DLBCL) lymphomas, chronic lymphocytic leukemia, Richter's Syndrome, and acute myeloblastic leukemia (AML). Durability for 6-12 months has been observed. Dose expansion is planned at 35mg/m^2 twice weekly in patients with relapsed/refractory DLBCL (N=15), MM (N=10) and at 40 mg/m^2 in AML (N=24). A separate Arm will evaluate the safety and tolerability of selinexor in patients with relapsed T-cell lymphomas (PTCL and CTCL). Additional cohorts exploring optimal twice weekly dosing (e.g., dosing on Days 1, 2 vs. 1, 3 versus 1, 4) are being enrolled.

Solid Tumor Malignancies In the dose escalation phase of study KCP-330-002, disease stabilization or responses for >4 months has been observed in patients with colon cancer, cervical adeno- and squamous cancers, and endometrial stromal sarcoma. Tumor shrinkage has also been observed in patients with melanoma, head and neck cancers, and Ewing sarcoma. Dose expansion at 35mg/m^2 twice weekly in patients with prostate, ovarian, squamous (head and neck, lung, and cervical), colon, and high-grade malignant gliomas are ongoing. Additional cohorts exploring twice weekly dosing as described above are being

explored. In addition, preliminary observations indicate that many of the progression events in the (primarily colorectal cancer) patients in the escalation portion of the phase I are related to liver (vs. lung or other non-liver) lesions. Therefore, the protocol for KCP-330-002 was amended to explore whether pre-treatment with low-dose acetaminophen, which reduces liver glutathione (GSH)-mediated metabolism of selinexor, can boost hepatic levels of selinexor (as observed in rats), and induce local tumor lesion shrinkage.

As of January 20, 2014, interim clinical data from nineteen patients enrolled in KCP-330-003 (OZM-050) were available. All patients received standard treatment for sarcoma and had progressive disease at study entry. Selinexor 30 mg/m2 was dosed orally twice weekly and showed similar tolerability following administration of both capsules and tablets when given under fasting conditions or with high or low fat meals. Of the 19 patients that received at least one dose of selinexor, 9 patients achieved stable disease by their first or second CT scan. In addition, 9 patients remained on study (>2 cycles) as of January 20, 2014.

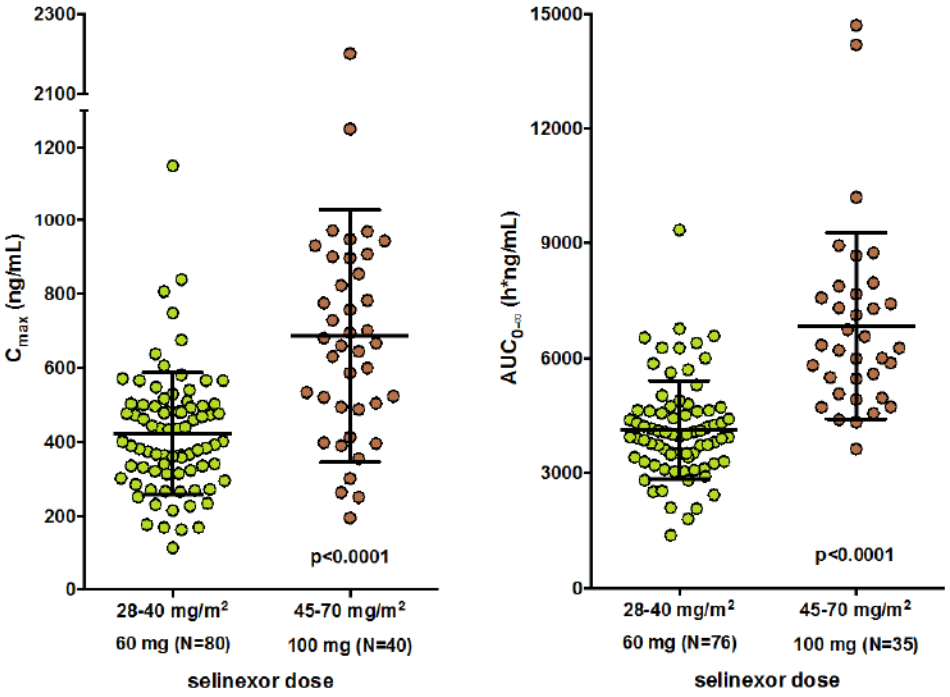
Clinical Pharmacokinetics

Detailed pharmacokinetic (PK) and pharmacodynamic (PD) analyses and serial tumor biopsies were performed in both KCP-330-001 and -002 studies and suggested a fairly proportional increase in Cmax and AUC with increasing dose, with no accumulation and without affecting half-life or clearance of selinexor. At 30 mg/m^2, $AUC_{0\text{-last}}$ (4375 ng*h/mL) was comparable to the anti-tumor exposure observed in mice and dogs. T_{max} (~3 h) and $T_{1/2}$ (6-7 h) were consistent across doses. A significant increase (2-20x) in XPO1 messenger ribonucleic acid (mRNA) levels (PD marker) in circulating leukocytes was observed at all doses, with higher doses demonstrating higher levels of XPO1 mRNA induction. Analysis of tumor biopsies confirmed nuclear localization of TSPs (e.g., p53, FOXO3A, IκB) and apoptosis of cancer cells following selinexor administration.

Selinexor PK data from eleven patients in study KCP-330-003 (OZM-050), suggest that oral selinexor in capsule or tablet forms show a clear difference between fasted and fed treatments, regardless of fat content of the meal. Patients being administered oral selinexor in clinical trials should be instructed to always take selinexor with food in order to prevent variations in plasma selinexor exposure related to prandial state. As there were no detectable differences between a high-fat or low-fat meal, no specific instructions with regard to meal size or content are required. There were no detectable differences in plasma selinexor exposure between the tablet and capsule formulations ($p > 0.05$); as such, all previous selinexor trials conducted with the capsule formulation should be considered supportive of safety in future trials conducted with tablets at a similar dose range. Moreover, these data indicate that the use of selinexor tablets at the same doses as previously used for capsules is appropriate.

Patients in this study will be dosed based on a fixed oral dose of selinexor rather than dosing per body surface area. This dosing regimen is supported by the accumulated PK data to date (see Investigator Brochure).
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). For this range, flat doses of 60 mg and 100 mg selinexor translate to BSA normalized dose ranges of 27-40 mg/m^2 and 43-70 mg/m^2, respectively. To evaluate PK for flat doses of 60 mg and 100 mg selinexor, C_{max} and $AUC_{(0-\infty)}$ values were compared for the equivalent, typical BSA-normalized dose

ranges Both C_{max} and $AUC_{(0-\infty)}$ were found to be significantly different ($p<0.0001$) for 60 mg and 100 mg selinexor.



1.4 Doxorubicin for Patients with Multiple Myeloma

There is extensive experience with the use of doxorubicin and liposomal doxorubicin for the treatment of multiple myeloma. Historically, patients with multiple myeloma received infusion doxorubicin in a regimen called VAD (vincristine, doxorubicin and dexamethasone). Because liposomal doxorubicin (LD) is associated with shorter infusion times and less cardiotoxicity, it was incorporated into the induction regimen instead of doxorubicin resulting in the DVD regimen. Outpatient DVD has been compared to VAD and resulted in similar response rates to VAD—with less alopecia, neutropenia and obviating the need for hospitalization[8]. However, it was associated with greater incidence of palmar plantar dysesthesias or hand-foot syndrome. More recently, LD in combination with bortezomib was found to be superior to bortezomib alone—showing a significant increased time to progression, 15-month survival rate and duration of response for the LD/bortezomib arm[2]. This led to the approval by the US Food and Drug Administration of LD for patients with relapsed and refractory multiple myeloma in 2007. We have evaluated the addition of LD to thalidomide and lenalidomide based therapy in the relapsed / refractory setting as well as in newly diagnosed myeloma with evidence of synergy[10, 22].

Given the erratic availability of LD preparations , this trial will utilize commercial sources of Liposomal doxorubicin. Commercial sources of liposomal doxorubicin are drugs with the same active ingredient, dosage, strength, and route of administration as the FDA-approved drug Doxil.

1.5 Investigator-initiated Phase I/II Clinical Trial of Selinexor, Liposomal Doxorubicin and Dexamethasone for Relapsed and Refractory Multiple Myeloma

1.5.1 Rationale for the Study

In our pre-clinical studies, we have observed that high-density drug resistant multiple myeloma cells, similar to those found in the bone marrow of myeloma patients, export topoisomerase II alpha (topo IIα) from the nucleus to the cytoplasm[12]. Under normal conditions, topoisomerases remove DNA tangles and relieve torsional stress and are also necessary for chromatin condensation during mitosis. Topo IIα does this by creating double-strand DNA breaks called cleavable complexes, allowing the DNA to unwind, essentially removing torsional stress. Topoisomerase directed drugs arrest Topo IIα protein in this cleavable complex formation, ultimately resulting in double-strand DNA breaks and induce apoptosis of the cancer cell. However, when Topo IIα is exported into the cytoplasm and is no longer in contact with nuclear DNA, it cannot form cleavable complexes thereby making the myeloma cells resistant to topoisomerase directed therapeutics such as doxorubicin[12, 13, 23].

The molecule that exports topo IIα from the nucleus to the cytoplasm is a chaperone / receptor protein called chromosome maintenance protein 1 (CRM1), or XPO1. CRM1 binds to a leucine-rich (hydrophobic) nuclear export signal peptide on the topo IIα protein [12, 13, 23] and escorts it through the nuclear pore complex where it is released into the cytoplasm. We have found that if we block CRM1 binding to topo IIα at the nuclear export signal peptide, topo IIα stays in the cell nucleus and the cells are made sensitive to topoisomerase inhibitors, essentially a reversal of density-dependent drug-resistance.

In general, the intracellular location of a protein is crucial to its normal functioning in a cell. Cancer cells utilize the processes of nuclear-cytoplasmic transport through the nuclear pore complex to effectively evade anti-cancer mechanisms [14, 18, 19]. Examples of nuclear proteins that are exported into the cytoplasm in cancer include the drug targets topo IIα and BCR-ABL [24] and tumor-suppressor proteins such as retinoblastoma [25], APC [26], p53 [27], p21 [28], and p27 [29]. In addition, CRM1-mediated export is increased in various cancers (reviewed in [18, 19]). The therapeutic potential of various CRM1 inhibitors has begun to be addressed in the laboratory. Compounds under investigation include ratjadone compounds [14, 30-33], KOS-2464 [34], FOXO export inhibitors[35], valtrate [36], acetoxychavicol acetate [37], and most recently CBS9106 [38] and small-molecule selective inhibitors of nuclear export / SINE™ compounds[21]. Recent publications have indicated that SINE™ compounds may be effective against various malignancies including leukemia [20, 21, 39-41], kidney cancer [42], mantle cell lymphoma [43], melanoma [44], and multiple myeloma (MM) [40].

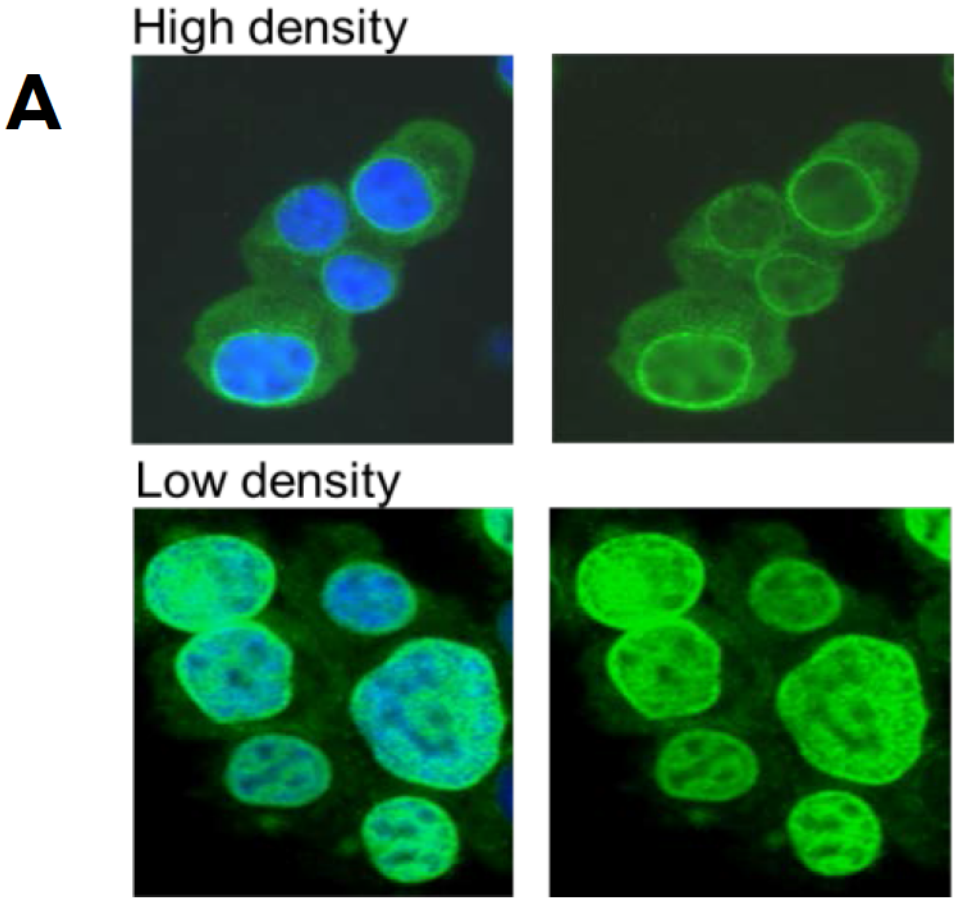
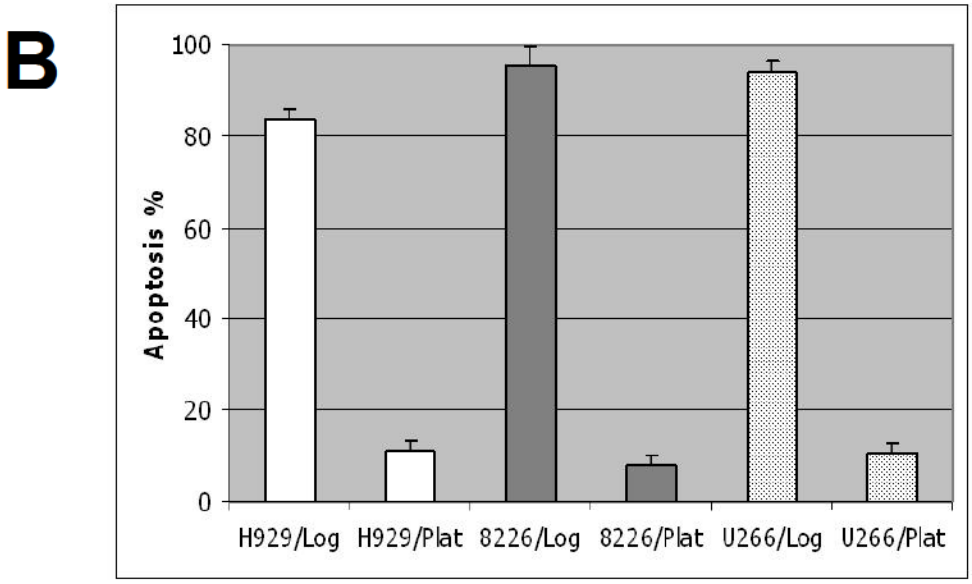


Figure 1. Drug Resistance in multiple myeloma and intracellular localization of topoisomerase IIα Human multiple myeloma cells grown at high densities; (**A**) export topo IIα to the cytoplasm and (**B**)(next page) are resistant to topo II inhibitors. High density cells were grown at 2 x10^6 for 20 hours and either stained with DAPI (blue) and topo IIα (green) (A) or treated with doxorubicin and assayed for apoptosis (B)(next page).



In multiple myeloma (MM), de novo drug resistance to topoisomerase II inhibitors occurs at high cell densities due to trafficking of topo IIα from the nucleus to the cytoplasm (Figure 1A) where it is no longer in contact with the DNA and thus unable to induce apoptotic cell death [12, 13, 23, 45] (Figure 1B). We have previously demonstrated that topo IIα is exported from the nucleus of human myeloma cells by a CRM1-dependent mechanism [12], and we have also identified the nuclear export signals (NES) for topo IIα at amino acids 1017-28 (site A) and 1054-66 (site B) [13](Figure 2). We found that site-directed mutation of NES 1017-28 (site A) blocked nuclear export of topo IIα [13] (Figure 2).

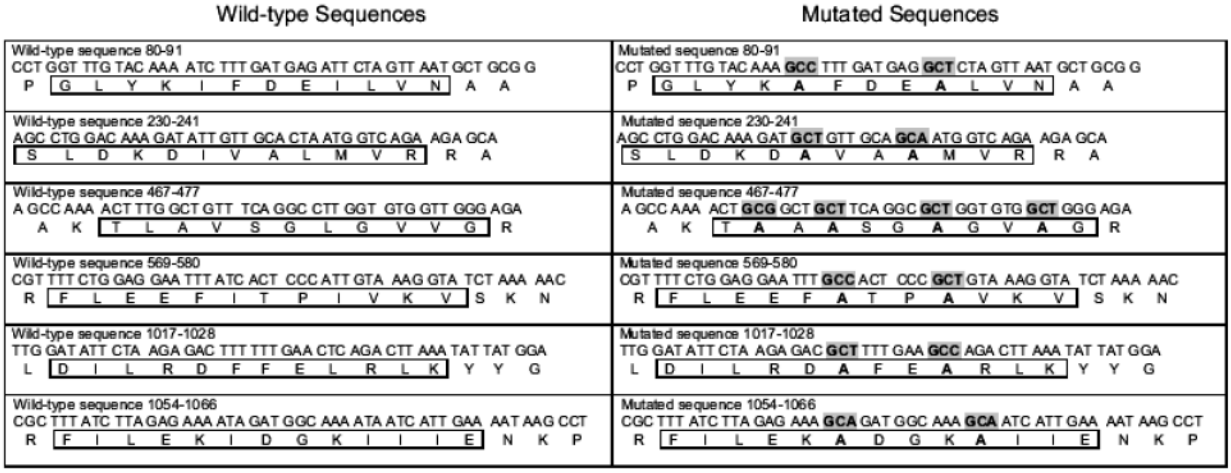


Figure 2. Site-directed mutagenesis. The figure compares nucleotide sequences from the wild-type topo IIα gene and the mutated sequences used in this study. Hydrophobic amino acid residues thought to be necessary for nuclear export were mutated to alanine using site-directed mutagenesis (gray boxes). Putative NES amino acid sequences are in boxes below their corresponding nucleotide sequences.

