Phase 1/2 Investigator Sponsored Study of Selinexor in Combination with High-Dose Melphalan Before Autologous Hematopoietic Cell Transplantation for Multiple Myeloma

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PROTOCOL SYNOPSIS

Phase 1/2 investigator sponsored study of selinexor in combination with high-dose melphalan before autologous hematopoietic cell transplantation for multiple myeloma

Principal Investigators:	Taiga Nishihori, MD
Study Design:	This is a phase 1/2, single institution, dose-escalation study (3 dose levels) to evaluate the combination of selinexor and high-dose melphalan as a conditioning regimen for autologous hematopoietic cell transplantation in patients with multiple myeloma. In phase 2 study, patients will be treated at recommended phase 2 dose (RPh2D)/maximum tolerated dose (MTD).
Primary Objectives:	1. The primary objective of the phase 1 study is to determine the RPh2D/MTD of conditioning regimen of selinexor plus high-dose melphalan. 2. The primary objective of the phase 2 study is to assess complete response (CR) conversion rate at 3 months post HCT.
Secondary Objective:	Secondary objectives are to estimate overall response rate (ORR) at 3 months post HCT, to estimate progression-free survival (PFS) and overall survival (OS), and to evaluate minimal residual disease (MRD) as an exploratory endpoint
Eligibility Criteria:	Eligible patients are $\geq$18 years of age with Karnofsky performance status of $\geq$ 70%, who have achieved partial response (PR) or very good partial response (VGPR) to systemic chemotherapy, received less than 4 lines of anti-myeloma therapy, and have adequate organ function.
Treatment Description:	In phase 1, selinexor at 40 mg (dose level 1), 60 mg (dose level 2) and 80 mg (dose level 3) will be given orally in combination with high-dose melphalan at 100 mg/m^2 (per day) intravenously on days -3 and -2 (a total melphalan dose of 200 mg/m^2 per patient). RPh2D/MTD dosing of selinexor will be used for phase 2 study. Autologous peripheral blood hematopoietic cell transplantation will be performed on day 0. A minimum of 2 x 10^6 CD34$^+$ peripheral blood stem cells per kilogram of patient's body weight will be infused for the transplant per the institutional standards.
Accrual Objective:	Up to 46 evaluable patients (3-6 per cohort, maximum 18 in phase 1 and 34 (22 PR and 12 VGPR) evaluable patients in phase 2) including the MTD cohort (n=6) from phase 1.
Accrual Period:	The estimated accrual time is 24 months
Study Duration:	Patients will be followed for 90 days after HCT

List of Abbreviations:

ABL	Abelson murine leukemia virus oncogene
AE	adverse event
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCR	breakpoint cluster region
BMP	basic metabolic profile
BSA	body surface area
CBC	complete blood count
CI	combination index or confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
Cmax	maximum concentration
CMP	complete metabolic profile
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
CRM1	chromosome maintenance protein 1
CT	computed tomography
CTCAE	common terminology criteria for adverse events (version 5.0)
DLCO	diffusing capacity
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EC_{50}	half maximum effective concentration
ECG	12-lead electrocardiogram
ECOG	Easter Cooperative Oncology Group
EMDR	environmental mediated drug resistance
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed paraffin embedded
FISH	fluorescence in situ hybridization
FLC	free light chain
FVC	forced vital capacity
G-CSF	granulocyte-colony stimulating factor (G-CSF)
GCP	Good Clinical Practice
GDP	guanosine diphosphate
	GR Glucocorticoid receptor
GTP	guanosine triphosphate
hCG	Human chorionic gonadotropin
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus

ICH	International Conference on Harmonization
IFE	immunofixation electrophoresis
IFM	Intergroupe Francophone du Myélome
IMWG	International Myeloma Working Group
IND	investigational new drug
IRB	Institutional Review Board
i.v. or IV	intravenous(ly)
kD	kiloDalton
LC-MRM	liquid chromatography coupled to multiple reaction monitoring mass spectrometry
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multiple uptake gated acquisition scan
NES	nuclear export signal
NLS	nuclear localization signal
NYHA	New York Heart Association
ORR	overall all response
OS	overall survival
PD	progression of disease
PFS	progression-free survival
PLT	platelet
PMC	Protocol Monitoring Committee
PO	by mouth
PR	partial response
PT/PTT	prothrombin time/partial thromboplastin time
RB1	retinoblastoma 1
RCD	Research Compliance Division
RNA	ribonucleic acid
	RPh2D Recommended phase 2 dose
RPR	rapid plasma reagin
SAE	serious adverse event
SD	stable disease
SINE	selective inhibitor of nuclear export
siRNA	small interfering RNA
SPEP	serum protein electrophoresis
SRC	Scientific Review Committee
$T_{1/2}$	half-life
Tmax	time to maximum concentration
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VGPR	very good partial response
VOT	vital organ testing
VZV	varicella zoster virus
WBC	white blood cell

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1.0 Hypothesis

We hypothesize that selinexor is synergistic with the alkylating agent melphalan and that the combination of selinexor and high-dose melphalan will increase the clinical efficacy and depth of response of multiple myeloma in autologous hematopoietic cell transplantation (HCT).

2.0 Background

2.1. Autologous hematopoietic cell transplantation for multiple myeloma

Multiple myeloma represents approximately 10% of all hematologic malignancies and remains a fatal plasma cell disorder.[1,2] The promising activity of high-dose melphalan in myeloma was demonstrated in the 1980s.[3,4] High-dose melphalan followed by autologous HCT offers progression-free and overall survival benefits over conventional chemotherapy and it remains an integral part of myeloma treatment strategy.[5-11] Nationally, there are over 6000 autologous HCT performed yearly for multiple myeloma and myeloma remains the single most common indication for autologous HCT based on the report from the Center for International Blood and Marrow Transplant Research (CIBMTR). However, relapse/progression of multiple myeloma remains inevitable even with lenalidomide maintenance therapy following autologous HCT.[12,13] In spite of extensive prior efforts to improve autologous HCT outcomes in multiple myeloma, high-dose melphalan remains the standard conditioning regimen for the past few decades. Therefore this represents an unmet medical need and a crucial opportunity for the development of a novel conditioning regimen for multiple myeloma.

2.2 Nuclear cytoplasmic transport mechanisms

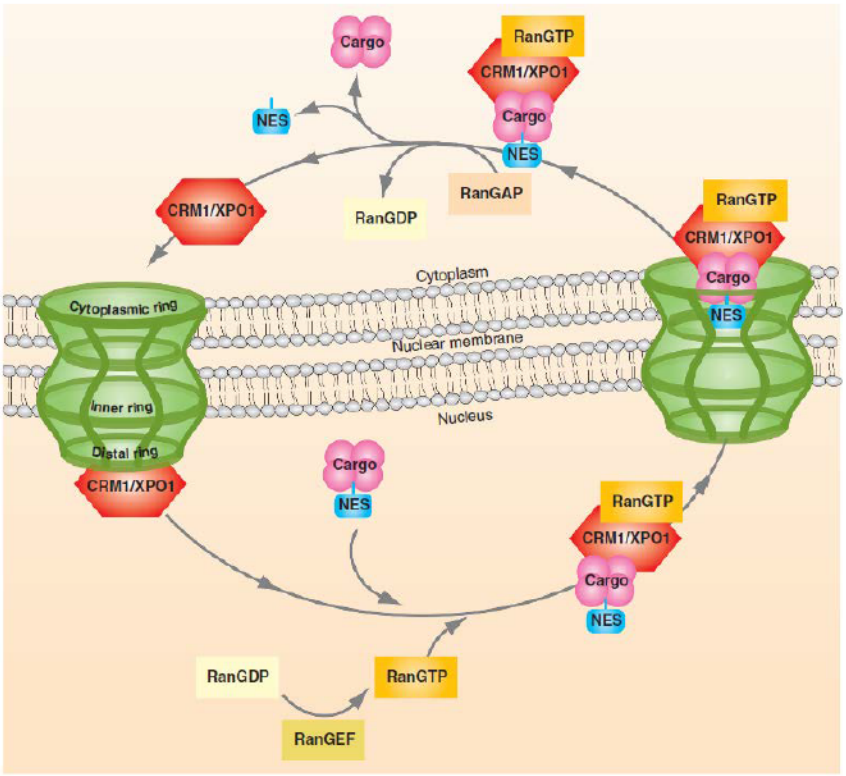
Critical cellular functions, such as DNA synthesis, RNA transcription and translation, and protein processing depend on the proper localization of proteins within specific intracellular compartments.[14] Growing evidence exists to suggest that the nuclear-cytoplasmic transport machinery is commonly disrupted in cancer cells, and that mislocalization of key regulatory proteins leads to carcinogenesis, cancer cell survival, drug resistance, cancer progression, and relapse.[15,16] Although smaller molecules passively diffuse across different cellular compartments, large molecules require regulated transport by signal- and energy-dependent mechanisms.[15] The nuclear pore complex is a large macromolecular assembly composed of nucleoporins and is embedded in the nuclear envelope. Nuclear pore complex mediates the active transportation of larger than 40-kD molecules between nuclear and cytoplasmic compartments.[16]

Many nuclear-cytoplasmic transport receptors belong to the karyorpherin β family of proteins. Karyopherin transport receptors recognize a nuclear localization signal (NLS) or nuclear export signal (NES) in the amino acid sequence of the cargo protein, and facilitate the transit in and out of the nucleus through the nuclear pore complex (importins and exportins).[17] There are three classes of nuclear-cytoplasmic transport signals: (a) basic amino acid NLS sequences recognized by a heterodimer composed of importins α and β;[18] (b) complex NLS possessing N-terminal hydrophobic/basic motif and C-terminal RX2-5PY motifs in karyopherin β cargo proteins;[19] (c) hydrophobic leucine-rich NES recognized by the ubiquitous transport receptor chromosome maintenance protein 1 (CRM1, also known as XPO1).[20,21] Currently, there are at least 19 karyopherin proteins identified in humans.[16,22] Evidence indicates that in humans nuclear-cytoplasmic export is largely regulated by XPO1.[23] XPO1 mediates the nuclear

transport of a small subset of RNAs and > 200 eukaryotic proteins that possess a canonical hydrophobic leucine-rich NES.[22]

The direction of transport across the nuclear pore complex is determined by the concentration gradient of the small GTPase Ran. Levels of RanGTP in the nucleus are known to be approximately 100-fold higher than those in the cytoplasm due to the location of the RanGTP exchange factor within the nucleus. In the cytoplasm, the majority of Ran is in the GDP-bound form. Once XPO1 is bound to its cargo, it forms a complex with RanGTP and exits the nucleus via the nuclear core complex.[16] After it leaves the nucleus, RanGTP undergoes hydrolysis by RanGAP and is converted to RanGDP, facilitating the dissociation of the XPO1 complex, and the cargo is subsequently released into the cytoplasm. The interactions between transport receptors and the Ran GTPase control bidirectional transport (Figure 1).