CRM1 inhibition using siRNA or ratjadone to block nuclear export of topoisomerase IIα and sensitize high-density drug resistant myeloma cells to doxorubicin

In these experiments, we repeated the finding that that myeloma cells grown at high density are highly resistant to topo II–directed chemotherapeutic drugs (Figure 1) and that drug resistance correlated with nuclear export of topo IIα (Figure 1). Based on these data, we proposed that blocking CRM1-mediated export of topo IIα may make myeloma cells more sensitive to topo II–active agents.

To evaluate whether blocking topo IIα export would sensitize cells, we knocked down CRM1 mRNA and protein expression in cells by transfection with CRM1-specific siRNAs and by using the CRM1-inhibiting drug ratjadone C (Figures 3 and 4) [14]. Ratjadone C was used in this study because it is a potent inhibitor of CRM1, has been shown to have anticancer properties, and has reduced toxicity in vitro compared to leptomycin B when used at low concentrations. CRM1 inhibition by siRNA and ratjadone C in human myeloma cells was found to prevent nuclear export of topo IIα in plateau density cell cultures (Figure 3). Depletion or inhibition of CRM1 by siRNA or ratjadone C caused high-density myeloma cells to become 4-fold more sensitive to the topo II inhibitors doxorubicin and VP-16 as measured by apoptosis (Figure 4)[14]. Depletion of topo IIα protein by specific topo IIα siRNA knockdown reversed this synergistic effect, indicating that topoIIα was the targeted molecule for CRM1 synergistic activity (data not shown). In addition, we found that blocking CRM1-mediated export sensitized patient myeloma cells obtained from bone marrow aspirates to the topo II poison doxorubicin (Figure 5). Normal peripheral blood mononuclear cells were not sensitized by CRM1inhibition (Figure 11). It is likely that these cells were not sensitized because they are not replicating at a high rate, unlike the myeloma cells, which double approximately every 24 h. In addition, normal cells do not export topo IIα; therefore, ratjadone C treatment would not affect intracellular localization.

When additional drugs were used in combination with ratjadone C, we found that myeloma cells were sensitized to the topo II inhibitors doxorubicin and VP-16 but not to the alkylating agent melphalan, or other myeloma chemotherapeutics such as dexamethasone and lenalidomide (data not shown). In conclusion, maintaining topo IIα in the nucleus by inhibition of CRM1 greatly enhanced the cytotoxic effect of the topo II inhibitors doxorubicin and VP-16 in high-density myeloma cells. Band depletion assays indicated that more DNA-topo IIα complexes were stabilized in cells when CRM1 was inhibited and these increased cleavable complexes resulted in increased strand breaks as measured by the comet assay and subsequent apoptosis[14].

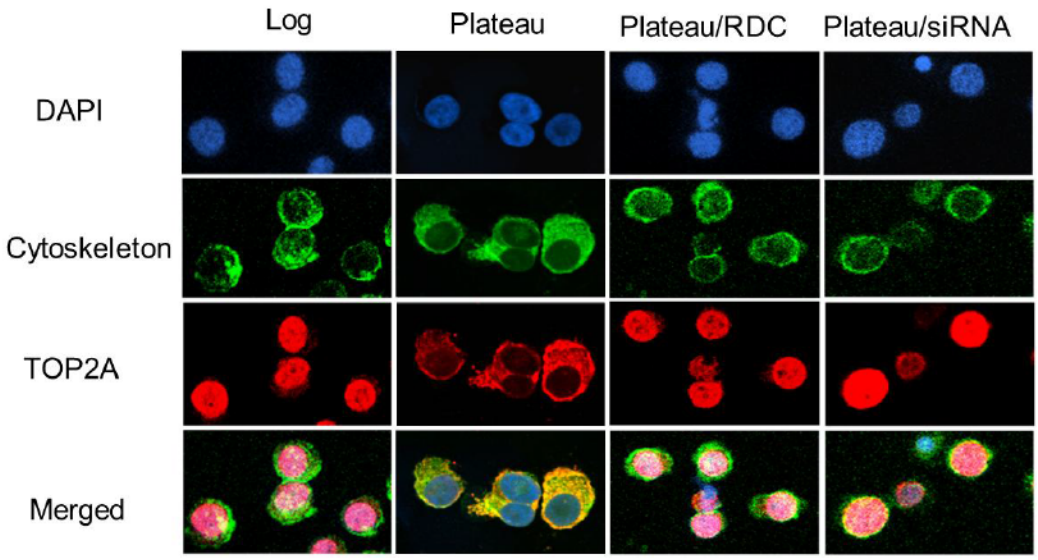


Figure 3. H929 topo IIα immunofluorescence. H929 human myeloma cells were grown at log and plateau densities, fixed with 4% paraformaldehyde, permeabilized with 0.25% Triton X-100, and stained for cytoskeletal protein (phalloidin-green), topo IIα (red), and DNA (DAPI-blue). Results indicate that topo IIα is present in the nucleus of log density cells and is exported from the nucleus in plateau density cells. However, nuclear export is blocked in plateau cells by a CRM1 inhibitor ratjadone C and by transfection with CRM1 specific siRNA. Under the conditions of this experiment, CRM1 siRNA knockdown was 69%.

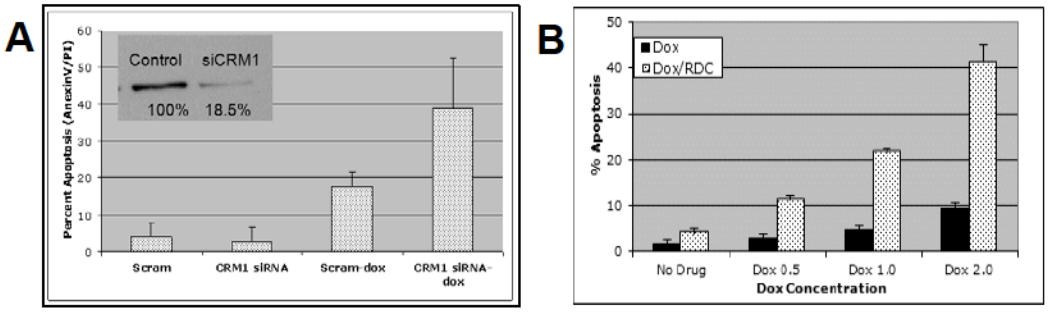


Figure 4. A) CRM1 knockdown using siRNA makes myeloma cells more sensitive to the topo IIα poison doxorubicin. H929 cells were transfected with siRNA, incubated at log-phase for 20 hours, and concentrated at plateau-phase conditions. At 48 hours cells were treated with the topo II inhibitor doxorubicin (2 μM) and assayed for apoptosis by Annexin V staining using flow cytometry, n=2. **Inset,** Western blot data for siRNA transfection. Percent knockdown was compared to control siRNA (scramble). CRM1 knockdown renders plateau density cells more sensitive to topo IIα inhibitors. **B) CRM1 inhibitor and topo IIα inhibitor synergy.** Myeloma cell line U266 was grown in culture for 20 hours at $2x10^6$ cells/ml. Cells were incubated with the CRM1 inhibitor ratjadone C (5 nM) for 20 hours. Cell were then treated with doxorubicin (0, 0.5, 1, and 2 μM) for four hours and assayed for caspase 3 staining by flow cytometry. Myeloma cells are made more sensitive to topo IIα inhibitors in a dose-dependent manner by inhibiting CRM1 export.

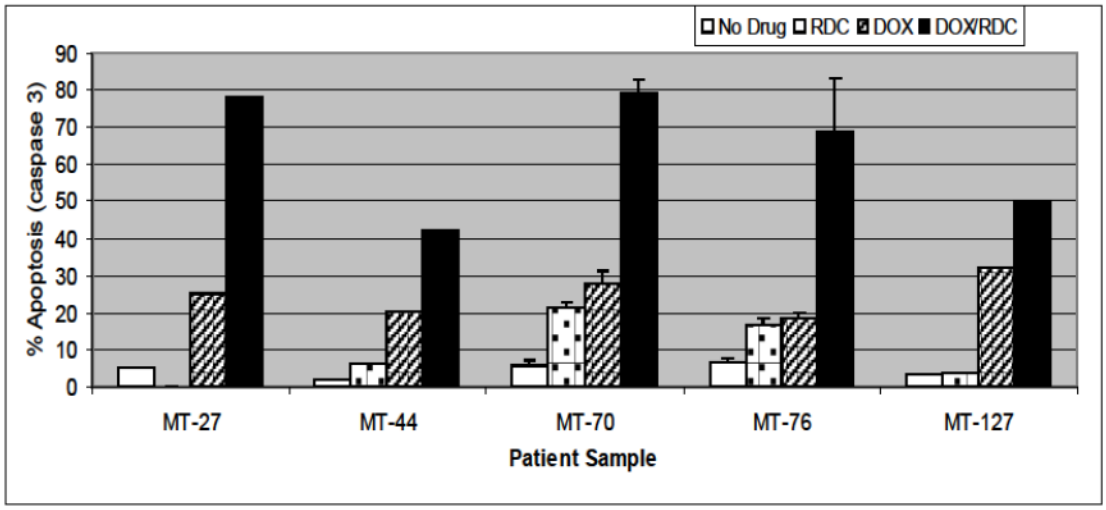


Figure 5. CRM1 inhibitor sensitizes patient myeloma cells to topo IIα drugs. Human bone marrow aspirates obtained from multiple myeloma patients were treated with RDC (5 nM) for 16 hours followed by doxorubicin (Dox; 2 μM) for 4 hours and assayed for cleaved caspase 3 to determine apoptosis. Cells treated with RDC were significantly ($p=0.0003$) more sensitive to doxorubicin (3-fold) than doxorubicin alone. Patient samples MT-70 and MT-76 were assayed twice in separate experiments and therefore contain standard error bars. All other patient samples were done in single experiments due to limited cell counts.

CRM1 inhibition sensitizes drug resistant human myeloma cells to topoisomerase II inhibitors both in vitro and ex vivo.

Selective Inhibitors of Nuclear Export / SINE™ compounds (Figure 6) prevent CRM1-mediated export of p53 and topoisomerase IIα (topo IIα) (Figure 7). SINE™ compounds CRM1-inhibiting activity was verified by nuclear-cytoplasmic fractionation and immunocytochemical staining of the CRM1 cargoes p53 and topo IIα in MM cells (Figure 7). We found that SINE™ molecules reduced cell viability and induced apoptosis when used as both single agents in the sub-micromolar range and when combined with doxorubicin, bortezomib, or carfilzomib but not lenalidomide, melphalan, or dexamethasone (Figure 8 and 9). The anti-cancer effect of SINE™ compounds/doxorubicin was also validated in a drug-resistant stromal cell culture model (Figure 10). Drug resistance induced by co-culture of myeloma cells with bone marrow stroma cells was circumvented by the addition of SINE™ molecules (Figure 10). In addition, CRM1 inhibition sensitized MM cell lines and patient myeloma cells to doxorubicin, bortezomib, and carfilzomib but did not affect peripheral blood mononuclear or non-myeloma bone marrow mononuclear cells as shown by cell viability and apoptosis assay (Figure 11). These preclinical studies showed that SINE™ molecules may be effective against MM in combination with drugs used to treat myeloma such as doxorubicin. Using both human MM cell lines and patient bone marrow samples, we found that SINE™ molecules were effective both as single agents and when combined with the chemotherapeutic drugs doxorubicin, bortezomib, or carfilzomib but not lenalidomide, melphalan, or dexamethasone. These data support the ongoing development of these small-molecule CRM1 antagonists in patients with MM.

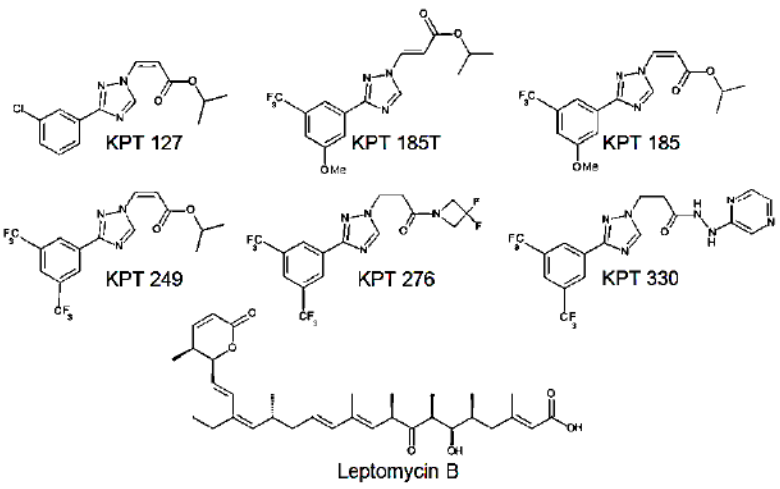


Figure 6. CRM1-targeted nuclear export inhibitors. Similar in mechanism to LMB, the SINE™ CRM1 inhibitors (KPT-127, KPT-185, KPT-249, KPT- 276, and KPT-330(Selinexor)) bind to the active site (CRM1 cysteine residue 528) and prevent transport receptor binding to the cargo protein. KPT-185T is the inactive trans-isomer of KPT-185.

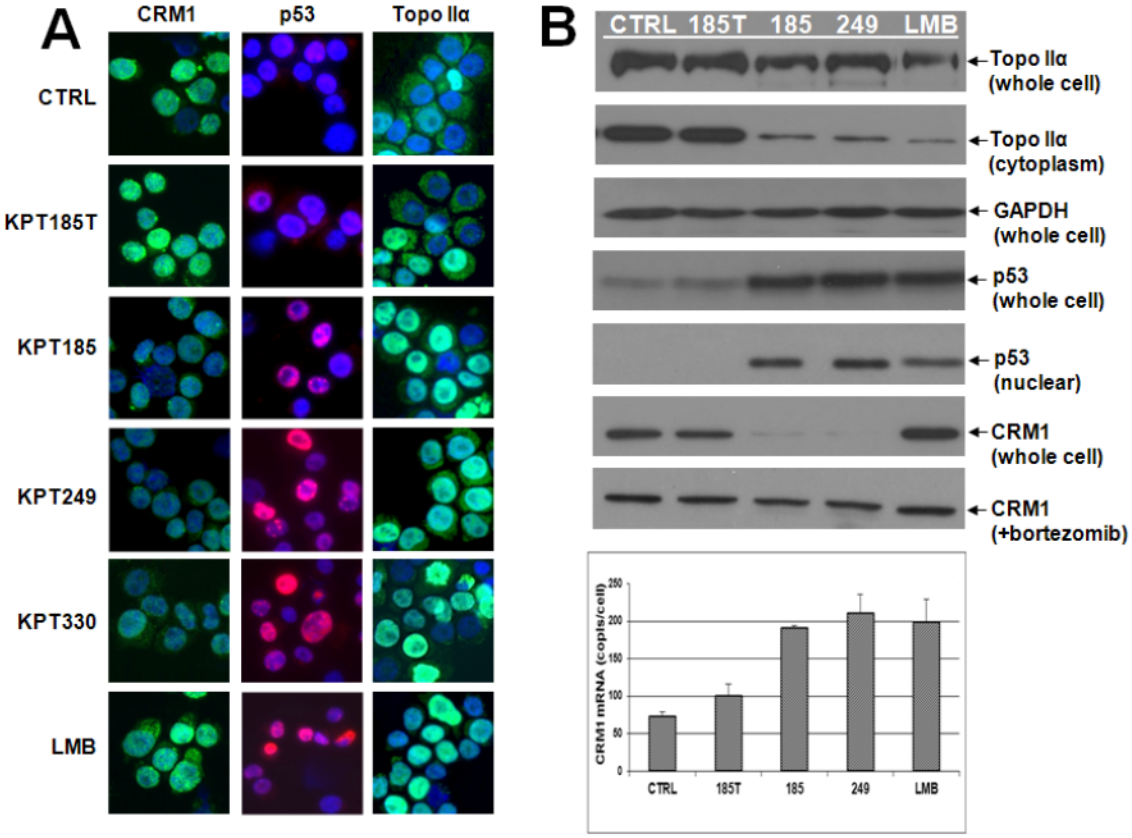


Figure 7. CRM1, p53, and topo IIα localization in SINE™ compound-treated cells. A) Immuno-fluorescence microscopy. Human H929 MM cells were treated with SINE™ compound or leptomycin B for 20 hours. Samples assayed for p53 and CRM1 were treated with 100 nM SINE™ compound and 10 nM LMB. Samples assayed for topoisomerase (topo) IIα were treated with 300 nM SINE™ compound and 100 nM LMB. Intracellular localization and expression of p53, CRM1, and topo IIα were examined by immunofluorescence

microscopy. Nuclei were counter-stained using DAPI (blue). **Column 1:** CRM1 (green) nuclear localization in low-density log-phase cells (2 x 10^5/ml) was increased in untreated controls, in KPT-185T treated cells, and in LMB-treated cells, but not in KPT-185, KPT-249, or KPT-330 treated cells. **Column 2:** p53 (red) was exported from the nucleus in low-density log-phase (2 x 10^5/ml) untreated control, and KPT-185T treated cells; however, cells treated with KPT-185, KPT-249, KPT-330, and LMB had increased nuclear accumulation of p53. **Column 3:** high-density (3 x 10^6/ml) untreated control cells exported topo IIα (green) to the cytoplasm (as did KPT-185T treated cells) and had low levels of topo IIα in the nuclei (blue/DAPI). KPT-185, KPT-249, KPT-330, and LMB prevented nuclear export of topo IIα; therefore, the nuclei were green (topo IIα).