Figure 1. Nuclear-Cytoplasmic Transport System (From Tan et al.)[23]



2.2.1 XPO1-mediated export and cancer

The hallmarks of carcinogenesis are the dysregulation of growth-regulatory proteins and functional inactivation of tumor-suppressor proteins.[24] Any mechanisms that could potentially enhance the nuclear export and/or cytoplasmic sequestration of tumor-suppressor proteins or growth-regulatory proteins, might result in their functional inactivation and lead to development and acceleration of tumorigenesis. Increased expression of XPO1 has been observed and correlated with poor prognosis or resistance to chemotherapy in a variety of solid tumor and hematologic malignancies including acute myeloid leukemia, chronic lymphocytic leukemia, lymphoma and multiple myeloma.[25] There is also accumulating evidence to suggest that XPO1

may mediate drug resistance in many tumor types facilitating the nuclear export of drug targets such as topoisomerases (topo IIα), galectin-3, and BCR-ABL.[15,26,27]

The nuclear protein topo IIα functions as a homodimer that disentangles DNA and relieves the torsional stress in supercoiled DNA caused by the DNA replication process.[28] Commonly used chemotherapy agents, such as doxorubicin and etoposide, inhibit topo IIα during DNA replication and produce cleavable complexes that lead to double-stranded DNA breaks and cell death.[29] It was shown that topo IIα must be localized within the nucleus and in physical contact with DNA in order for the DNA damage to occur.[26] Nuclear export of topo IIα to the cytoplasm via XPO1 has been associated with resistance to topo IIα inhibitors in myeloma cells, and reversal of the topo IIα inhibitor-resistant phenotype can be induced by the XPO1 inhibitors such as ratjadone C or Leptomycin-B, or by siRNA-mediated knockdown of XPO1 protein expression.[26] Depletion of XPO1 by siRNA or ratjadone C has also been shown to be synergistic with doxorubicin and etoposide.[26]

Based on the cumulative evidence of contribution of nuclear transport dysregulation in neoplastic phenotype and drug resistance, growing interest exists in targeting the nuclear transport mechanism as a therapeutic strategy in oncology. It is hypothesized that targeted inhibition of XPO1 results in forced nuclear retention and activation of several important tumor-suppressor proteins (such as p53) and growth-regulatory proteins.

2.3. Selective inhibitors of nuclear export (SINE)

There are several compounds developed as the new small-molecule inhibitors of XPO1, also known as selective inhibitors of nuclear export (SINE). These compounds may share a similar structure with the N-azolylacrylate analog PFK050-638, a highly specific and reversible small-molecule XPO1 inhibitor that was originally designed to prevent nuclear export of the HIV-1 Rev protein.[30] Karyopharm Therapeutics has developed a number of SINE™ compounds including KPT115, KPT127, KTP185, KPT251, KPT276, KPT330 (selinexor), and KPT335 (verdinexor) that inhibit XPO1-mediated export of cellular proteins such as p53, RB1, and topo IIα.

Preclinical studies of these SINE compounds demonstrated dose-dependent cytotoxicity for many hematologic malignancies including acute myeloid leukemia, acute lymphoblastic leukemia, mantle cell lymphoma and chronic lymphocytic leukemia.[31-35] These highly specific inhibitors of XPO1 are water soluble, and they bind to the reactive site Cys528 residue by forming a covalent bond.[36] SINEs have also been shown to be selectively cytotoxic to neoplastic cells with a half maximum effective concentration (EC_{50}) of 10 to 1,000 nmol/L versus > 5 to 20 μmol/L in non-neoplastic cell lines.

2.3.1 Selinexor clinical experience

As part of the phase 1 clinical trial of selinexor in patients with advanced hematological malignancies (KCP-330-001), patients with multiple myeloma were treated with either single-agent selinexor or selinexor in combination with low-dose (20 mg) dexamethasone, both dosed twice weekly. Forty-four patients with multiple myeloma whose disease was relapsed and/or refractory to all available classes of approved therapies with a mean of 5.7 prior therapies and progressing on study entry have been enrolled in the trial as of July 7th,2014. Of these 44 patients, 34 received single-agent selinexor therapy and ten patients were treated with selinexor in combination with low-dose dexamethasone.

Among 29 patients receiving single-agent selinexor therapy, best responses include 1 partial response (PR) (3%), 6 minor response (MR) (21%), 16 stable disease (SD) (55%), and 6 progressive disease (PD) (21%) (see Table 1). It should also be noted that some patients treated with single-agent selinexor also received very low doses of dexamethasone (12 mg with each dose of selinexor) or another glucocorticoid as part of supportive care.

Table 1. Responses in evaluable multiple myeloma patients - Study KCP-330-001 (as of 12/1/2014)

Treatment	N	CBR	ORR	sCR	PR	MR	SD	PD
Selinexor Low $\leq$ 30mg/m^2	15	4 (27%)	-	-	-	4 (27%)	8 (53%)	3 (20%)
Selinexor High $\geq$ 35mg/m^2	14	3 (21%)	1 (7%)	-	1 (7%)	2 (14%)	8 (57%)	3 (21%)
Total Selinexor (Low + High)	29	7 (24%)	1 (3%)	-	1 (3%)	6 (21%)	16 (55%)	6 (21%)
Selinexor (45 mg/m^2) + Dex (20 mg)*	9	8 (89%)	6 (67%)	1 (11%)	5 (55%)	2 (22%)	-	1 (11%)

*One patient was not evaluable.
Abbreviations: CBR = clinical benefit response (MR+PR+sCR); Dex = dexamethasone; MR = minor response; N = number of patients; NE = non-evaluable; ORR = overall response rate (PR+sCR); PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease.
Source: Chen 2014

In this study, ten patients were treated with 45 mg/m^2 body surface area (BSA) (~80 mg) of selinexor and 20 mg of dexamethasone, both dosed twice weekly. This dose of dexamethasone is the standard low dose dexamethasone (40 mg weekly or 20 mg twice weekly) used with other anti-myeloma drugs, including lenalidomide or pomalidomide. The patients enrolled in the study had received a median of 6.5 prior courses of therapy. All had received prior therapy with at least one proteasome inhibitor (e.g., carfilzomib and/or bortezomib), at least one immunomoduatory drug (IMiD) (e.g., lenalidomide and/or pomalidomide), and glucocorticoids (typically two or more times), while nine of the ten patients also received hematopoietic cell transplantations including high-dose alkylating agents (Table 2).

As of December 15th, 2014, the best responses (Table 1) among nine patients who received selinexor plus dexamethasone were one stringent complete response (sCR) (11%), 5 PRs (55%), 2 MRs (22%), and 1 PD (11%). One patient was non-evaluable. The clinical benefit rate (CBR) was 89% and the overall response rate (ORR) was 67%. Eleven additional patients with multiple myeloma were dosed with selinexor 60 mg/m^2 (~100 mg) in combination with 20 mg dexamethasone in the ongoing study, but this dose was found to be poorly tolerated due to high levels of grade 3 fatigue, nausea and vomiting (Chen 2014). In the heavily pre-treated phase 1 population, several patients have remained on this combination for > 6 months (Table 2).

Table 2.Multiple myeloma treatment history and time on treatment - Study KCP-330-001 (12/1/2014)

Patient	MM Type	Max. % Change	Response	# Prior Therapies	Prior Therapies	Study Days
76	IgG-κ	- 71%	PR	7	Dox-Vinc-Dex, TD-Dex, Carfil-Dex, VRD, Cyclo-Pred-BCNU, Dox-Carf-Dex	301+
77	FLC-λ	-	NE	8	Len-Dex, Cyclo-Etop-Cis-Mel-Dex-ASCT, VRD, Carf-Cyclo-Dex, Carf-Cyclo-Dex-Len, Carm-TDC,Cis-Etop-Cyta-Vel-Mel, Cyclo-Carf-Pom-Dex, Vor-Len-Dex	15
79	FLC-κ	-53%	PR	3	TD-Pred-Dex-ASCT, Cyclo-Vel-Dex, Len-Dex	52
81	FLC-κ	-99%	sCR	5	Vinc-Adria-Dex-ASCT, ASCT-Len-Dex, Cyclo-Pred, Pom-Carf-Dex	280
84	IgG-κ	-84%	PR	9	Vel-Dex, ASCT, Len-Dex, Vel-Dex, Vel, Carfil, Pom-Dex, Carf, DT-PACE-TD	170
90	IgG-κ	41%	PD	5	Cyclo-Vel-Len-Dex (x2), Carf-Mel-ASCT, Cyclo-Vel-Dex, Pom-Carf-Dex	31
92	IgA-κ	-55%	PR	10	Vel-Dex, VRD-ASCT, Len, Reolysin, TG02, Carfil-Dex, Carfil-Cyclo-Dex, Carfil-Pom-Dex	121
93	IgG-κ	-41%	MR	9	VAD, VTD+ASCT, Vel-Len-Dex, Experim, Carfil-Panob, Len-Elotu-Dex, Experim, Pom-Dex, Benda-Pom-Dex	114
98	IgG-λ	-48%	MR	16	Len-Dex, ASCT (x2), Vel-Len-Dex, Vid-Len, Benda-Vel-Dex, VAD, Ritux, Vel-TD, Carfil-Dex, Carfil-Dex-Cis-Adria, Len-Ritux-Inter, Carfil-Pom, Vel-TD-Dex-Adria-ATRA-Arsenic Trioxide, Len-Dex, TG02-Carfil	79
99	IgA-κ	-82%	PR	6	Sal, TD-Dex, Len, ASCT, Ibrut, Vel-Dex	201+

+ Patient still on study as of 12/15/2014.
Abbreviations: Adria = adriamycin; ASCT = autologous stem cell transplantation; ATRA = all trans retinoic acid; BCNU = bis-chloroethylnitrosourea; carfil = carfilbomide; Carm = carmustine; Cis = cisplatin; Cyclo = cyclophosphamide; Dex = dexamethasone; Dox = doxorubicin; DT = thalidomide and dexamethsone; Etop = etoposide; FLC = free light chain; ID = identification number; Ig = immunoglobulin; Len = lenalidomide; MR = minor response; NE = non-evaluable; PACE = cisplatin, doxorubicin, cyclophosphamide, and etoposide;PD = progressive disease; PR = partial response; Pred = prednisone; sCR = stringent complete response; TD = thalidomide and dexamethasone; Vinc = vincomycin; VRD = Revlimid (lenalidomide), Velcade (bortezomib) and dexamethasone; # = number;
Source: Chen 2014

Adverse events in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Compared with selinexor given alone, fewer AEs were reported in patients receiving selinexor plus dexamethasone, particularly levels of nausea, consistent with dexamethasone's reduction in selinexor related side effects of nausea, anorexia, and fatigue.