B) CRM1, p53, and topo IIα protein expression in SINE™ compound **-treated cells.** H929 cells were treated with 100 nM of each CRM1 inhibitor for 20 hours at high-density (3 x 10^6/ml) growth conditions. Whole cell lysates assayed for topo IIα protein demonstrated minimal change in total amount of topo IIα; however, cytoplasmic fractions showed that the nuclear export of topo IIα was inhibited by KPT-185, KPT-249, and LMB. GAPDH protein (loading control) showed that equal amounts of protein were loaded for topo IIα. H929 cells were also treated with 100 nM of each CRM1 inhibitor for 20 hours at log-phase growth conditions. Whole cell lysates assayed for p53 showed that total cellular p53 increased in cells treated with CRM1 inhibitors when compared to untreated and KPT-185T treated control samples. Nuclear fractions isolated from treated cells and assayed by Western blot demonstrated that nuclear p53 increased when cells were exposed to the active CRM1 inhibitors KPT-185, KPT-249, and LMB. KPT-185 and KPT-249, but not LMB or KPT-185T, decreased CRM1 protein expression in whole cell lysates. However, when cells were treated with the proteasome inhibitor bortezomib, CRM1 protein levels did not decrease. Treated cells were also assayed for CRM1 mRNA levels. We found that all CRM1 inhibitors had significantly ($P < 0.05$) increased mRNA levels as compared to untreated and KPT-185T treated controls.

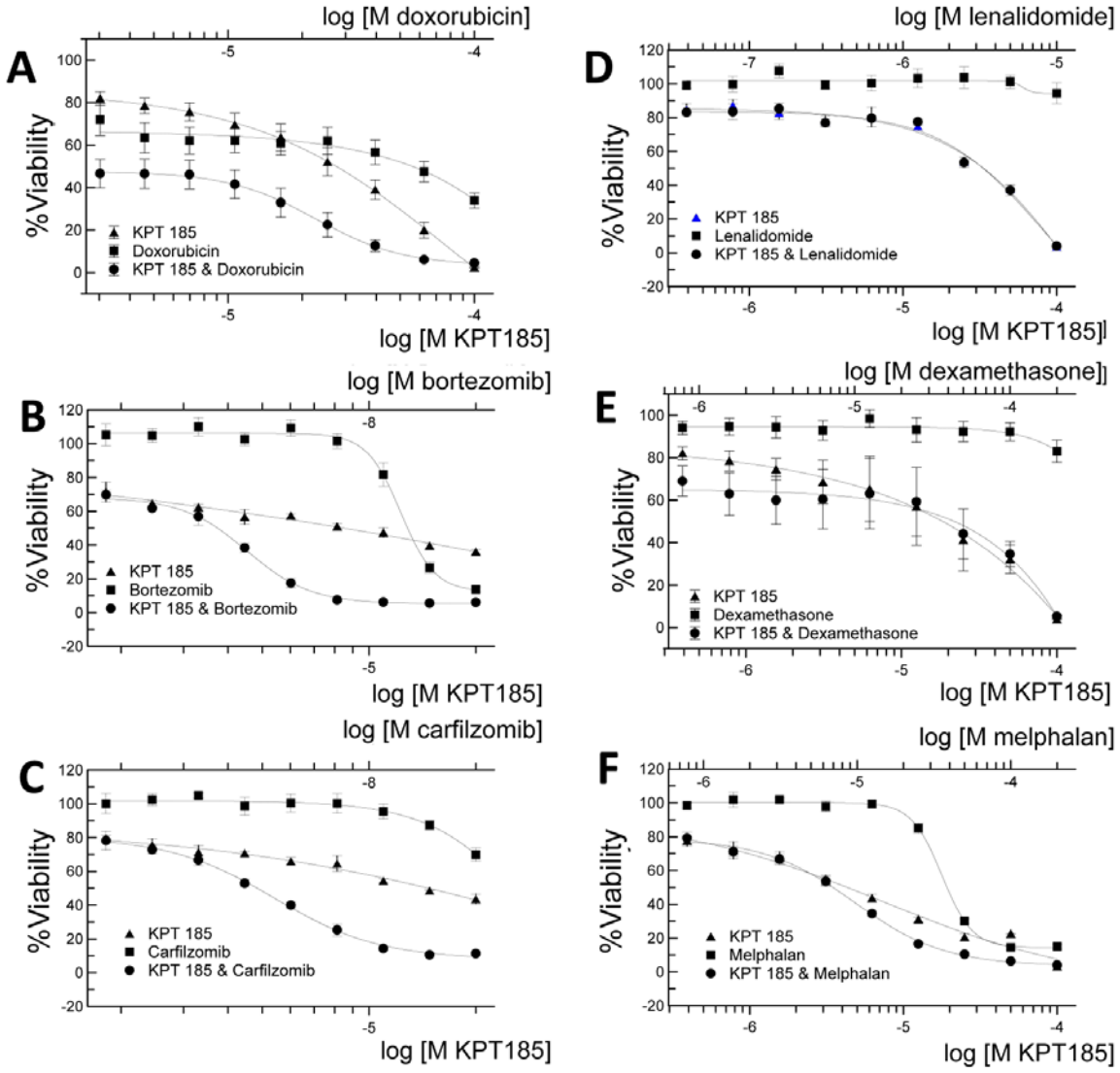


Figure 8. SINE™ compound molecules work synergistically with doxorubicin, bortezomib, and carfilzomib in H929 cells. SINE™ compound KPT-185 was serially diluted, added to the wells containing H929 MM cells grown at plateau densities (2 x 10^6/ml), and incubated overnight at 37°C and 5% CO_2. Doxorubicin (A), bortezomib (B), carfilzomib (C), lenalidomide (D), dexamethasone (E), and melphalan (F) were serially diluted and added the following day, and the plates were incubated an additional 24 hours. Samples were assayed for cell viability (CellTiter-Blue reagent) in replicates of 2-4. Percent viability versus drug concentration was plotted. SINE™ compounds were found to be synergistic with doxorubicin (CI=0.377), bortezomib (CI=0.410), and carfilzomib (CI=0.322), additive with melphalan (CI=0.849), and non-synergistic/antagonistic for lenalidomide (CI>2.0) and dexamethasone (CI>2.0) in H929 cells.

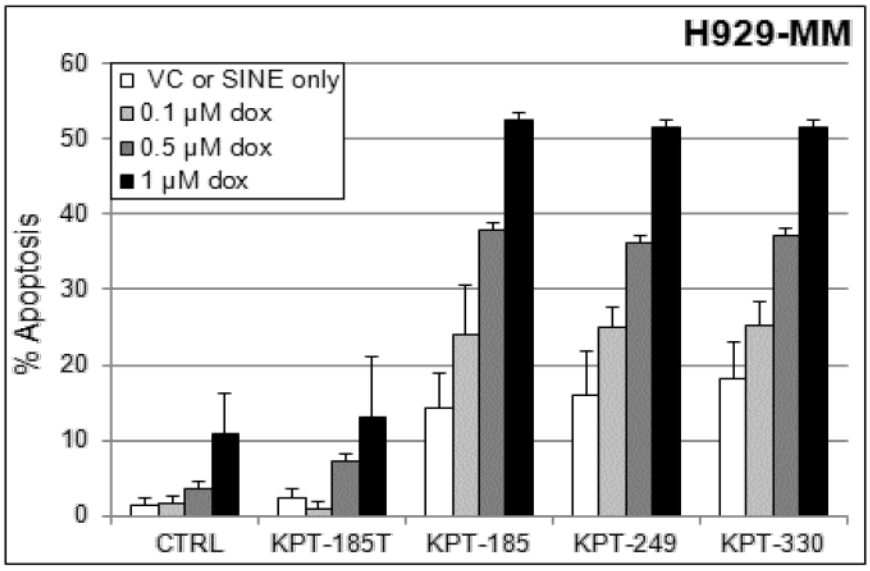


Figure 9. Human myeloma cells are sensitized to doxorubicin. High-density (3.0 x 10^6 cells/ml) H929 cells were treated concurrently with 300 nM SINE™ compound and doxorubicin (dox; 0.1, 0.5, or 1 µM) for 20 hours and assayed for apoptosis by activated caspase 3. Apoptosis was induced in SINE™ compound /doxorubicin-treated cells in a dose-dependent manner ($P < 0.021$).

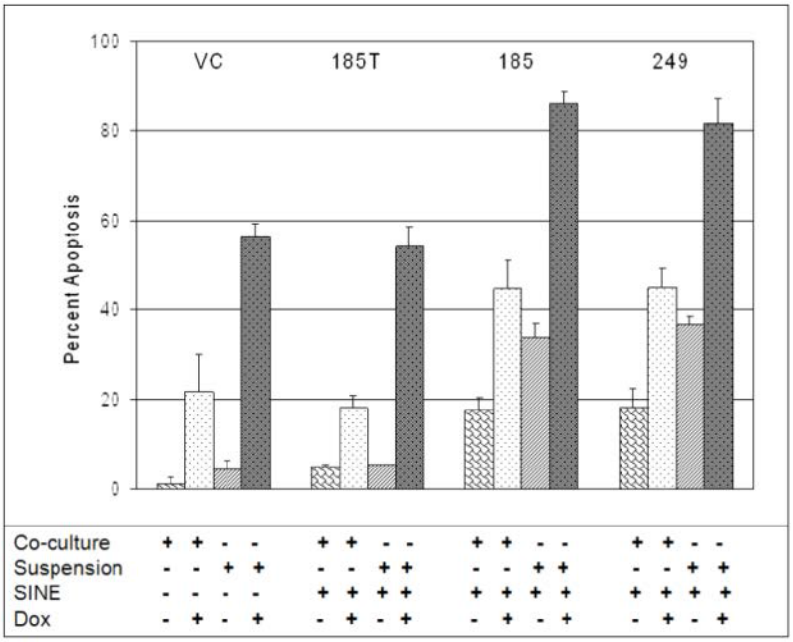
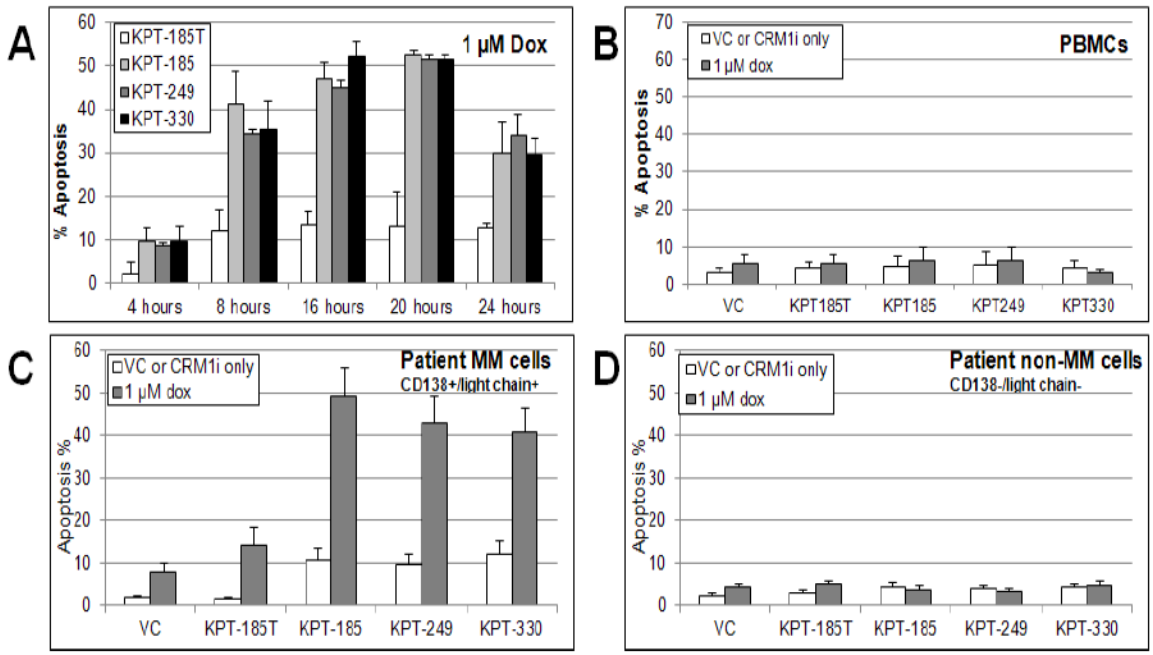


Figure 10. Stromal cell co-culture induced drug resistance. H929 myeloma cells (5 x10^5) co-cultured with HS-5 cells (5 x10^5) are drug-resistant to CRM1 inhibitors (P=0.0001) and doxorubicin (P=0.0002) when used as a single agent compared with H929 cells grown in suspension. When compared to doxorubicin alone (columns 1 and 3 of the VC group (vehicle control)) (P<0.0001) or the inactive trans-isomer KPT-185T (P<0.02), both KPT-

185 and KPT-249 sensitized H929 cells when used in combination with doxorubicin. SINE™



compounds sensitized both suspension cells and co-cultured myeloma cells to doxorubicin.

Figure 11: CRM1 inhibition sensitized MM cell lines and patient myeloma cells to doxorubicin but did not affect peripheral blood mononuclear or non-myeloma bone marrow mononuclear cells. A) H929 myeloma cells were incubated concurrently with SINE™ compound (100 nM) and 1 μM doxorubicin over a time course of 4, 8, 16, 20, and 24 hours. MM cells demonstrated significant ($P < 0.05$) apoptosis beginning at 8 hours with co-treatment of SINE™ compound and doxorubicin. **B)** Human peripheral blood mononuclear cells (PBMC) from normal donors (n=3) were unaffected by treatment with SINE™ compound (300 nM) and were not sensitized to doxorubicin. **C and D)** CRM1 inhibitors sensitize patient myeloma cells (n=12) to doxorubicin **(C)** but do not sensitize non-myeloma cells **(D).** This indicates that SINE™ compound may specifically inhibit neoplastic cells in MM patients.

Summary: Rationale

Drug resitance in multiple myeloma is correlated to the nuclear export of topo IIα by the export receptor CRM1. Blocking nuclear export sensitizes drug-resistant human myeloma cells to chemothearpeutic agents. In a study published recently in our lab [46]we examined the cytotoxic effects of selinexor in MM cells. We showed by immunofluorescence microscopy and nuclear-cytoplasmic fractionation that these molecules were able to prevent nuclear export of the tumor suppressor protein p53 and the nuclear drug target topo IIα. Cell viability data demonstrated that selinexor was effective as a single agent against human myeloma H929 and 8226 and HL-60 AML cells at nanomolar concentrations but was up to 239-fold less toxic to normal cells. Selinexor, when used in combination with the anti-MM agents doxorubicin, was found to sensitize drug-resistant MM cells in both the

high-density cell culture model and in co-culture with HS-5/GFP bone marrow stromal cells[46].

Combining selinexor with doxorubicin induced apoptosis and decreased cell viability of myeloma cells synergistically. The synergistic effects of selinexor with the myeloma drug doxorubicin was dose dependent, and time-course studies performed in high-density drug-resistant MM cultures showed that apoptosis was induced after a 8-hour co-treatment with doxorubicin/ selinexor. Normal human peripheral blood mononuclear cells were unaffected by selinexor treatment and were not sensitized to doxorubicin. In studies done on MM patient bone marrow mononuclear cells, selinexor-doxorubicin co-incubation synergistically induced activated caspase 3 in CD138/light-chain double-positive myeloma cell populations but not in CD138/light-chain double-negative non-myeloma cells, indicating that selinexor may specifically inhibit neoplastic cells in MM patients. We found that CRM1 protein levels are decreased by selinexor. Interestingly, CRM1 mRNA levels were increased by both selinexor and LMB even with the concurrent decrease of CRM1 protein found in selinexor -treated cells[46].

Recent publications on the effects of selinexor on AML have shown that selinexor has anti-proliferative effects on AML cell lines and primary AML samples. In addition, when used as a single agent, selinexor induced apoptosis and accumulation of p53 in the nucleus of AML cells. We found parallel results in human MM cell lines and in patient MM bone marrow mononuclear cells with selinexor as a single agent; in addition, selinexor sensitized MM cells both in vitro and ex vivo to doxorubicin[46].

High-density drug-resistant MM cell lines and cells made resistant by stromal cell co-culture were sensitive to selinexor treatment. Selinexor induced apoptosis both as a single agent and in combination with doxorubicin as compared to the inactive trans-isomer ($P<0.02$) or DMSO vehicle control ($P<0.0001$). Selinexor was found to sensitize both suspension cells and co-cultured myeloma cells to doxorubicin.

These data support the current clinical study investigating the combination of selinexor with doxorubicin in MM

1.5.2 Rationale for Starting Dose and Dosing Schedule

In this trial, we propose weekly dosing of selinexor in combination with LD and dexamethasone. Dexamethasone will be given at a total of 40 mg weekly per myeloma therapy standard. The starting dose of LD will be 20 mg/m^2 IV on D1. Selinexor will be given orally on days 1, 8, and 15 of the cycle. The starting dose of selinexor will be 40 mg/m^2 (~68 mg) weekly, taking into account for the potential overlapping toxicities with LD (thrombocytopenia, nausea). In the ongoing Phase 1 study (KCP-330-001) in patients with hematological malignancies, a dose of 45 mg/m^2 twice weekly (90 mg/m^2 weekly) cleared DLT; currently dosing at 60 mg/m2 (120 mg/m^2 weekly). Therefore, the starting dose in this study of 40 mg/m^2 selinexor twice weekly, based on prior regimens, would correspond to a weekly dose of 80 mg/m^2, which was found to be tolerable in prior studies. Of note, doses as low as 3 mg/m^2 have shown biological and clinical activity.

Importantly, our preclinical studies suggest synergism between doxorubicin and selinexor when selinexor is given prior to doxorubicin, and we have recommended a loading dose of selinexor for the first 2 weeks on the trial.

Of note, cohort 2m and 3m have used a one week (one dose of selinexor 80 mg) loading phase only.