In addition to patients with multiple myeloma achieving durable responses and disease control on selinexor single-agent therapy, selinexor with low-dose dexamethasone showed activity with

rapid M-protein reductions and good tolerability, even in patients with disease refractory to pomalidomide.

Bone marrow biopsies from a total of nine multiple myeloma patients were obtained prior and 3-4 weeks post-selinexor treatment initiation. An overall reduction in plasma cell involvement was observed in all patients. Specifically, histology showed that post-treatment marrows had noticeably fewer myeloma cells and increased areas of adipocytes and dense hematopoiesis, typical of normal marrow. Increases in nuclear staining of CRM1 provide evidence of the tumors' direct response to selinexor.

Additional clinical trials of selinexor in multiple myeloma are in progress: a phase 1/2 study of selinexor (starting dose of 40 mg/m^2 on days 1, 8, and 15) plus pegylated liposomal doxorubicin for relapsed/refractory multiple myeloma (NCT02186834) and a phase 1 study of selinexor, carfilzomib, and dexamethasone combination in patients with relapsed or refractory multiple myeloma (NCT02199665).

2.4. Preclinical studies demonstrating synergy between selinexor and alkylating agent melphalan

Sullivan and Turner at Moffitt Cancer Center investigated the combination of selinexor and melphalan in myeloma preclinical models. In addition to assessing apoptosis by flow cytometry for activated caspase 3 in human myeloma cell lines and primary cells, they also measured cell viability using the CT-Blue viability assay to determine IC_{50} (Table 3) and combination index (CI) values (Table 4). The IC_{50} values for XPO1is (KPT-330 (selinexor), KOS-2464, KPT-8602) were found to be much greater in high-density myeloma cell lines (2-4 X 10^6 cells/ml) compared with low-density cell lines (2-6 X 10^5 cells/ml)—for example, the IC_{50} for KPT-330 (selinexor) in low-density H929 and 8226 cells is 100-300 nM and 5-18 µM in high-density cells (Table 3). Low-density MM cells are also more sensitive to MEL than higher density cells.

Table 3. IC_{50}'s in Human Myeloma Cell lines and PBMC's of Melphalan and XPO1i's*

Drug	Cell line	Mean (µM)	SEM	n
KOS-2464	NCI-H929 LD	0.00227	0.000581	3
	NCI-H929 HD	0.267	0.0832	7
	RPMI 8226 LD	0.00584	0.00183	5
	RPMI 8226 HD	0.103	0.0296	5
	Human PBMC's	20.4	6.24	4
Melphalan	NCI-H929 LD	4.68	1.71	4
	NCI-H929 HD	38.7	4.71	13
	RPMI 8226 HD	94.7	7.63	2
	Human PBMC's	31.2	10.5	4
KPT-330	NCI-H929 LD	0.101	0.014	7
	NCI-H929 HD	5.43	2.08	14

	RPMI 8226 LD	0.276	0.0973	6
	RPMI 8226 HD	17.8	5.48	5
	U266 HD	5.78	1.96	4
	Human PBMC's	16.9	1.06	9
KPT-8602	NCI-H929 LD	0.0417	0.0069	3
	NCI-H929 HD	1.04	0.454	3
*IC_{50}'s determined after a 48 hour drug exposure using CellTiter-Blue viability assay. HD, high-density cells (2-4 X 10^6 cells/ml); LD, low-density cells (3-6 X 10^5 cells/ml). n = number of independent experiments. PBMC's, human peripheral blood mononuclear cells.				

Combination of selinexor and melphalan was examined either with concurrent exposure for 48 hours to 2 agents or sequential (selinexor followed by melphalan or melphalan followed by selinexor). CI values for human H929 myeloma cells treated at high or low densities with XPO1i's + melphalan in different drug sequences show that: (1) high-density myeloma cells generally show more synergism (CI < 1) when treated with XPO1i's + melphalan either concurrently or when the XPO1i is given before melphalan; (2) low-density myeloma cells show less synergism from any drug sequence (CI 0.83-0.96); (3) a control leukemia cell line (HL-60) shows more additive (CI = 1) or antagonistic (CI > 1) response when treated with the drug combination; and (4) Peripheral blood mononuclear cells (PBMCs) show minimal synergism when treated with KPT-330 → melphalan (Table 4). These data suggest that XPO1i's and melphalan be given either concurrently or in the order XPO1i → melphalan when treating patients with high-dose melphalan followed by autologous HCT.

Table 4. Combination Index Values for Melphalan combined with selinexor (KPT-330), KPT-8602 or KOS-2464 in H929 Myeloma Cells Assessed by CT-Blue Viability Assay*

Cell line	Drug Administration: concurrent (+) or sequential (→)	Concentration range: Drug 1	Concentration range: Drug 2	CI (mean)	CI (SEM)	n
NCI-H929 HD	KOS-2464 + MEL	390 pM – 100 nM	391 nM – 100 µM	0.691		1
NCI-H929 HD	KOS-2464 → MEL	39.1 pM – 5 µM	3.9 nM – 100 µM	0.362	0.216	3
NCI-H929 HD	KPT 330 + MEL	78.1 pM – 2 µM	7.8 nM – 200 µM	0.370	0.109	6
NCI-H929 HD	KPT 330 → MEL	78.1 pM – 20 µM	7.8 nM – 200 µM	0.491	0.074	9