The following dose levels will be evaluated in this trial:

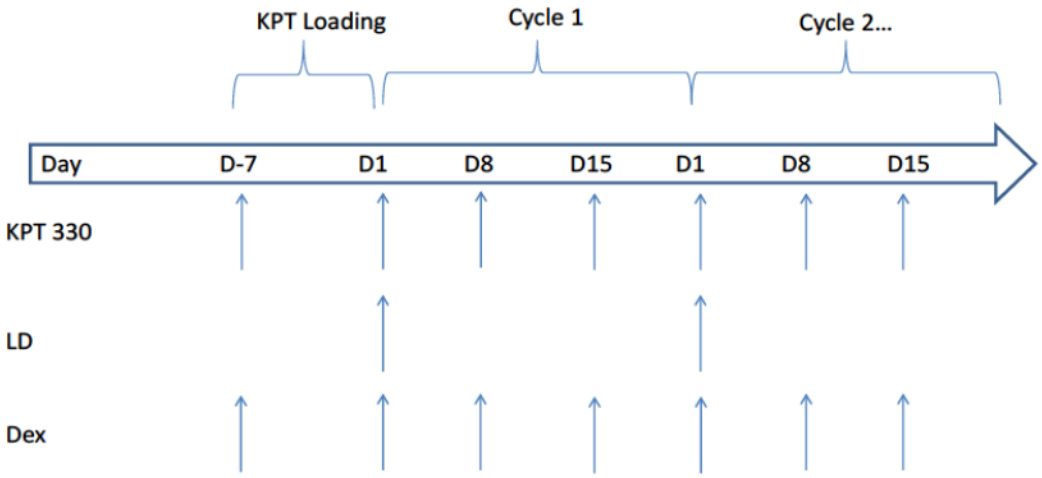
Dose level	Number of selinexor doses during loading	LD IV on D1	Selinexor PO	Dexamethasone* PO D1, 8, 15
-1	4 (Days-14, -11,-7, -4)	20 mg/m²	40 mg D1, 8, 15	40 mg
1	4 (Days-14, -11,-7, -4)	20 mg/m²	40 mg/m² (~68 mg) D1, 8, 15	40 mg
2	4 (Days-14, -11,-7, -4)	20 mg/m²	80 mg D1, 8, 15	40 mg
1m	1 (day -7 only)	20 mg/m²	60 mg D1, 8, 15	40 mg
2m	1 (day -7 only)	20 mg/m²	80 mg D1, 8, 15	40 mg
3m	1 (day -7 only)	20 mg/m²	80 mg D1,3,8, 10	40 mg
4m	1 (day -7 only)	30 mg/m²	80 mg D1,3,8, 10	40 mg

* For patients with intolerance to 40 mg of dexamethasone or who are older than 75 years, the starting dose of dexamethasone will be 20 mg on the same schedule

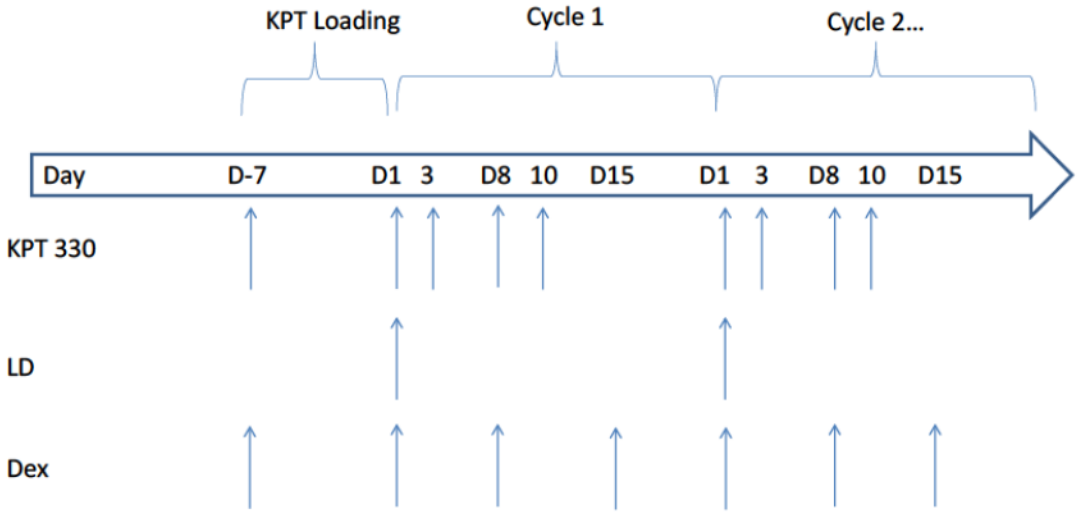
LD is administered at least 2 hours (but less than 4hours) after selinexor administration on day 1 of each induction cycle

Patients enrolled on cohort 2m will have a 1 week loading phase and selinexor will be administered on days 1,8,15 of the cycle (see below).

Dose level 2m was found to be the recommended phase II dose and will be the dose level used in the phase II / expansion cohort.



Patients enrolled on cohort 3m and 4m will have a 1 week loading phase and receive Selinexor on days 1,3, 8, 10 of the cycle (see below)



After amendment 5, patients will start dosing on dose level 2m

1.5.3 Study Population and Sample Size

Up to 47 patients with relapsed and refractory myeloma will be the included in this trial: up to 24 patients on the phase I study and 23 on the phase II trial. Responses in 3 or more of the 13 patients treated at the RP2D will establish the rationale for enrollment of 16 additional patients.

1.5.4 Assessment for Response

The uniform response criteria of the international myeloma working group (IMWG) will be used for response assessment (see Appendix A) [47].

2 OBJECTIVES

2.1 Primary Objective

For the phase I portion, the primary objective is to determine the safety and recommended phase II dose (RP2D) of selinexor in combination with LD and dexamethasone in patients with relapsed and refractory myeloma.

In the phase II portion, the primary objective is to evaluate the efficacy (overall response rate—partial response and better) of selinexor and LD and dexamethasone in patients with relapsed and refractory myeloma.

2.2 Secondary Objectives

To estimate the progression-free (PFS), duration of response (DOR), and overall survival (OS) in patients with relapsed and refractory myeloma treated with this combination.

To estimate the clinical benefit rate (minimal response and better) of the combination in relapsed and refractory myeloma.

3 INVESTIGATIONAL PLAN

3.1 Overview of Study Design and Dosing Regimen

This is a investigator-sponsored phase I/II study to evaluate the effectiveness and tolerability of oral selinexor in combination with liposomal doxorubicin and dexamethasone in patients with relapsed and refractory multiple myeloma. This study will be conducted at H. Lee Moffitt Cancer Center and Research Institute, Wayne State University / Karmanos cancer center and Virginia Commonwealth University Massey Cancer Center.

After the initial screening visit and registration in the study, eligible patients will receive selinexor on day -7= at a dose of 80 mg in addition to dexamethasone 40 mg. After 1 week of dosing with selinexor and dexamethasone, patients will receive weekly selinexor at a starting dose of 80 mg (cohort 2m) in combination with liposomal doxorubicin at a starting dose of 20 mg/m^2, and dexamethasone at 40 mg orally weekly.

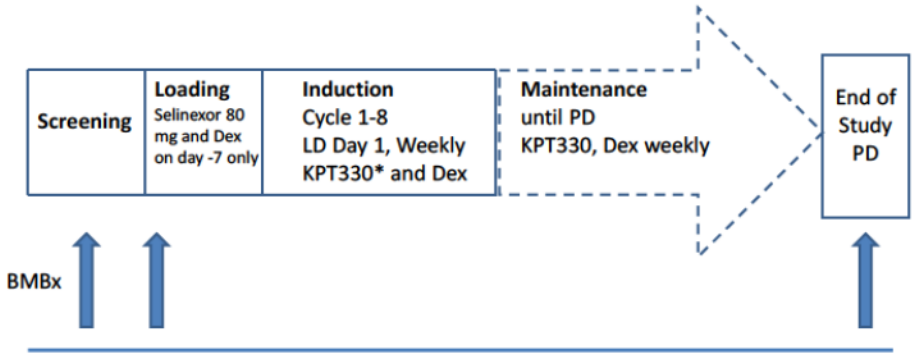
During the treatment period, patients will undergo physical examination and assessment of tumor response (paraprotein assessment) every 3 weeks per the IMWG uniform response criteria.

Patients will be treated until progression of disease or the development of unacceptable toxicities. All patients will then undergo a final visit (end of treatment visit).

3.1.1 Definition of Treatment Cycle and Duration

The study will consist of 4 phases. A screening phase, a loading phase, an induction phase (DLT evaluable period in the phase I), and maintenance phase.

Study Schema



KPT330: Selinexor
Dex: Dexamethasone
LD: Liposomal Doxorubicin IV
PD: Progressive Disease
BMBx: Bone Marrow Biopsy and Aspiration (screening, day-7, end of study)
* Patients on cohort 3m and 4m will receive selinexor on d1,3,8,10 of the cycle

Loading phase is 1 week with selinexor and dexamethasone. Induction cycles are repeated every 21 days. Patients will receive up to 8 cycles of selinexor in combination with liposomal doxorubicin and dexamethasone. After 8 cycles, patients experiencing a clinical benefit (stable disease or better) will continue on selinexor (administered at the tolerated dose orally once weekly) as a single agent until disease progression or unacceptable toxicity. Maintenance cycles are 28 days in duration.

Study drug administration may be delayed for toxicity according to protocol Section 8.

3.1.2 Criteria to Proceed with a New Cycle of Therapy during Induction

Given that patients entering the trial may have baseline cytopenias due to their underlying disease, the criteria to initiate a new cycle of therapy will largely be a reflection of resolution of drug induced myelosuppression despite a possible background level of disease related myelosuppression.

For the phase I patients: subjects may start a new cycle or cycle 1 day 1 when the ANC is greater than 800/mm^3 and the platelet count is greater than 30,000/mm^3. In addition, non-hematologic toxicities must have recovered as described in Section 8. If a patient does not meet the criteria to initiate cycle 1 day 1 because of cytopenias encountered in the loading phase, the patient may be allowed to proceed with cycle 1 day 1 with growth factor or transfusion support after discussion between the treating physician and principal

investigator, however the patient will not be considered evaluable for DLT and will be replaced during the phase I.

Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

For the phase II patients: For patients with baseline (at the time of eligibility) grade 3 thrombocytopenia or neutropenia, a new cycle of therapy (or cycle 1 day 1) can be started when the ANC is greater than 800/mm^3 and the platelet count is than 30,000/ mm^3. In addition, non-hematologic toxicities must have recovered as described in Section 6.1. For example, if a patient initial platelet count was 40,000/mm^3, the patient may be able to restart another cycle on day 1 if his/her platelet count is greater than 30,000/mm^3.

For patients without baseline grade 3 thrombocytopenia or neutropenia, a new cycle of therapy (or cycle 1 day 1) can be initiated when the ANC is greater than 800/mm^3 and the platelet count is greater than 50,000/mm^3. In addition, non-hematologic toxicities must have recovered as described in Section 6.1

For patients who do not meet criteria to start cycle 1 day 1 because of hematologic adverse events encountered during the loading phase, patients may be allowed to proceed with cycle 1 after discussion between the treating physician and principal investigator provided the patient will receive growth factor and /or transfusion support during cycle 1.

Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If study drug dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If study drug dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of the causative agent.

If recovery from toxicities is prolonged beyond 7 days, then the dose of selinexor, Liposomal doxorubicin or dexamethasone will be decreased by one dose level depending on which agent is felt to be the causative factor or more likely contributing factor.

3.1.3 Criteria to Proceed with a New Cycle of Therapy During Maintenance

It is expected that responding patients (stable disease or better) will proceed to maintenance therapy with selinexor and dexamethasone, and typically this would be associated with an improvement of disease-related parameters. In addition, long-term maintenance therapy needs to be associated with less long-term toxicities. To start a new cycle of maintenance, the following criteria must be met:

ANC is greater or equal to 1,000/mm^3

Platelet count is greater or equal to 30,000/mm^3

In addition, non-hematologic toxicities must have recovered as described in Section 6.1

3.1.4 End of Treatment Visit

Patients that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, 28 days after the last dose of study medication.

3.2 Study Duration

The study is planned to start in Q2 2014 with respect to first patient in (FPI). With an expected accrual rate of 3 patients every 5 weeks, and a total number of 47 patients planned, the anticipated enrolment period is 20 months. Hence, the last patient will be included not later than Q1 2016. The length of treatment period will be approximately 3 months, leading to the last patient off study-treatment in Q2 2016.

4 PATIENT SELECTION

This Investigator Initiated trial will be conducted in compliance with the protocol, GCP and all applicable regulations.

4.1 Inclusion Criteria

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

1. Written informed consent in accordance with federal, local, and institutional guidelines
2. Age ≥ 18 years
3. Patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, which must include lenalidomide and a proteasome inhibitor. Patients must have disease refractory to the most recent therapy. Refractory myeloma is defined as progressive disease during or within 60 days of last therapy. Patients must have previously received or be ineligible for (or refused) autologous stem cell transplant.
4. Patients must have measurable myeloma paraprotein levels in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour urine collection sample) or by free light chain (involved free light chain greater than 100 mg/L).
5. ECOG performance status of 0-1. ECOG 2 allowed if due to bone disease.
6. Must have an echocardiogram or MUGA indicating LVEF ≥ 50% within 42 days prior to first dose of study drug.
7. Adequate hematological function:
    a. In the phase I portion: absolute neutrophil count (ANC) ≥1000/mm^3, platelet count ≥50,000mm^3. GCSF is not allowed during screening or during the first cycle for phase I patients.
    b. In the phase II portion, if the patient had significant bone marrow involvement (BM plasma cells ≥ 50%), a platelet count ≥30,000mm^3 and absolute neutrophil count (ANC) ≥ 1000/mm^3 is required. GCSF is allowed during screening and therapy for all phase II patients. Alternatively, with less BM involvement, an ANC ≥ 1000/mm^3, and platelet count ≥50,000mm^3 is required.
8. Adequate hepatic function within 14 days prior to loading phase (day -14): total bilirubin <2 times the upper limit of normal (ULN) (except patients with Gilbert's

syndrome who must have a total bilirubin of < 3 times ULN), and alanine aminotransferase (ALT) <2.5 times ULN.

9. Adequate renal function within 14 days prior to loading: measured or estimated creatinine clearance of ≥ 30 mL/min, (Cockroft and Gault)
10. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

4.2 Exclusion Criteria

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

1. Patients who are pregnant or lactating
2. Radiation, chemotherapy, or immunotherapy or any other approved anticancer therapy ≤2 weeks prior to day -7 (beginning of loading phase)
3. Major surgery within four weeks before Day -7
4. Myocardial infarct within 6 months before enrollment, New York Heart Association (NYHA) Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
5. Prior cumulative exposure to doxorubicin (including liposomal preparation) > 350mg/m2
6. Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose; patients with controlled infection or on prophylactic antibiotics are permitted in the study;
7. Known to be HIV seropositive;
8. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen)
9. Any underlying condition that would significantly interfere with the absorption of an oral medication.
10. Grade >2 peripheral neuropathy at baseline.
11. Serious psychiatric or medical conditions that could interfere with treatment
12. Participation in an investigational anti-cancer study within 3 weeks prior to day -7 (beginning of loading phase)
13. Concurrent therapy with approved or investigational anticancer therapeutic. Patients are allowed to receive corticosteroids for the treatment of non-malignant disorders in doses not to exceed the equivalent of prednisone 20 mg/day
14. Patients with coagulation problems and active bleeding in the last month (peptic ulcer, epistaxis, spontaneous bleeding)
15. Patients who have had a previous allogeneic transplant within 6 months and have evidence of clinically significant graft versus host disease.

4.3 Patient registration

All subjects must be registered with the MCRN Coordinating Center to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number and randomization information, if indicated. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with supporting documentation to the MCRN via email at [redacted], Monday through Friday between 8:00AM and 5:00PM (EST).

5 STUDY CALENDAR

	Screening		Loading	Cycle 1			Cycles 2-8	Maintenance	Final Visit EOT
Visit window (+/-3 working days)	Within 28 days prior to start of therapy	Within 14 days prior to start of therapy	Day --7	Day 1	Day 8	Day 15	Day 1, 8 and 15 ± 2 days	Day 1 ± 2 days	30 days ± 7 days
Informed consent[1]	x								
Inclusion and exclusion criteria		x							
Demographics / Medical history[2]	x								
Pregnancy test (if applicable)[3]		x	x	x			x	x	x
Body height, weight, & BSA[4,]		x	x[19]	x[19]			x[19]	x[19]	x[19]
Vital signs[5, 19]	x		x	x	x	x	x	x	x
Physical examination and ECOG[6]	x		x[19]	x[19]			x[19]	x[19]	x[19]
Ophthalmologic exam[7]	x[7]								
12-lead ECG[19], echocardiogram (or MUGA)[8]	x							x	x
Urine analysis[9, 19]	x								
Hematology[10, 19]		x	x	x	x	x	x	x	x
Serum chemistry[11, 19]		x	x	x	x	x	x	x	x
Coagulation test (PT, PTT) [12, 19]		x							
Bone marrow aspiration and biopsy[13]	x		x						x
Assessment of disease status[14]	x		x	x			x	x	x
Chest radiograph[15, 19]	x								
Selinexor dosing in clinic[16]			x	x	x	x	x	x	
LD dosing in clinic[17]				x			x		
Pharmacokinetics and pharmacodynamics[18]			x	x	x	x	x		
Adverse events			x	x	x	x	x	x	x
Concomitant medication[19]		x	x	x	x	x	x	x	x

Study Assessment Footnotes

[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 types and number of prior regimen, refractoriness to immunomodulatory agents and / or proteasome inhibitors, prior anthracycline and total cumulative dose, 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. During cycles 2-8, a pregnancy test is obtained on day 1 of the cycle only.

[4] Height will be measured at screening only. During cycles 2-8 and maintenance, weight is obtained on day 1 of the cycle only.

[5] Vital signs: blood pressure, pulse and temperature. During loading, vital signs are obtained on day -7. During cycles 2-8, vital signs are obtained on day 1 of the cycle only. During maintenance, vital signs are obtained on day 1 of the cycle only.

[6] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom directed. During cycles 2-8 and maintenance, physical exam is obtained on day 1 of the cycle only. During loading, physical exam is only on day -7

[7] Full ophthalmological exam: required at screening and if clinically indicated (change in symptoms develop and especially if there is a baseline cataract or age related macular degeneration). Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, color vision test. Dilated fundoscopy and slit lamp exam

[8]Echocardiogram or MUGA is required at baseline, at the completion of induction, at discontinuation from the study and as clinically indicated. In addition, in patients who have received a cumulative anthracycline dose >350 mg/m2, an echocardiogram will be obtained after every 2 cycles of LD.

[9] Urine analysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated. This will be obtained on screening and as clinically indicated

[10] Hematology: hemoglobin, white blood cell (WBC) count, absolute neutrophil counts and platelets. During loading, a hematology sample is obtained on day -7. During cycles 2-8 and maintenance, hematology sample is obtained on day 1 of the cycle only.

[11] Serum Chemistry: Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, and Glucose, Calcium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, LDH, Total Protein, Albumin. During screening only, this will also include amylase, lipase, uric acid, TSH and creatine kinase. During loading, a chemistry sample is obtained on day -7. During cycles 2-8 and maintenance, chemistry sample is obtained on day 1 of the cycle only.

[12] Coagulation test include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT)

[13] A bone marrow aspirate and biopsy will be performed at baseline, on day-7 (at least 2 hours after selinexor administration) and at the end of treatment in case of progressive disease. The screening bone marrow will include standard cytogenetics, FISH and gene expression profiling by MyPRS. In addition, bone marrow biopsy and aspirate on screening and day-7 will be used for PD markers. Finally, CD138 positive cells from the screening bone marrow aspirate and the end of treatment bone marrow aspirate will be frozen in pellets for future molecular characterization by next generation sequencing. If a patient has <5% involvement plasma cells in the bone marrow in screening, a repeat bone marrow biopsy is not needed on day -7 (loading).

[14] Disease status will be measured by assessment of myeloma paraprotein and measurement of plasmacytomas (if applicable). Specifically patients will have a serum protein electrophoresis, 24h urine for protein electrophoresis and serum free light chain assay during screening, start of the loading phase, on day 1 of every cycle. In addition, patients will have a skeletal survey at baseline, and at progression. Finally, patients with

plasmacytomas should have measurement of their plasmacytomas at baseline, and every 2 cycles using a modality at the discretion of the treating physician.

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

[16] Selinexor will be administered in the clinic on day -7, cycle 1 days 1,8,15, cycle 2-8 days 1, and day 1 of maintenance cycles. Patients will self-dose with selinexor on other days. Dexamethasone will be taken at home by the patients with breakfast. Patients on cohort 3m and 4m will receive Selinexor in the clinic on day -7, cycle 1 day 1and 8 and cycle 2-8 and maintenance cycles day 1.

[17] LD will be administered intravenously in the clinic on day 1 of cycle 1-8.

[18] Blood for selinexor (PK) will be obtained on day -7, cycle 1 day 1, 8 and 15. Blood for free doxorubicin (PK) will be obtained on cycle 1 day 1, 8 and 15. Plasma and blood leukocytes for pharmacodynamics (XPO1 inhibition and select cytokine assays) will be obtained on day -7, Cycle 1 day 1 and 15, and Cycle 2 day 1. Please see Appendix C for detailed blood sampling plan.

[19] These assessments will not be collected in the electronic case report forms (eCRF) but continue to be performed for safety. Adverse events related to laboratory assessment or ECG will continue to be captured in the adverse event eCRF

6 TREATMENT PLAN

Please refer to the Study Calendar (Section 5) for an overview.

The investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study. All patients have to provide written Informed Consent 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.

Patients not meeting the eligibility criteria will not be enrolled into the study.

6.1 Study Assessments

6.1.1 Efficacy Assessments

The clinical activity of selinexor will be evaluated for its effects on disease response criteria in terms of best response, duration of response, progression-free survival (PFS) and overall survival (OS). Disease status will be measured by the uniform response assessment of the International Myeloma Working Group.

The baseline disease assessment must be recorded and measured within 28 days prior to treatment start. During the treatment period, disease assessments will be performed every cycle, and as clinically indicated.

6.1.2 Translational Analyses

We will evaluate the ex vivo efficacy of selinexor and doxorubicin in patient specimens. In addition, we will evaluate the impact of cellular localization of topo IIα at baseline and post treatment on the efficacy of the combination.

In addition, we plan to measure levels of XPO mRNA by qRT-PCR (as well as ARRDC3, NGFR, SLC family, PLCO) as well as levels of selected plasma cytokines after therapy with selinexor (IL1α, TNFα, IL-6, MCP1, INFγ, VEGFα, IL-8, IFNα, IL-10).

6.1.3 Safety Assessments

Throughout the treatment period until one month after the last dose of study medication, patients will be assessed for all adverse events. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be used for grading. If necessary, the patient may be withdrawn from the study treatment.

- **Medical history** will include baseline symptoms as well as a detailed history of prior cancer therapies including types and number of prior regimens, refractoriness to immunomodulatory agents and / or proteasome inhibitors, prior anthracycline and total cumulative dose, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.
- **Concomitant medications** will be documented throughout treatment phase until the EOT visit.
- **Adverse events** (see also Section 7.1): All patients will be closely monitored for adverse events during the course of the trial and for up to one month after the last dose of study medication.

6.1.4 Definition of a Dose Limiting Toxicity (DLT)

DLT is defined as any of the following occurring in the first cycle that is *not* due to cause other than drug toxicity (the loading phase dosing has already cleared DLT and found to be tolerable and will not be included in the DLT evaluation)

- ≥ 1 missed doses (out of 3 doses) in 21 days at the target dose due to study drug toxicity
- Discontinuation of a patient due to a toxicity that is not due to cause other than drug toxicity before completing cycle 1
- Grade ≥ 3 nausea/vomiting or diarrhea while taking optimal supportive medication
- Any other Grade ≥3 non-hematological toxicity except alopecia, steroid induced hyperglycemia or electrolyte abnormalities correctable with supportive therapy
- Grade ≥ 3 AST or ALT elevation lasting longer than 7 days
- Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm3] lasting ≥7 days
- Febrile neutropenia (ANC<1000/mm3 with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour);
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding

6.1.5 Laboratory Assessments

Safety blood samples include complete blood count, clinical chemistry, including liver function test, and coagulation.

6.2 Study Procedures

6.2.1 Screening Procedures

All patients will be screened and screening procedures performed within 28 days prior to the start of induction treatment. These include the following:

Signed written informed consent	Obtained prior to any study specific assessments
Demographics and medical history	• Age, gender, ethnic background, and race

	• Details on prior cancer therapy, including types and number of prior regimens, refractoriness to immunomodulatory agents and / or proteasome inhibitors, prior anthracycline and total cumulative dose, as well as discontinuations due to intolerability or any other serious illness. • Previous and concurrent relevant diseases • Current symptoms and/ or residual toxicities from prior therapies
Pregnancy test (if applicable) (within 1 week of loading phase)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years. In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation
Physical examination and vital signs (within 4 weeks of loading phase)	• Body height and weight • BSA • Blood pressure, pulse, temperature • Physical examination
Ophthalmologic exam (within 4 weeks of loading phase)	Full ophthalmologic exam: required at screening and when clinically indicated. Prior to dilation: best corrected visual acuity, visual field examination via automated perimetry, tonometry, color vision test. Dilated fundoscopy and slit lit exam.
Cardiac evaluation (within 4 weeks of loading phase)	12-lead ECG, echocardiogram or MUGA will be obtained at screening
Urine analysis (within 4 weeks of loading phase)	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology (CBC) (within 2 weeks of loading phase)	Hemoglobin, white blood cell (WBC) count, absolute neutrophil count and platelet count
Serum chemistry (within 2 weeks of loading phase)	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, amylase, lipase, creatinine kinase, LDH, TSH
Coagulation (within 2 weeks of loading phase)	Prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT)
Assessment of disease status (within 4 weeks of loading phase)	The disease status will be assessed by serum protein electrophoresis, 24h urine for protein electrophoresis and serum free light chain assay
Chest radiograph (within 4 weeks of loading phase)	Both, posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days prior to start of therapy.

Concomitant medication	Concomitant medication currently used
Bone Marrow Biopsy and Aspirate (within 4 weeks of loading phase)	A bone marrow aspiration and biopsy will be obtained at screening

6.2.2 Treatment Phase

During the treatment phase the following assessments are to be performed:

Physical examination and vital signs	• Body weight • BSA • Blood pressure, pulse, temperature • Physical examination (symptom directed)
Cardiac evaluation	12-lead ECG and echocardiogram as clinically indicated. Echocardiogram or MUGA is required at at the completion of induction. In addition, in patients who have received a cumulative anthacycline dose >350 mg/m2, an echocardiogram will be obtained after every 2 cycles of LD
Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years to exclude that a pregnancy occurred under treatment
Hematology	Hemoglobin, white blood cell (WBC) count, absolute neutrophil count and platelet count
Serum chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, LDH
Assessment of disease status	The disease status will be assessed by serum protein electrophoresis, 24h urine for protein electrophoresis and serum free light chain assay on day -14 and every cycle
Adverse events and concomitant medication	Assessed on an ongoing basis
Bone Marrow Biopsy and Aspirate	A bone marrow aspiration and biopsy will be obtained during the loading phase at least 2 hours after the administration of selinexor

6.2.3 End of Treatment

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug.

At the EOT visit, the patients will undergo the following assessments:

Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years to exclude that a pregnancy occurred under treatment
Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination
Cardiac evaluation	12-lead ECG, echocardiogram or MUGA
Hematology	Hemoglobin, white blood cell (WBC) count, absolute neutrophil count and platelet count
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, LDH
Assessment of disease status	The disease status will be assessed by serum protein electrophoresis, 24h urine for protein electrophoresis and serum free light chain assay
Adverse events and concomitant medication	Assessed on an ongoing basis
Bone Marrow biopsy and Aspirate	A bone marrow aspiration and biopsy will be obtained at the end of treatment and before the initiation of another therapy in patients with progressive disease

6.3 End of Study

6.3.1 Planned Treatment of the Patients after End of Treatment Phase

After completion of the study at routine follow-up (EOT), patients will generally be treated at the discretion of the investigator according to medical routine.

6.3.2 Removal of Patients from Treatment

Subjects 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 subjects should be avoided.

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

- Disease progression
- Non-compliance with visits and assessment which indicates a potential health hazard to the patient
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion

- Pregnancy
- Termination of the study by the sponsor

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT should be performed, if possible. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. 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 case report form.

6.4 Study Discontinuation

The whole 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

7 INVESTIGATIONAL MEDICINAL PRODUCT

7.1 Selinexor

7.1.1 Preparation and Administration of Selinexor

Product: Selinexor (KPT-330)

Classification: Cell biological modifier: Apoptosis inducing agent

Mechanism of action: Selinexor is a Selective Inhibitor of Nuclear Export / SINE™ compound that specifically blocks nuclear export by slowly-reversible covalent binding to XPO1 (also called CRM1) protein.

7.1.2 Formulation

Tablets for selinexor oral administration will be supplied in 20 mg tablets in wallet-sized blister packs (12 tablets per blister pack).

7.1.3 Labelling

Each wallet size blister package of selinexor tablets will be labelled in accordance with current ICH GCP, FDA and specific national requirements. Blister packages for take-home use will require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose).

7.1.4 Storage

Selinexor tablets will be stored at ambient or refrigerated temperatures between (36 – 86 °F) or (2–30 °C) in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

7.1.5 Drug Accountability

Study drug for the study are provided by the Karyopharm Therapeutics Inc. and will be labeled as per the applicable regulations. Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy.

Study drug accountability records will be maintained at the pharmacy and will be available for review.

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

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

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of unused material.
All clinical drug supplies must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm Therapeutics or designee for destruction. Drug supplies will be counted and reconciled at the site before being returned. The study site will be required to maintain a log of the temperature where the study medication is stored.

7.1.6 Selinexor Dosing Information

After the initial screening visit and registration in the study, patients will receive selinexor – at a dose of 80 mg on day -7. After the loading phase, patients will receive selinexor at a starting dose of 40 mg/m^2 on D1, 8, 15 for cohort 1.

Selinexor is to be taken within 30-minutes of solid food consumption together with ≥120 mL (8 ounces) of water.

7.2 Liposomal Doxorubicin

7.2.1 Preparation of Liposomal doxorubicin

Commercial supply of Liposomal doxorubicin will be used for this trial

Liposomal doxorubicin is available as 2 mg/ml concentrate solution for infusion in 25 ml and 10 ml vials.

The appropriate dose of liposomal doxorubicin up to a maximum of 90 mg must be diluted in 250 ml of 5% Dextrose Injection USP prior to administration. Doses exceeding 90 mg should be diluted in 500 ml of 5% dextrose injection USP prior to administration. Diluted liposomal doxorubicin should be refrigerated at 2°C to 8°C and administered within 24 hours. Liposomal doxorubicin should not be used with in line filters and should not be

mixed with other drugs. It should not be used with any other diluent other than Dextrose injection 5%. Partially used vials should be discarded.

Liposomal doxorubicin is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

7.2.2 Formulation and Administration of Liposomal doxorubicin

When administering Liposomal doxorubicin, precautions should be taken to avoid extravasation, which may occur with or without a stinging or burning sensation, even if blood returns well on aspiration of the infusion needle.

Liposomal doxorubicin must not be given by the intramuscular or subcutaneous route. Liposomal doxorubicin is not a clear solution but a translucent, red liposomal dispersion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Serious and sometimes life-threatening or fatal allergic/anaphylactoid like infusion reactions have occurred. Medications to treat such reactions, as well as emergency equipment should be available for immediate use. To minimize the risk of infusion-related reactions, the initial rate of administration is 1 mg/min. If no infusion related adverse events are observed, the rate of infusion can be increased to complete administration of the drug over one hour.

7.2.3 Storage of Liposomal doxorubicin

Liposomal doxorubicin is stored at 2°C-8°C and is not frozen

7.2.4 Dosing Information

During the induction phase, patients will receive liposomal doxorubicin at a starting dose of 20 mg/m2 on Day 1 of the cycle at least 2 hours (but less than 4 hours) after the administration of selinexor.

7.3 Dexamethasone

Commercial dexamethasone will be used for this trial. Dexamethasone is available in 4 mg tablets. Dexamethasone should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

7.3.1 Dosing Information

Patients will be instructed to take Dexamethasone 40 mg (10 tablets) orally once weekly with meals (ideally with breakfast to minimize insomnia). Patients 75 years or older and patients previously intolerant to 40 mg dosage will be allowed to receive 20 mg (5 tablets) once a week.

8 TOXICITIES, RISKS, AND AE-RELATED DOSE MODIFICATIONS

8.1 Selinexor

8.1.1 Selinexor Toxicity Overview

Selinexor is currently in clinical development and has not been FDA-approved for use. Human experience with selinexor is currently limited and the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with NCI CTCAE 4.03. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs grade >1 and SAEs will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

8.1.2 Risks Associated with Selinexor

As of June 2013, 96 human patients have been treated with selinexor. Across these trials, 9 patients of 97 (9.3%) have reported at least one SAE that is at least possibly related to study drug. Side effects observed in these patients include:

Very common side effects (≥10%):
Nausea
Vomiting
Diarrhea
Anorexia
Hyponatremia
Dehydration
Blurred vision
Thrombocytopenia
Anemia
Neutropenia
Leucopenia
Fatigue
Weight Loss
Dysgeusia
Dizziness

Common side effects (≥1-10%):
Constipation
Dry mouth
Creatinine Increased
Worsening of pre-existing cataracts
Febrile neutropenia
Dyspnea
Syncope
Confusion
Pneumonia

Sepsis

Uncommon side effects (>0.1-1%):
Cognitive disturbance
Altered balance

Rare side effects (>0.1-1%):
Acute cerebellar syndrome – symptoms can include a sudden loss of coordination, balance, or slurred speech

Reproductive risks

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study.

8.1.3 Dose Modifications for Selinexor

Based on observations from the ongoing Phase I studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from ~12mg/m² to 35mg/m². At the present time, we do not know how to predict which patient's tumors will respond to lower doses, nor can we predict tolerability. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, therapy is initiated at 80mg weekly. In patients with tolerability issues on selinexor, we recommend reducing the selinexor dose. In addition, if patient is experiencing one or more Grade ≤2 toxicities such as fatigue or anorexia, then 1-2 doses of selinexor can be held, and dosing resumed at current dose.

Toxicity will be graded according to NCI CTCAE, version 4.03; the therapy modifications described below are applied according to this severity grading. If drug-related toxicity requires a treatment delay of more than 4 weeks, then the patient is taken off protocol treatment. Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

Phase I data in patients with both solid and hematologic malignancies indicate that selinexor is associated with minimal laboratory abnormalities. Therefore, provided that it is clinically indicated, patients should be treated aggressively with supportive care to reduce

Table 1: Prespecified dose modifications for adverse events related to study drug

toxicities and permit selinexor dosing to be maintained at the same or reduced doses/frequency as indicated below.

Dose levels 1	60 mg D1,8, 15
Dose levels -1	40 mg D1,8,15
Dose levels -2	20 mg-D1,8,15

Dose levels 2	80 mg D1,8, 15
Dose levels 3	80 mg D1,3,8, 10

Intra-patient dose escalation for selinexor will be allowed at the discretion of the treating physician and principal investigator provided the above dose level was found to be tolerable (cleared DLT). This will apply to patients in the induction (after cycle 1) and maintenance phase only.