NCI-H929 HD	MEL → KPT 330	195 nM – 200 µM	78.1 pM – 20 µM	0.565	0.244	3
NCI-H929 HD	KPT 8602 + MEL	625 pM – 4 µM	15.6 nM – 100 µM	0.685	0.022	3
NCI-H929 HD	KPT 8602 → MEL	625 pM – 4 µM	15.6 nM – 100 µM	0.674	0.114	3
NCI-H929 HD	MEL → KPT 8602	15.6 nM – 100 µM	625 pM – 4 µM	0.745	0.069	3
NCI-H929 LD	KPT 8602 + MEL	625 pM – 4 µM	15.6 nM – 100 µM	0.961	0.097	3
NCI-H929 LD	KPT 8602 → MEL	625 pM – 4 µM	15.6 nM – 100 µM	0.902	0.247	3
NCI-H929 LD	MEL → KPT 8602	156 pM – 2 µM	625 pM – 4 µM	0.831	0.162	3
HL-60	KPT 330 + MEL	156 pM – 2 µM	7.8 nM – 100 µM	1.023	0.154	2
HL-60	KPT 330 → MEL	156 pM – 2 µM	7.8 nM – 100 µM	0.897	0.046	3
HL-60	MEL → KPT 330	7.8 nM – 100 µM	156 pM – 2 µM	1.273	0.158	3
PBMC's	KPT 330 → MEL	97.7 nM – 100 µM	195 nM – 200 µM	0.874	0.164	5

*For concurrent treatment (+), cells were treated with drugs for 48 h; for sequential treatment (→), cells were treated with the first drug for 24 h followed by a 24 h exposure to the second agent. HD, high-density cells (2-4 X 10^6 cells/ml); LD, low-density cells (3-6 X 10^5 cells/ml); CI, combination index where CI < 1 (synergy), CI = 1 (additive), and CI > 1 (antagonism); PBMC's, human peripheral blood mononuclear cells; n = number of independent experiments.

Figure 2 shows that when high-density myeloma cells (2-4 X 10^6 cells/ml) are treated concurrently with either 300 nM selinexor (KPT-330) or KPT-8602 and bifunctional alkylating agents (melphalan and 4HC) that significant synergistic apoptosis is seen in all three human myeloma cell lines.

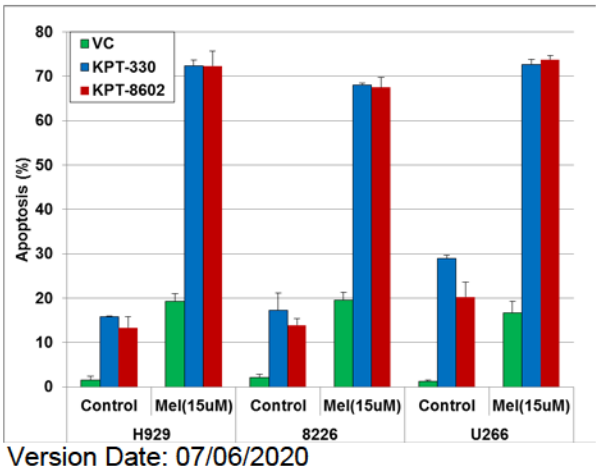


Figure 2: Small-molecule inhibitors of XPO1 sensitize human myeloma cell lines to melphalan. High-density H929 (3x10^6 cells/ml), 8226 (2x10^6 cells/ml) and U266 (4x10^6 cells/ml) human myeloma cells were treated concurrently with selinexor (KPT-330) (300nM) or KPT-8602 (300 nM) +/- melphalan (15 µM) for 20 hours. The combination of selinexor (KPT-330)/melphalan (*P* = 2.2x10^{-6} to 0.0032) or KPT-8602/melphalan (*P* = 1.2X10^{-7} to 0.0031) synergistically increased apoptosis (activated caspase 3) in myeloma cell lines over single agent melphalan (n=3).

In Figure 3, 8226 myeloma cells were treated concurrently with either selinexor (KPT-330) or KOS-2464 (another XPO1i) and escalating concentrations of melphalan. Apoptosis was significantly increased at all concentrations of melphalan by both XPO1i's, while human PBMCs were unaffected by the drug combination. Note that when high-dose melphalan is used to treat patients with multiple myeloma, C_{max} blood levels are as high as 9 µM (our unpublished pharmacokinetic data), within the range of our experimental conditions.