8.1.4 Dose Adjustment Guidelines for Selinexor-Related Toxicities

Table 2 Selinexor-related toxicity management guidelines

Toxicity and Intensity	Dose Modification
Fatigue (common)	
Grade 1	Ensure adequate caloric intake and assess volume status. Rule out other causes of fatigue such as pain, anemia, or adrenal insufficiency.
Grade 2	Ensure adequate caloric and fluid intake and assess volume status. If fatigue does not improve with conservative measures, consider dose reduction selinexor by one level.
Grade 3	Ensure adequate caloric and fluid intake and assess volume status. Interrupt selinexor dosing until resolved to Grade ≤2, reduce dose of selinexor by 1 level
Anorexia (common)	
Grade 1	Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®).
Grade 2	Add high-calorie supplements (e.g., Ensure®). Consider olanzapine 2.5 - 5mg po qhs (especially if nausea or sleep disturbance present). Consider megesterol acetate 400-800mg daily. Consider dronabinol (Marinol®). Skip intermittent doses of selinexor while supportive medications are instituted. If Grade 2 anorexia does not resolve after institution of supportive medications, reduce selinexor dose by 1 level.
Grade ≥ 3	Interrupt dosing with selinexor. Add high calorie supplements. Use supportive medications alone or in combinations. Restart selinexor at 1 dose level reduction once anorexia resolves to Grade ≤2. If Grade 2 anorexia persists with supportive medications, reduce dose of selinexor another dose level.
Nausea/Emesis (common)	
Grade 1	5-HT3 antagonists, D2 antagonists, olanzapine 5mg qhs or 2.5mg bid, NK1 antagonists, or dronabinol (Marinol) or combinations can prevent nausea in the majority of patients.
Grade 2	Implement one or more combinations of anti-nausea medications. If nausea does not

	resolve to Grade ≤1, reduce dose of selinexor by one dose level.
Grade 3	Implement one or more combinations of anti-nausea medications and interrupt dosing of selinexor. Selinexor may be restarted with one dose level reduction when nausea is Grade ≤2 and adequate caloric and fluid intake have been achieved.
Hematologic	
Neutropenia (rare)	
Grade 1 (ANC < LLN - 1500/mm3) Grade 2 (ANC < 1500 - 1000/mm3) Grade 3 (ANC < 1000 - 500/mm3)	Maintain dose level The use of growth factors during selinexor treatment is permitted during the phase II and after cycle 1 is completed in the phase I.
Grade 4 (ANC < 500/mm3)	Hold study treatment until ANC returns to >800/mm^3. Dose reduce LD (if appropriate) and consider growth factor support.
Febrile neutropenia, or fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x 10^9/L, fever ≥ 38.5°C)	Hold study treatment until patient has stabilized. Dose reduce LD (if appropriate) and consider a dose reduction in selinexor
Thrombocytopenia (Platelets) (uncommon)	
Grade 1 (PLT < LLN - 75,000/mm^3) Grade 2 (PLT < 75,000 – 50,000/mm3)	Maintain dose level.
Grade 3 (PLT < 50,000 -25,000/mm^3) without bleeding	Maintain dose level
Grade 4 (PLT < 25,000/mm^3) without bleeding	Delay study treatment until resolved to ≤ grade 3. Dose reduce LD (if appropriate) and / or selinexor Platelet transfusions may be given to support platelet levels in patients with clear clinical benefit from selinexor.
Grade ≥3 with bleeding	Delay study treatment until resolved to ≤ grade 2, reduce dose by 1 level when resolved.
Hyponatremia (common)	
Grade 1 (Lower Limit of Normal to 130nM)	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes.
Grade 3 (120-130nM)	Discontinue selinexor until resolved to grade ≤1 then consider reducing dose by 1 level

	especially if another cause is not identified. Check renal function, serum and urinary electrolytes, and rule out other causes.
Diarrhea (uncommon)	
Grade 1 (despite maximal anti-diarrheal medication)	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of selinexor.
Grade 2 (despite maximal anti-diarrheal medication)	Hold therapy. If diarrhea returns as ≥ Grade 2, then reduce selinexor dose by one dose level until resolved to ≤ grade 1
Grade 3/4 (despite maximal anti-diarrheal medication)	Delay selinexor until resolved to ≤ grade 2, then follow guidelines above.
Other adverse events	
Grade 1 or 2	Maintain dose level and initiate standard supportive care.
Grade 3	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level
Grade 4	Discontinue selinexor and rule out other causes. If other causes of Grade 4 adverse event are uncovered, selinexor may be re-initiated at 1 dose level reduction.
All dose modifications should be based on the worst preceding toxicity. Isolated values of ≥ grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of GGT, 5'NT, or other liver enzymes should be performed. ≥ Grade 3 anemia judged to be a hemolytic process secondary to study drug will require interruption of study treatment until resolved to ≤Grade 1. Selinexor may then be re-instituted at 2 levels below original dose. ≥ Grade 3 lymphopenia considered clinically significant will require dose interruption until resolved to ≤ grade 2, then reduce by 1 dose level. Patients are allowed dose reductions to a minimum dose of 5mg/m2. If a patient requires a dose interruption of > 28 days, then the patient must be discontinued from the study. Patients who discontinue the study for a study related adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals until resolution or stabilization of the event, whichever comes first. a. Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) otherwise specified values.	

- For all ≥ Grade 3 hematological or non-hematological AEs that are NOT selinexor related: After consultation with the principal investigator and at the discretion of the treating physician, selinexor dosing may be maintained provided that the patient can continue to take the agent by mouth, or via other enteral route.

8.2 Liposomal doxorubicin

8.2.1 Liposomal doxorubicin Toxicity Overview

liposomal doxorubicin is approved for the treatment of patients with multiple myeloma. The toxicity profile has been well described overall. Measures to ensure patients' safety, including the use of stringent inclusions and exclusion criteria, will be taken.

8.2.2 Risks Associated with Liposomal doxorubicin

The toxicity profile of Liposomal doxorubicin has been well established and includes the following common toxicities

- **Dermatologic:** Alopecia, Hand-foot syndrome (multiple myeloma, 19%), Rash (multiple myeloma, 22%)
- **Gastrointestinal:** Constipation (multiple myeloma, 31%), Diarrhea (multiple myeloma, 46%), Loss of appetite (multiple myeloma, 19%), Nausea (multiple myeloma, 48%), Stomatitis, Vomiting (multiple myeloma, 32%)
- **Neurologic:** Asthenia (multiple myeloma, 22%)
- **Other:** Fatigue (multiple myeloma, 36%), Fever (multiple myeloma, 31%)

Serious toxicities include the following:

- **Cardiovascular:** Cardiomyopathy, Heart failure (multiple myeloma, 3%)
- **Dermatologic:** Radiation recall syndrome
- **Hematologic:** Anemia (multiple myeloma, 25%), Myelosuppression, Neutropenia (multiple myeloma, 36%), Thrombocytopenia (multiple myeloma, 33%)
- **Hepatic:** Hyperbilirubinemia
- **Immunologic:** Anaphylactoid reaction, Infusion reaction

8.2.3 Dose Modifications for Liposomal doxorubicin

Prespecified dose modification for Liposomal doxorubicin (liposomal doxorubicin) guideline for Liposomal doxorubicin will be as shown below:

Dose Level 1: LD 20 mg/m2

Dose Level 2: LD 30 mg/m2

Dose Level -1: LD 15 mg/m2

Dose level -2: LD 10 mg/m2

A dose of Liposomal doxorubicin below 10 mg/m2 will not be planned

8.2.4 Dose Adjustment Guidelines for Liposomal doxorubicin

Table 3: Guideline for the management of Liposomal doxorubicin toxicities

Toxicity and Intensity	Dose Modification
Stomatitis	
Grade 1 (painless ulcers, erythema, or mild soreness)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and re-dose at the prior dose
Grade 2 (painful erythema, edema, or ulcers, but can eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, Liposomal doxorubicin should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose. If patient experienced previous Grade 3-4 toxicity, discontinue Liposomal doxorubicin
Grade 3 (painful erythema, edema, or ulcers, and cannot eat) Grade 4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease Liposomal doxorubicin dose by 1 dose level and return to original dose interval. If after 2 weeks there is no resolution, Liposomal doxorubicin should be discontinued.
Hand Food Syndrome HFS (Palmar Plantar Dysesthesias)	
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease DOXIL® dose by 1 dose level.
Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, Liposomal doxorubicin should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue treatment at previous dose and dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a decrease in 1 dose level
Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing) **Grade 4** (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease Liposomal doxorubicin by 1 dose level and return to original dose interval. If after 2 weeks there is no resolution, Liposomal doxorubicin should be discontinued.
Neutropenia	
Grade 1, 2, 3	Maintain dose level. Growth factor support is permitted during the phase II portion and the

	phase I after cycle 1.
Grade 4	Hold study treatment until ANC returns to >800/mm3. Reduce Liposomal doxorubicin by 1 dose level. Recommend growth factor support if not already implemented
Febrile Neutropenia	Hold study treatment until patient has stabilized. Dose reduce LD by 1 dose level and recommended growth factor support
Thrombocytopenia	
Grade 1,2,3 without bleeding	Maintain dose level
Grade 4 or grade 3 with clinical bleeding	Delay study treatment until resolved to thrombocytopenia is resolved to grade 3 or less and bleeding stopped. Reduce LD by 1 dose level. Platelet transfusion are allowed per routine clinical care
Serum Bilirubin (when not related to Gilbert's Syndrome)	
1.2 – 3.0 mg/dL	Reduce LD by 25%
> 3 mg/dL	Reduce LD by 50%
Cardiac Toxicities	
Arrhythmia ≥ grade 2	Hold Liposomal doxorubicin until resolved to ≤ grade 1. Decrease Liposomal doxorubicin by 1 dose level
Arrhythmia ≥ grade 3	Discontinue Liposomal doxorubicin. Patients may continue on selinexor if there is a clinical benefit in the opinion of the investigator
Congestive heart failure ≥ grade 2	Discontinue Liposomal doxorubicin. Patients may continue on selinexor if there is a clinical benefit in the opinion of the investigator
Asymptomatic decrease in ejection fraction by 20% or more	Discontinue Liposomal doxorubicin
Other non-hematologic Adverse Events	
Grade 1, 2	Maintain dose level and initiate standard supportive care
Grade 3	Delay dose until resolved to grade 1 or less, then reduce by 1 dose level
Grade 4	Discontinue Liposomal doxorubicin

8.3 Dexamethasone

8.3.1 Dexamethasone Toxicity Overview

The toxicity profile of dexamethasone has been well studied and this agent is commonly used for the treatment of patients with multiple myeloma

8.3.2 Risks Associated with Dexamethasone

Common toxicities include the following:

- **Cardiovascular:** Hypertension
- **Dermatologic:** Atrophic condition of skin, Impaired skin healing
- **Endocrine metabolic:** Cushing's syndrome, Decreased body growth
- **Immunologic:** increase risk of infections
- **Ophthalmic:** Cataract (5%), Raised intraocular pressure (25%)
- **Psychiatric:** Depression, Euphoria
- **Respiratory:** Pulmonary tuberculosis

Serious adverse events are as follows:

- **Cardiovascular:** Cardiomyopathy
- **Endocrine metabolic:** Hyperglycemia, Primary adrenocortical insufficiency
- **Gastrointestinal:** Pancreatitis
- **Musculoskeletal:** Osteoporosis
- **Ophthalmic:** Conjunctival hemorrhage (22%), Glaucoma

8.3.3 Dose Modifications for Dexamethasone

The following dose levels of dexamethasone will be considered

Dose level 1: 40 mg days 1, 8, 15

Dose level -1: 20 mg days 1, 8, 15

Dose level -2: 10 mg days 1, 8, 15

Dose level -3: 4 mg days 1, 8, 15

Note that patients previously intolerant to 40 mg of dexamethasone weekly and patients older than 75 years of age will be recommended to start on dose level -1.

8.3.4 Dose Adjustment Guidelines for Dexamethasone

Table 4: Guideline for the management of Dexamethasone toxicities

Toxicity and Intensity	Dose Modification
Dyspepsia, gastric or duodenal ulcer	
Grade 1 -2	All patients will receive proton pump inhibitor

	therapy as prophylactic therapy If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose levels
Grade 3	Hold dexamethasone until symptoms adequately controlled. Reduce by 2 dose levels along with concurrent therapy with proton pump inhibitors such as omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Pancreatitis	
Any grade	Discontinue dexamethasone and do not resume
Edema	
Grade 3 or higher	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures decrease dose by 2 dose levels from the initial dose; discontinue dexamethasone and do not resume if symptoms persist despite reduction.
Confusion or mood alteration	
Grade 2 or greater	Hold dexamethasone until symptoms resolve to ≤ grade1.Reduce dose by 2 dose levels from current dose. If symptoms persist despite above measures, discontinue dexamethasone
Muscle Weakness	
> Grade 2 (symptomatic and interfering with function or activities of daily living)	Decrease dexamethasone dose by 1 dose level; If weakness persists despite above measures decrease dose by 2 dose levels from the initial dose. Discontinue dexamethasone if symptoms persist despite reduction.
Hyperglycemia	
Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level decrements until levels are satisfactory
Other non-hematologic Adverse Events	
Grade 1, 2	Maintain dose level and initiate standard supportive care
Grade 3 / 4	Delay dose until resolved to grade 1 or less, then reduce by 1 dose level

9 SAFETY GUIDANCE FOR INVESTIGATORS

9.1 Concomitant Medication and Treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). Patients should minimize the use of products containing acetaminophen, which can interfere with the metabolism of selinexor. For combination painkillers containing acetaminophen it is recommended that single agent opiates (when clinically acceptable) be substituted.

All patients will receive prophylactic proton pump inhibitors. In addition, all patients will receive prophylactic treatment to prevent anorexia, fatigue and nausea which includes one of the following:

1- Olanzepine 5 mg PO qhs or 2.5 mg PO BID, 0-3 days before the first dosing day of selinexor
2- Mirtazapine 15 mg PO qhs, 0-3 days before the first dosing day of selinexor
3- Neurokinin 1 receptor blockers such as Aprepitant, phosaprepitant or similar

If an increased risk of adverse effects due to olanzepine is anticipated, olanzepine can be omitted. However it is recommended that mirtazapine or other appetite stimulating serotonergic agent be used. Additional standard supportive care agents may be used as needed (prn). Specifically, it is recommended (although not mandated, that patient receive antimicrobial prophylaxis given the increased risk of infections seen in patients with advanced myeloma. For example, fluoroquinolone prophylaxis could be considered. Supportive care may be tapered or discontinued in cycle 2 or later in patients who tolerate selinexor well.

9.1.1 Permitted Concomitant Medication

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

9.1.1.1 Prevention of pregnancy

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

9.1.1.2 Use of blood products

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

Appropriate anti-coagulation is allowed during the study (eg: LMW heparin, direct factor Xa inhibitors, etc). Warfarin is allowed during the study provided that 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, G-CSF or GM-CSF, growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

9.1.1.3 Glucocorticoid therapy

Patients must receive corticosteroid therapy as part of the treatment regimen. Additional corticosteroid are allowed for the treatment of non malignant conditions (inflammatory disorders or adrenal insufficiency) provided the dose does not exceed the equivalent of 20 mg of prednisone daily

9.1.1.4 Radiation Treatment

The need for radiation therapy is generally considered to be a treatment failure. However, an exception (that is patients allowed to remain in the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not by themselves fulfill a criterion for disease progression

9.1.1.5 Proton pump inhibitors

The use of proton pump inhibitors (for example omeprazole) will be required for the prevention of dexamethasone toxicity as is clinical practice

9.1.1.6 Bisphosphonate

The use of bisphosphonate for the prevention of skeletal related events due to myeloma is allowed per routine clinical care.

9.1.1.7 IVIG

The use of intravenous immunoglobulins for the prevention of recurrent infections in patients with hypogammaglobulinemia is allowed per routine clinical practice

9.1.2 Prohibited Medication

Patients should minimize the use of products containing acetaminophen. For combination painkillers containing acetaminophen it is recommended that single agent opiates (when clinically acceptable) be substituted, particularly on the days of selinexor dosing.

Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids as specified herein, is not allowed.

Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

Other investigational agents should not be used during the study.

Inactivation of selinexor by glutathione conjugation is a significant metabolic pathway in vitro and in vivo, including in humans. This process can be mediated in the absence of

proteins, indicating that it is thermodynamically favorable. In vitro studies using human liver microsomes confirm in vivo findings that selinexor undergoes minimal CYP450 metabolism. Therefore, administration of selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen and ethyl alcohol. It should be noted that studies of selinexor in combination with acetaminophen are to begin in late 2013 and therefore that these recommendations are empirical. It should also be noted that recreational ethanol ingestion is associated with glutathione depletion; therefore, the use of products containing ethanol should be minimized or avoided on selinexor dosing days.

9.2 Supportive Care Guidelines

Supportive measures for optimal medical care shall be provided during participation in this clinical trial. Supportive care including anti-nausea / anti-emetic therapy, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. As needed and per individual study site institutional guidelines, prophylactic therapies, including antivirals, antifungals, and antibiotics, may be administered to ameliorate risks associated with non-malignant disorders or of immune system compromise.

9.2.1 Anorexia

Based on clinical observations with over 90 patients treated with selinexor across this and the companion protocol in advanced hematologic tumor patients (OZM-040), the dose limiting toxicities (DLTs) are primarily related to anorexia with poor caloric and fluid intake leading to weight loss, fatigue and nausea. Therefore, it is strongly recommended that patients at risk for anorexia, weight loss, and/or fatigue receive strong nutritional counseling, high caloric beverages with adequate electrolyte levels (e.g., Ensure®), prophylaxis with appetite-stimulating agent(s), and anti-emetic agents. Patients with proper nutritional support and counseling have remained on selinexor for >11 months. There is no correlation between initial BMI or weight and the development of anorexia.

In patients with problematic food/liquid/caloric intake, a patient log of food and drink should be considered and monitored by the treatment team.

Fresh juices, simple carbohydrates, as well as ginger can improve appetite before the meal; ginger may also improve dysgeusia.

Supportive care for anorexia should be given promptly. The site can consider prophylactic treatment in case of cachexia or previous anorexia associated with anti-cancer therapies. Active treatment of anorexia should start with the first sign of decreasing appetite or loss of weight. Standard appetite stimulants are allowed and strongly recommended. In particular, megesterol acetate (Megace®), olanzapine and glucocorticoids, have been most useful in improving appetite in many patients treated with selinexor .

The recommended dose of megesterol acetate is 400mg – 800mg po/d. Lower doses have also been effective. Olanzapine may be given as 5.0mg po qhs (also improves sleep and reduces nausea); divided doses of olanzapine (e.g., 2.5mg po qam and qpm) may also be used but can increase sedation. Combination of megesterol acetate at 400mg qd + olanzepine 5.0mg qhs has been reported to be synergistic and most effective in a recent meta-analysis.

In cases of anorexia grade ≥ 3, combination treatment with daily megesterol acetate 400mg + olanzepine 5.0mg is strongly recommended for long-term use.

Dronabinol (Marinol) has shown some activity in both nausea/emesis and anorexia in patients treated with elinexor . In patients who do not respond to, or are intolerant of, the above agents, oxandrolone (Anavar®) should be considered. The recommended dose of oxandrolone is 2.5-10mg given 2-4 times per day to maximum dose of 20mg per day.

If constipation occurs, then laxatives should be given as constipation can contribute to anorexia and loss of appetite.

9.2.2 Fatigue

Fatigue may be related to underlying malignancy, selinexor side effects, side effects of other agents or concurrent morbidities. Fatigue may also be related to anorexia and/or dehydration, so caloric and fluid intake should be optimized in all patients (please see above aggressive guidelines for maintenance of food and fluid intake).

Glucocorticoids use may reduce fatigue. In patients with persistent fatigue, oxandrolone as described above should be considered. Dose interruptions and/or reductions may also improve fatigue due to selinexor, but may lead to loss of disease control.

9.2.3 Emesis

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

9.2.3.1 Acute Emesis

Acute emesis is not a major observation with selinexor but has been reported. Selinexor associated nausea/emesis generally responds to D2-antagonists, 5-HT3 antagonists, or combinations of agents.

5-HT3 receptor antagonists (Zofran® 8 mg od on days of dosing) — First-generation 5-HT3 receptor antagonists all appear equally effective at preventing nausea/emesis at the recommended doses. A single dose of a 5-HT3 receptor antagonist prior to therapy is equivalent to a multiple dose schedule. The efficacy of 5-HT3 receptor antagonists is significantly improved when they are combined with glucocorticoids. If first-generation 5-HT3 receptor antagonists+dexamethasone do not adequately control emesis, second generation 5-HT3 receptor antagonists (e.g., palonosetron) should be considered. Second generation 5-HT3 receptor antagonists also improve delayed nausea/emetic response.

Neurokinin-1 receptor antagonists (e.g., aprepitant or fosaprepitant, Emend®) – should be considered in case of uncontrolled emesis with standard treatments as described above. Neurokinin-1 receptor antagonists should be given with combination of dexamethasone and first or second generation 5-HT3 receptor antagonists.

Additional treatment: Metoclopramide Hydrochloride 10mg, 30 min before meal (up to 4 time a day) or prochlorperazine (standard doses) have been effective in many patients. Dronabinol (Marinol) has shown some activity in both nausea/emesis and anorexia in patients treated with selinexor . Lorazapeam can be added to the combination treatment of

5-HT3 receptor antagonists +dexamethasone, e.g., at night, but has been less effective in elinexor associated nausea/emesis.

9.2.3.2 Delayed Emesis - > 24h after treatment.

Management — selinexor is infrequently associated with delayed, resistant emesis. Many of the regimens associated with delayed emesis are classified as high-emetic risk, and professional guidelines recommend the use of an NK1 receptor antagonist (either NK-1 blockers e.g., aprepitant on days 1 to 3 or fosaprepitant on day 1 only), plus a glucocorticoids on days 1 to 4, along with a 5-HT3 receptor antagonist (particularly second generation agents) on day 1. This regimen is effective against both acute and delayed emesis. The data supporting the individual components of this regimen are reviewed below.

Olanzapine — Conventional antiemetics are more successful at preventing emesis than in preventing nausea, particularly delayed nausea. Olanzapine 10 mg once daily (typically given at night to mitigate sedative effects) was proven effective in both anti emesis and nausea control. It may also be useful for management of breakthrough emesis, and to improve food intake in patients with anorexia.

Granisetron transdermal patch — A transdermal preparation of granisetron should be consider in patients that have uncontrolled emesis/nausea >grade 2 under best supportive treatment

Ginger — Supplemental ginger added to foods or at doses of 0.5, 1.0gm powder daily total dose, usually in divided doses. Ginger may also improve dysgeusia.

Additional agents can be added, including lorazepam or alprazolam, olanzapine, a dopaminergic D2-antagonist (e.g., prochlorperazine, thiethylperazine, haloperidol), or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist.

9.2.4 Diarrhea

Diarrhea is common at up to 32% (mostly Grade 1), which responds to standard anti-diarrheal agents. Fluid replacement is important to prevent dehydration, fatigue and electrolyte abnormalities (*e.g.*, hyponatremia).

9.2.5 Thrombocytopenia

The etiology of thrombocytopenia in patients treated with Selinexor is unclear. Selinexor did not cause thrombocytopenia in preclinical toxicology studies (i.e., in animals without prior anticancer therapies), and closely related SINE compounds (i.e., KPT-335) has not caused thrombocytopenia in dogs with newly diagnosed or first relapsed Non-Hodgkin's Lymphoma.

Grade ≥3 thrombocytopenia can be treated with growth factors romiplostim (N-plate®), eltrombopag (Promacta®), rIL-11 (Neumega®) may be used throughout the study.

Dose reduction should then be considered.

9.2.6 Hyponatremia

Hyponatremia (Grade 3) has been reported in 8 patients out of 50 as of May 31, 2013; one of these cases was pseudohyponatremia due to hyperglycemia (not associated with selinexor). None of these cases have been symptomatic. Most of the patients had anorexia, nausea, vomiting and/or diarrhea. Two of the patients with Grade 3 hyponatremia have third-space fluid accumulation or resolution (e.g., ascites, edema). Adequate fluid and

caloric intake, including electrolyte rich beverages rather than free water, has lead to reversal of the hyponatremia.

9.2.7 Liver Enzyme Increase

Liver toxicities in rodents and monkeys were not observed in the GLP toxicology studies. To date, significant liver toxicity has not been reported in patients treated with selinexor. Patients should minimize their use of alcohol and acetaminophen as these drugs may deplete hepatic glutathione which could alter selinexor metabolism. Glutathione (GSH) replacing agents such as N-acetylcysteine or S-adenosylmethionine may be considered if selinexor induced liver dysfunction is suspected.

10 CORRELATIVE STUDIES AND PHARMACOKINETICS

10.1 Exploratory Correlative Studies (See Correlative Flowchart below)

Bone Marrow Aspirates Summary: Bone Marrow aspirates will be collected from patients at the time of screening and at relapse. Mononuclear cells isolated from patient aspirates will be assayed for drug sensitivity (EC50). A portion of these aspirates will be aliquoted, CD138 selected and stored for subsequent molecular characterization by next generation sequencing. A portion of the lymphocyte fraction will be incubated overnight in the presence of selinexor (100nm & 300nM) and cytospin slides made to assay the intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, p53, XPO1, IkBα, histone control, and possibly other biomarkers of relevance with and without treatment with selinexor.

Myeloma Patient Bone Marrow Biopsy Microarrays Summary: The bone marrow biopsies collected at screening, day-7 and at relapse will be used to construct a tumor microarray for biomarker analysis. Plasma cells in tumor microarrays will be identified by lambda or kappa light-chain staining and examined for the expression and intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, p53, XPO1, IkBα, histone control, and possibly other biomarkers of relevance before and after *in vivo* treatment with selinexor.

Myeloma Patient Bone Marrow Aspirates at Screening: Patient bone marrow aspirates collected during screening will be used to evaluate the predictive value of baseline *ex vivo* sensitivity with selinexor +/- doxorubicin and if adequate sample is available selinexor +/- dexamethasone and KPT-8602 +/- dexamethasone. The lymphocyte fraction of patient bone marrow aspirates will be isolated by ficoll-gradient centrifugation and incubated overnight in the presence of selinexor (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- doxorubicin (2 μM), and if adequate sample available selinexor (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- dexamethasone and (10 μM). KPT-8602 (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- dexamethasone (10 μM). *Ex vivo* sensitivity will be assayed in CD-138/light chain double positive myeloma cells by flow cytometry and activated caspase 3 apoptosis assay for EC50 analysis. Assay order of importance based on cell numbers will be selinexor, selinexor+dexamethasone, selinexor+doxorubicin, KPT-8602 and KPT-8602+dexamethasone.

A portion of the lymphocyte fraction will be incubated overnight in the presence of selinexor (100nm & 300nM) and cytospin slides made to assay the intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, p53, XPO1, IkBα, histone control, and possibly other biomarkers of relevance with and without treatment with selinexor. The

intracellular location of topoisomerase IIα, p53, XPO1, IkBα and histone control seen in plasma cells from the aspirates will be compared to that seen in the biopsy tissue arrays.

Cells from the lymphocyte fraction of the bone marrow aspirate will be isolated using CD-138 magnetic bead selection. DNA from CD-138 positive myeloma cells will be isolated and interrogated for specific mutations by whole genomic DNA sequencing. In addition, gene expression of RNA isolated from CD-138 positive myeloma cells will be assayed by microarray analysis.

Myeloma Patient Bone Marrow biopsy at day-7: Bone marrow biopsies collected day-7 will be used to construct a tumor microarray for biomarker analysis. Plasma cells in tumor microarrays will be identified by lambda or kappa light-chain staining and examined for the expression and intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, p53, XPO1, IkBα, histone control, and possibly other biomarkers of relevance.

Myeloma Patient Bone Marrow Aspirates at Relapse: Patient bone marrow aspirates collected at relapse will be used to evaluate the predictive value of baseline *ex vivo* sensitivity with selinexor +/- doxorubicin and if adequate sample is available selinexor +/- dexamethasone and KPT-8602 +/- dexamethasone. The lymphocyte fraction of patient bone marrow aspirates will be isolated by ficoll-gradient centrifugation and incubated overnight in the presence of selinexor (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- doxorubicin (2 μM), and if adequate sample available selinexor (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- dexamethasone and (10 μM). KPT-8602 (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- dexamethasone (10 μM). *Ex vivo* sensitivity will be assayed in CD-138/light chain double positive myeloma cells by flow cytometry and activated caspase 3 apoptosis assay for EC50 analysis. Assay order of importance based on cell numbers will be selinexor, selinexor+dexamethasone, selinexor+doxorubicin, KPT-8602 and KPT-8602+dexamethasone.

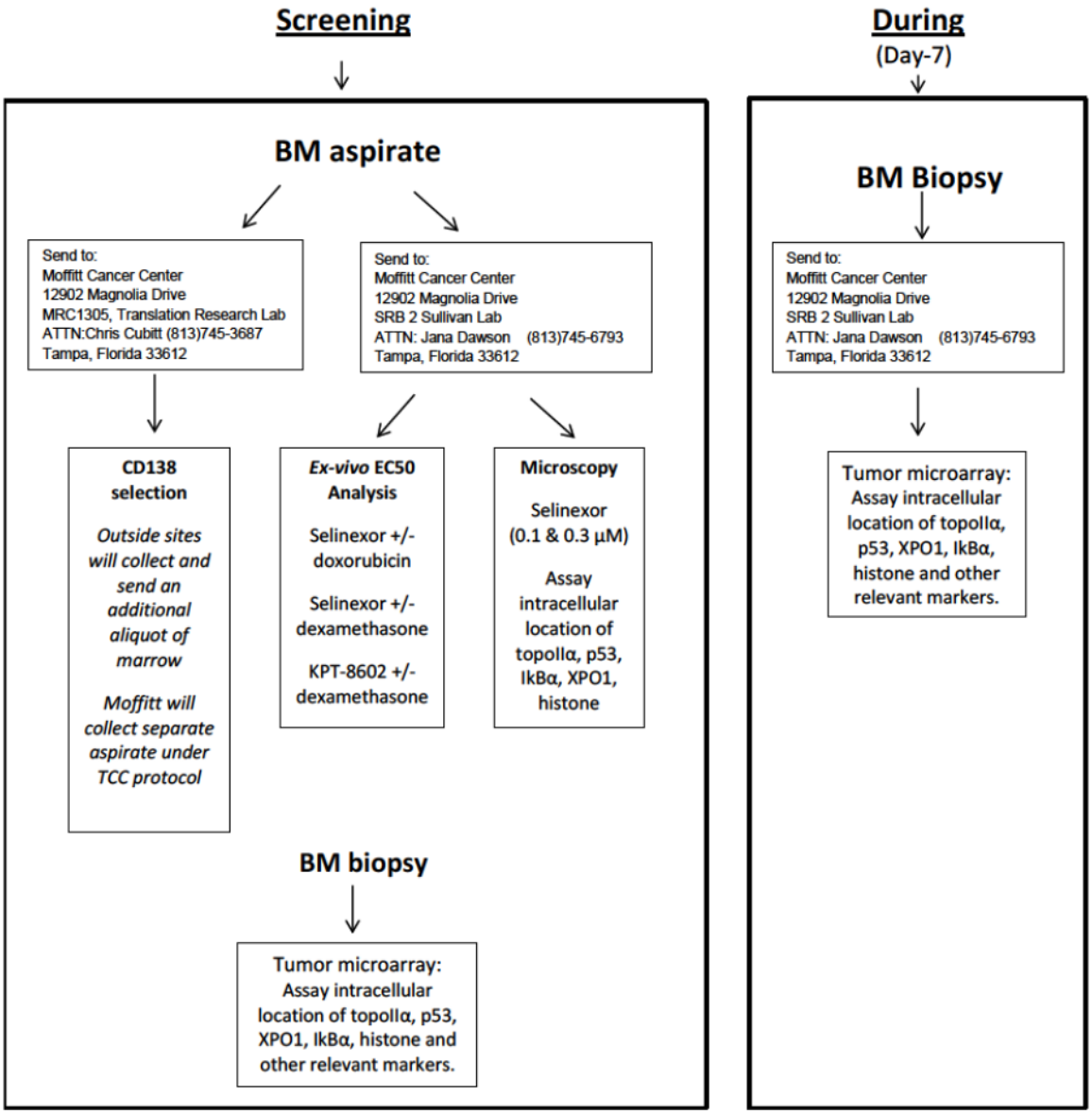
A portion of the lymphocyte fraction will be incubated overnight in the presence of selinexor (100nm & 300nM) and cytospin slides made to assay the intracellular location (nucleus versus cytoplasm) of topoisomerase IIα, p53, XPO1, IkBα, histone control, and possibly other biomarkers of relevance with and without treatment with selinexor. The intracellular location of topoisomerase IIα, p53, XPO1, IkBα and histone control seen in plasma cells from the aspirates will be compared to that seen in the biopsy tissue arrays.

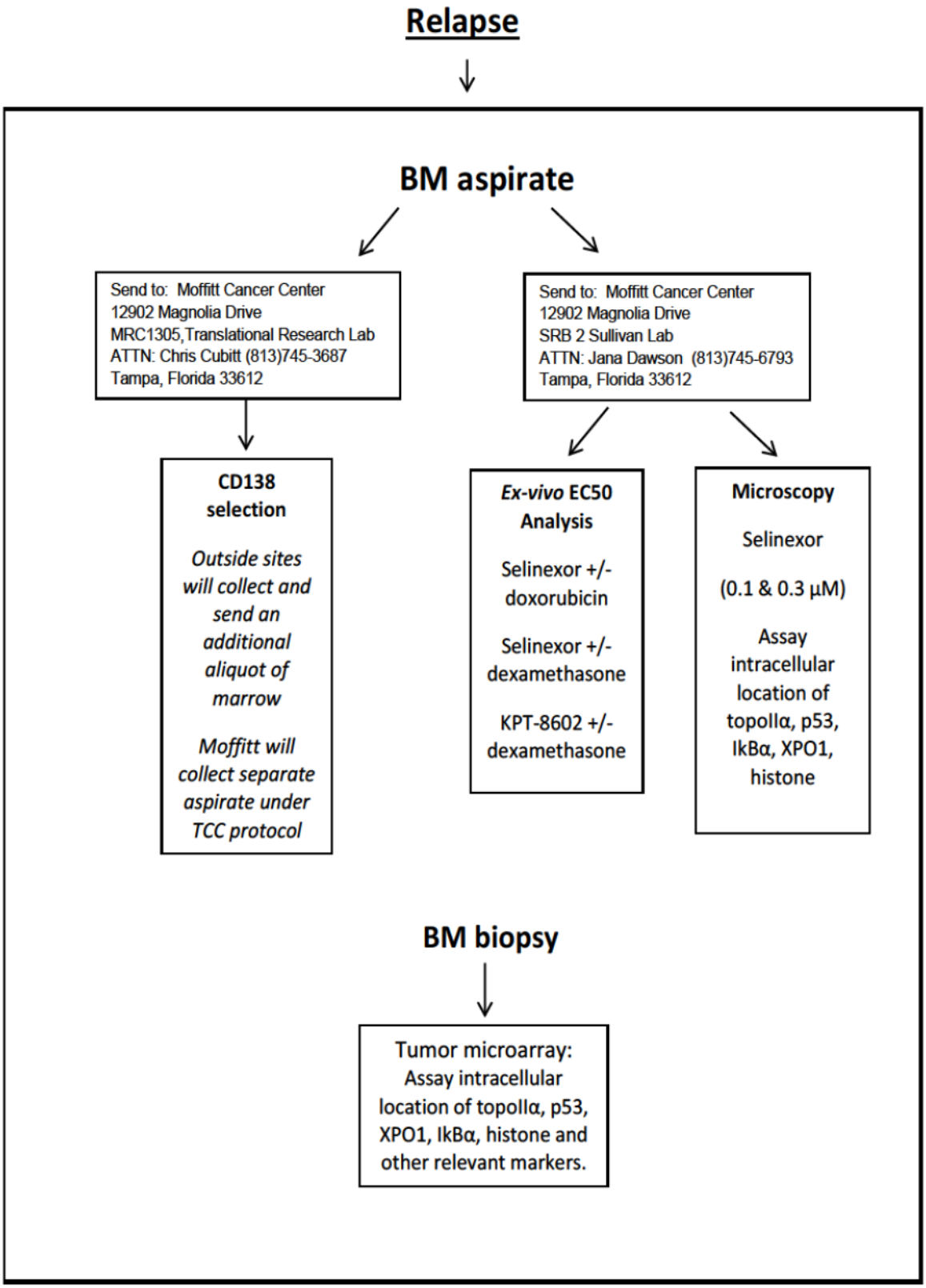
Cells from the lymphocyte fraction of the bone marrow aspirate will be isolated using CD-138 magnetic bead selection. DNA from CD-138 positive myeloma cells will be isolated and interrogated for specific mutations by whole genomic DNA sequencing. In addition, gene expression of RNA isolated from CD-138 positive myeloma cells will be assayed by microarray analysis.