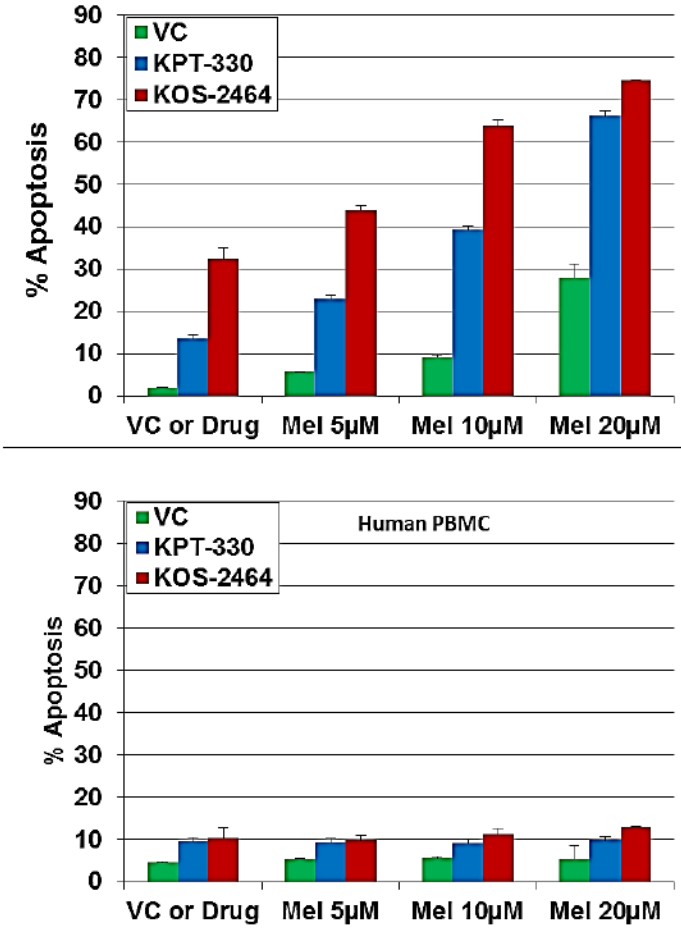


Figure 3: XPO1i's sensitize human myeloma cells to melphalan (A) High-density ($2x10^6$ cells/ml) human 8226 myeloma cells treated with selinexor (KPT-330) ($P = 5.5x10^{-5}$ to 0.0003) or KOS ($P = 3.5x10^{-5}$ to 0.0002) were sensitized to melphalan (apoptosis) in a dose-dependent manner when compared to melphalan alone (n = 2). **(B)** Normal human PBMCs were not affected by XPO1i/melphalan treatment (n = 5). Drugs were added concurrently and both XPO1i's were at 300 nM.

In addition to the human myeloma cell line data, they have also treated human primary plasma cells *ex vivo* with selinexor (KPT-330) and KOS-2464 (Figure 4). Plasma cells were identified as $CD138^+$/light $chain^+$ from newly diagnosed (Figure 4A) and relapsed (Figure 4C) patients, and showed significant synergistic apoptosis when treated with 10 µM melphalan + 300 nM XPO1i compared to melphalan alone. CD138/light chain double negative cells from patient bone marrow aspirates were found to be unaffected by drug treatment (Figure 4B and 4D).

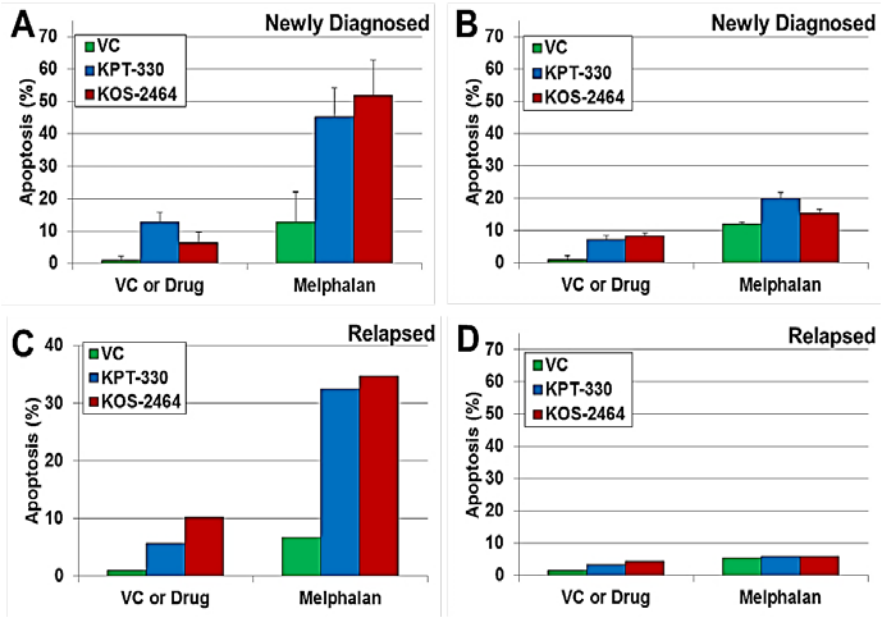


Figure 4. KOS-2464 and Selinexor (KPT-330) sensitize newly diagnosed and relapsed patient myeloma cells to melphalan. Bone marrow mononuclear cells were isolated and treated with XPO1i's (300 nM) +/- melphalan (10 µM) for 20 hours. Cells were fluorescently labeled with antibodies against activated caspase 3, CD138, and light chain (kappa or lambda). **(A)** Newly diagnosed (n=4) and **(C)** relapsed (n=3) myeloma patient samples were sensitized by selinexor and KOS-2464 to melphalan vs single agent melphalan (P = 0.014 to 0.008) as shown by increased apoptosis. **(B, D)** Non-myeloma CD138/light-chain double-negative patient cells were not sensitized to apoptosis by XPO1i's.

They have also generated preliminary data examining the possible mechanism(s) of synergy between selinexor (KPT-330) and melphalan in myeloma cell lines. An alkaline comet assay (Figure 5) shows that the XPO1i, selinexor (KPT-330) (100 nM), increases melphalan-induced DNA interstrand crosslinking (ICL)'s in high-density H929 cells across a range of melphalan of 1-10 µM.