LD

Plasma and blood leukocytes will be obtained from patients during the loading phase on day -7 (pre dose, post dose 4 hours and if possible 8 hours), Cycle 1 Day 1 (pre dose, post dose 4 hours and 8 hours), Cycle 1 Day 8 (pre dose, post dose 4 hours), Cycle 1 Day 15 (pre dose, and post dose 4 hours), and Cycle 2 Day 1 (pre dose, and post dose 4 hours) and XPO1 inhibition (by qRT-PCR for XPO1) and levels of key cytokines will be assessed as a potential biomarker for response in an exploratory analysis (see appendix C for schedule of sample collection). These assays will be done at Karyopharm.

Correlative Flowchart




Relapse
BM aspirate
Send to: Moffitt Cancer Center
12902 Magnolia Drive
MRC1305,Translational Research Lab
ATTN: Chris Cubitt (813)745-3687
Tampa, Florida 33612
Send to: Moffitt Cancer Center
12902 Magnolia Drive
SRB 2 Sullivan Lab
ATTN: Jana Dawson (813)745-6793
Tampa, Florida 33612
CD138 selection
Outside sites will collect and send an additional aliquot of marrow
Moffitt will collect separate aspirate under TCC protocol
Ex-vivo EC50 Analysis
Selinexor +/- doxorubicin
Selinexor +/- dexamethasone
KPT-8602 +/- dexamethasone
Microscopy
Selinexor
(0.1 & 0.3 µM)
Assay intracellular location of topoIIα, p53, IkBα, XPO1, histone
BM biopsy
Tumor microarray: Assay intracellular location of topoIIα, p53, XPO1, IkBα, histone and other relevant markers.

10.2 Limited Pharmacokinetic Studies

Patients enrolled on the phase I and phase II parts of this study will also have peripheral blood collected for limited PK analyses of selinexor and LD. See appendix C for schedule of sample collection. We will correlate blood levels of selinexor and LD with the expression and intracellular location of the proteins described above.

11 STATISTICAL CONSIDERATIONS

11.1 Endpoints

11.1.1 Primary Endpoint

Phase 1: determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combination of selinexor, Liposomal doxorubicin, and dexamethasone in patients with relapsed and refractory multiple myeloma

Phase 2: determine the overall response rate per the modified uniform response criteria of the international myeloma working group (partial response and better)

11.1.2 Secondary Endpoints

- Clinical benefit rate (minimal response and better)
- Progression free survival
- Duration of response
- Overall survival
- Safety – NCI CTC version 4.03.

11.2 Sample Size Justification

A standard 3+3 design will apply in the phase I part of the trial. Given 4 dose levels are planned, the number of patients enrolled would be between 12 and 24 patients.

For the phase II study, a single-arm Simon Two stage design will be used[48].

Thirteen eligible patients will be enrolled in the first stage (including the 6 patients from the phase I treated at the RP2D). If 3 or more partial responses are noted, another 16 patients will be enrolled. If 8 or more patients achieve a partial response or better, the combination is deemed active. Under this two-stage optimum design, there would be a 90.7% chance of detecting a tumor response rate of at least 40% and a response rate of 15% or less would lead to the conclusion that the regimen lacks antitumor activity at a 0.05 significance level. The probability of early stopping (in stage I) is 0.058 if the true response rate of the combination is 40%.

11.3 Study Population Definition

For both Phase I (MTD) and Phase II (Open Label Treatment):

- Safety Population – all patients who take at least one dose of study medication.

For the determination of the MTD, if a patient does not complete 1 cycle of therapy for reasons other than toxicity and without having a DLT, he/she will be replaced as they would not be evaluable for the determination of the MTD.

For Phase II:

The Intent-to-Treat (ITT) population will be used for all analyses and is defined as all patients eligible for therapy. ITT patients who have inadequate data post-baseline to assess efficacy according to the criteria for response will be considered treatment failures for analysis.

In order to determine if any bias results from including untreated patients or patients lost to follow-up in the primary ITT analysis, an additional analysis will be conducted on patients who are protocol-compliant (per protocol population (PPP)). Patents with major protocol violations will be excluded from this population. Patients who have inadequate post baseline data will be excluded from this analysis

11.4 Study Design

The phase I portion of the trial will be a standard "3+3" design. The details of this design are listed as follows.

Number of patients with DLT	Escalation Decision Rules
0/3	Enter 3 patients at the next higher dose level.
≥2	Dose will be de-escalated to the prior lower dose level. Three additional patients will be enrolled to that lower dose cohort unless 6 patients had been treated at that lower dose. If ≤1 of 6 patients experience DLT, then this lower dose will be declared the MTD.
1/3	Enter 3 more patients at this dose level. If 0 of 3 patients experience DLT, proceed to the next higher dose level. If ≥1 patient suffers DLT, then dose will be de-escalated to the previous lower level. Three additional patients will be enrolled to that lower dose cohort unless 6 patients had been treated at that lower dose. If ≤1 of 6 patients experience DLT, this lower dose level will be declared the MTD.
≤1 out of 6 at highest dose level	This is the MTD/recommended phase II dose. At least 6 patients must be entered at the MTD/recommended phase II dose.

Four dose level escalations of oral selinexor / LD are planned. The number of patients needed for the determination of the MTD can thus vary from 6 to 24 patients. For Phase 1 MTD Portion, dose limiting toxicities (DLTs) will be summarized at the conclusion of each dose level, and reviewed by the investigators and the Protocol Monitoring Committee and

the decision to proceed to the next dose level will be made accordingly. The MTD is defined as the highest dose that causes one or less patients out of 6 to have a DLT.

The phase II portion is a single-arm Simon optimum two stage design.

11.5 Analysis of the Phase I

For the phase I, the primary objective is to determine the maximum tolerated dose of selinexor in combination with liposomal doxorubicin and dexamethasone. Patients' demographic and clinical characteristics will be summarized using descriptive statistics. All toxicities and DLTs will be listed for each patient and summarized for each dose level.

11.6 Analysis of the Phase II

For the primary endpoint in Phase II trial, we are interested in comparing the overall response rate of this combination with historical efficacy data using liposomal doxorubicin and dexamethasone in patients with relapsed and refractory myeloma. The overall response rate and its 95% confidence will be calculated using the method proposed by Atkinson and Brown[49]. This confidence interval takes into account the nature of the two-stage Simon design.

The secondary endpoints include progression-free survival (PFS), overall survival (OS), safety, and duration of response. Patients will be followed for survival and progression until termination of the study. PFS is defined as the time from start of treatment to death of any cause, disease progression, or the date of last follow-up, whichever comes first. OS is defined as the time from start of treatment to death of any cause or the date of last follow-up, whichever comes first. The time-to-event data will be estimated using the Kaplan-Meier method. The median of PFS and OS and 95% confidence intervals will be computed. The effect on time-to-event data adjusting for other factors (such as age and tumor stage) will be analyzed using the Cox proportional hazards regression models.

As the exploratory endpoints, the association between the change of each biomarker (e.g., nucleus to cytoplasm ratio, p53, CRM1, lκB and NFκB) from screening to day 1 of cycle 1 and the response to the therapy will be examined by the Satterthwaite t-test or the Wilcoxon rank sum test. The appropriate transformation such as log-transformation may be considered if necessary. In addition, we will examine if the disease progression is associated with the change from screening to date of progression or from day 1 of cycle 1 to date of progression. No multiplicity adjustment is planned due to the nature of exploratory study. A two-sided p-value of < 0.05 will be considered significant. We expect that 12 or more of 29 patients in Phase II are responders. With a two-sided significance level of 5%, 29 samples will provide 80.4% power to detect an effect size (mean difference divided by standard deviation) of 1.2 when the numbers of responders and non-responders are 12 and 17, respectively.

The safety analyses will be performed using data from all subjects who receive any study drug. The severity of the toxicities will be graded according to the NCI CTCAE v 4.0 whenever possible. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE v 4.0 Grade 3 or higher, study-drug-related events, and serious adverse events will be listed separately. Cross tabulations will be provided to summarize frequencies of abnormalities.

12 REGULATORY CONSIDERATIONS

12.1 Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

12.2 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study must be maintained in the Investigator's study files.

12.3 Subject Confidentiality

In compliance with United States federal regulations, Karyopharm requires the Investigator to permit its representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.
Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.4 Study Record Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in

the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

12.5 Premature Discontinuation of the Study

The responsible local clinical Investigator as well as Karyopharm has the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 Adverse Events

(All serious adverse events (SAE) must be reported to Karyopharm within 24 hours of the investigational staff's knowledge; this includes any event that occurs during the participation of the trial regardless of associated therapy, severity or relationship)

Adverse events which occur during screening and before the initiation of the treatment phase of the trial will not be captured / reported as they are not related to treatment.

13.2 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Suspected positive pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. 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 inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important. Severe Adverse Events which occur during screening and before the start of study therapy will not be collected and reported.

13.3 Adverse Drug Reporting

Toxicity will be scored using CTCAE Version 4.03 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. Note that only adverse events that are greater than grade 1 will be captured in the case report forms and reported.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in ONCORE, the electronic data capture system. The SAE must be reported by email (affiliate.research@Moffitt.org) to the MCRN within 2 working days.

13.4 Karyopharm Drug Safety Contact information

[redacted]

13.5 Investigator Reporting Responsibilities

13.5.1 Reporting to FDA

The conduct of the study will comply with all FDA safety reporting requirements.
IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report

Serious adverse events will be forwarded to FDA by the Sponsor-Investigator according to 21 CFR 312.32.

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

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present.

Adverse drug reactions that are Serious, Unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator/physician shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

Participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Karyopharm Therapeutics and H. Lee Moffitt Cancer center, and H. Lee Moffitt Cancer center will be responsible for reporting to FDA.

13.5.2 Reporting to karyopharm

In addition to reporting to the FDA, Sponsor-Investigator will forward completed SAE and pregnancy forms to representatives of karyopharm. Forms will be completed and emailed to [redacted]

Address and Phone Number of person/sponsor responsible for SAE management

[redacted]

IN ADDITION, scanned form must be emailed to the following recipients:

[redacted]

The Sponsor / investigator is responsible for providing 6-month Adverse Reaction Reports (all AEs assessed as causality related to Karyopharm investigational product) to Karyopharm [redacted] throughout the duration of the study. These reports are to contain listings of non-serious (expected or unexpected) adverse reactions and serious or non-serious expected adverse reactions which were collected during the 6-month report cycle

The Sponsor is responsible for obtaining any additional follow-up information regarding safety reports, upon request from Karyopharm.

Karyopharm will inform the Sponsor regarding any SUSAR detected in other clinical studies, ISTs, or Compassionate Use as promptly as possible upon becoming aware of same

13.5.3 Reporting to the IRB

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy. The following SAE are reported to the IRB: Unexpected, related events which increase the risk of harm to subjects.

13.6 Adverse Events Updates / IND Safety Reports

Karyopharm Therapeutics shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

14 DATA MANAGEMENT

14.1 Data Collection

The Clinical Research Coordinators and Investigators of each site will be responsible for the recording of the site's data into the electronic data capture system, ONCORE.

To obtain access to Oncore, the site research staff must complete an Oncore Access Request Form and a Moffitt Information Systems Confidentiality Agreement (provided in the MCRN Handbook at the site initiation visit) and submit both to the Coordinating Center. Once the completed forms are received, the site coordinator will receive VPN access, logon/password, and information on how to access Oncore using the VPN. The MCRN Coordinating Center will provide Oncore training to the site once initial access is granted and on an ongoing basis, as needed.

14.2 Protocol Monitoring Committee

The Protocol monitoring committee (PMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a

risk/benefit analysis in this subject population. The purpose of the PMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The PMC may request additional meetings or safety reports as deemed necessary upon discussion with the principal investigator. The PMC may stop the study following review of results from each interim analysis.

14.3 Study Monitoring and Auditing

14.3.1 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The principal investigator is responsible for every aspect of the design, conduct and actions of all members of the research team as well as final analysis of the protocol.

Investigators, or a designated member, must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Karyopharm Therapeutics or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.
The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Karyopharm Therapeutics representative so that the accuracy and completeness may be checked.

14.3.2 Site Responsibilities

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center.

Sites must provide a copy of their informed consent to the MCRN coordinating center for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the MCRN staff for review and approval prior to resubmission to the IRB.

The MCRN Coordinating Center must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Authority Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)

7. Updated Investigator/Personnel documents (CVs, licenses, Conflict of Interest statements, etc.) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed
9. Signed protocol specific Task Order

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and MCRN research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The MCRN utilizes the EDC system, Oncore. Oncore training will be scheduled, if indicated, with the appropriate staff from the site.

A conference call/study meeting will be held weekly for the phase I and monthly for the phase II to review patient enrollment and accrual, safety and toxicity data, and treatment results, as available.

14.3.3 Monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with currently approved protocol / amendments, good clinical practice (GCP) and applicable regulatory requirements. Monitoring at external sites will be per Moffitt policy.

15 PROTOCOL AMENDMENTS OR DEVIATIONS

15.1 Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed and approved by Karyopharm Therapeutics. Amendments should only be submitted to IRB/EC after consideration of Karyopharm Therapeutics review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

15.2 Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

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APPENDIX A: Response Criteria

Response Category	Response Criteria[a]
Stringent CR (sCR)	CR as defined below plus 1. Normal free light chain (FLC) ration and 2. Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
Complete Remission (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
Very Good Partial Remission (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
Partial Remission (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal Remission (MR)	25-49% reduction in serum paraprotein and a 50-89% reduction in urine light chain excretion. A 25-49% reduction in the size of soft tissue plasmacytoma must be demonstrated is applicable
Stable Disease (SD) [e]	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)[f]	**Requires only one of the following**: Increase of ≥ 25% from baseline in: □ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[g] □ Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) □ the difference between involved and uninvolved sFLC levels (In patients without measurable serum and urine M-protein levels), the absolute increase must be > 10 mg/dl. □ the size of existing bone lesions or soft tissue plasmacytomas as well as definite development of new bone lesions or soft tissue plasmacytomas □ Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) that can be attributed solely to the plasma cell disorder.

a. All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response criteria.
b Confirmation with repeat biopsy not necessary.
c Presence/absence of clonal cells is based upon the κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ration reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.
d Applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements: Serum M-protein ≥ 0.5 g/dl, Urine M-protein ≥ 200 mg/24hour, Serum FLC assay involved FLC level ≥ 10 mg/dl provided serum FLC ration is abnormal. e. Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates).
f All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
g For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL. Progression can also be defined by a 25% increase in the serum M component or M spike provided that the increase is >0.5 g/dL.

APPENDIX B: Performance Status Criteria

Performance Status Criteria

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

APPENDIX C: Laboratory PK/PDn Events Schedule – Blood Draws

	TIME POINT	TOTAL VOLUME OF BLOOD (mL)	PK[1]	Selinexor PK	Free Doxorubicin PK	PDn[2]	
			1 tube x 2 ml or 4 ml			Cytokines 1 tube x 2ml	Leukocytes 2 tubes x 2ml
	KPT Loading Day -7						
1	Pre-dose	9	2	X		2 ml	2 x 2.5 ml
2	2 hr (±30 min) post dose	2	2	X			
3	4 hr (±20 min) post dose	7	2	X			2 x 2.5 ml
4	8 hr (±30 min) post dose	7	2	X			2 x 2.5 ml
	Cycle 1, Day 1						
5	Pre-dose (within 120 min before dosing)	11	4	X	X	2 ml	2 x 2.5 ml
6	2 hr (±20 min) post dose	4	4	X	X		
7	4 hr (±20 min) post dose	9	4	X	X		2 x 2.5 ml
8	8 hr (±30 min) post dose	9	4	X	X		2 x 2.5 ml
	Cycle 1, Day 8						
9	Pre-dose (within 120 min before dosing)	11	4	X	X	2 ml	2 x 2.5 ml
10	2 hr (±10 min) post dose	2	2	X			
11	4 hr (±20 min) post dose	7	2	X			2 x 2.5 ml
	Cycle 1, Day 15						
12	Pre-dose (within 120 min before dosing)	11	4	X	X	2 ml	2 x 2.5 ml
13	2 hr (±20 min) post dose	2	2	X			
14	4 hr (±20 min) post dose	7	2	X			2 x 2.5 ml
	Cycle 2 , Day 1						
15	Pre-dose (within 120 min before dosing)	7				2 ml	2 x 2.5 ml
16	4 hr (±10 min) post dose	5					2 x 2.5 ml

Time 0will be relative to the administration of Selinexor or Liposomal doxorubicin depending on which PK is obtained.. Note that LD is administered at least 2hours but not more than 4h after selinexor

[1]PK sampling: Blood (2 mL) for selinexor (PK) will be obtained on day -7, cycle 1 day 1, 8 and 15 and assayed by Karyopharm. Blood (2 mL) for free doxorubicin (PK) will be obtained on cycle 1 day 1, 8 and 15 and assayed by the Translation Research Core – Clinical Pharmacology Lab.

[2]PDn sampling: Plasma and blood leukocytes for XPO1 inhibition and select cytokine assays will be obtained on day -7, Cycle 1 day 1, 8, and 15, and Cycle 2 day 1 and assayed by Karyopharm.