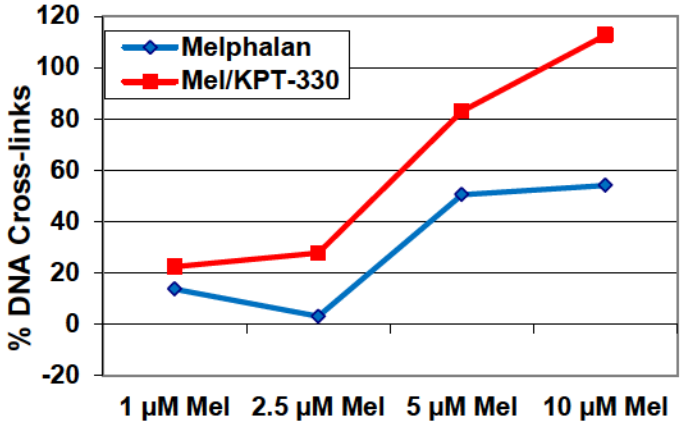


Figure 5. Alkaline Comet Assay showing increased melphalan-induced DNA ICL's from the addition of selinexor (KPT-330). High-density H929 myeloma cells (3 x 10^6 /ml) were exposed to the XPO1i, selinexor (KPT-330) (0.1 µM), for 20 hr followed by melphalan (1, 2.5, 5, & 10 µM) for 2 hr. Drugs were removed and cells incubated another 3 hr to allow cross-links to form. Cells were exposed to 900 rads (X-Rad 160 X-ray biological irradiator) and alkaline comet assays were performed immediately (Trevigen Inc). 50 cells per treatment were analyzed and % cross-linking was determined using the formula *1-[(comet moment drug treat + 900 rads) - (comet moment no drugs no XRT control) / (comet moment no drug + 900 rads) - (comet moment no drugs no XRT control)] X 100*. Images and data analysis were performed using a Loats Comet Analysis System (Loats Assoc. Inc).

Similar results were seen when measuring γH2AX by flow cytometry in H929 cells treated with melphalan + selinexor (KPT-330); Selinexor (KPT-330) significantly increases melphalan-induced DNA damage (Figure 6).

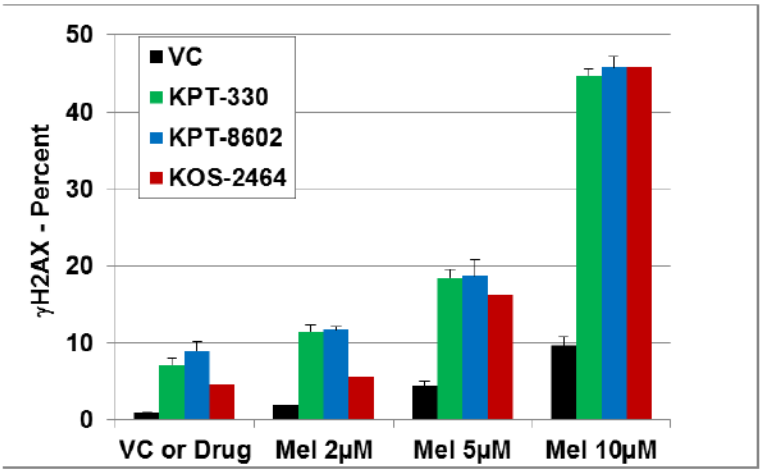


Figure 6: Mechanism for XPO1i/melphalan synergy. Human H929 myeloma cells were treated with XPO1i's +/- melphalan and assayed for γH2AX. Data are expressed as the percentage of treated cells expressing high-levels of γH2AX. XPO1 inhibition by selinexor (KPT-330), KPT-8602 and KOS-2464 increased the effectiveness of 10 μM melphalan to induce double strand DNA breaks versus melphalan control as shown by γH2AX expression ($P = 0.005$, $P = 0.001$ *and* $P = 0.0005$ respectively) and in a dose-dependent manner.

Finally, H929 cells were treated with melphalan, selinexor (KPT-330), and the combination and found by Western immunoblotting to have increased cellular expression of IKKα, NFκB, FANCL and FANCF when treated with melphalan—with a significant decrease of all four proteins with the addition of selinexor (KPT-330) (Figure 7). These preliminary data suggest that XPO1i's augment melphalan-induced DNA damage and may also block the repair of the DNA damage—both of which could result in synergistic cell kill.

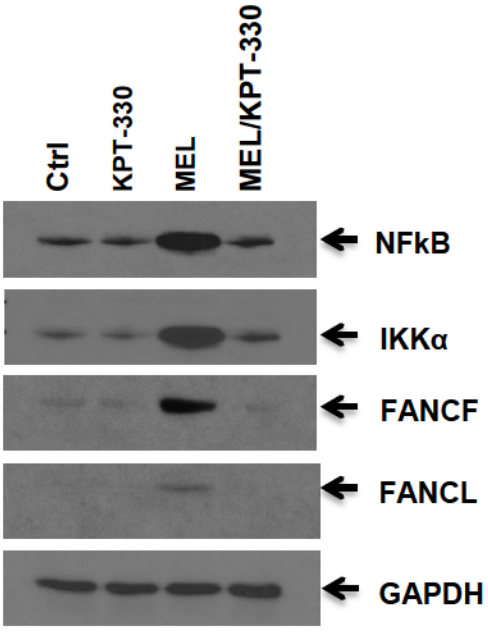


Figure 7: Western blot of Fanconi anemia (FA) and NFκB pathway members with XPO1i + melphalan. High-density H929 myeloma cells (3 x10^6/ml) were treated for 6 hr with melphalan (10 μM), selinexor (KPT-330) (300 nM) or in combination. Whole cell lysates were separated by SDS PAGE and assayed by Western blot. Melphalan was found to increase DNA repair enzymes FANCF and FANCL, and cell proliferation proteins NFkB and IKKα. However, when the XPO1i, selinexor (KPT-330) was added, total cellular FANCF, FANCL, IKKα, and NFkB were decreased. Melphalan/selinexor (KPT-330) synergy may be due, in part, to an increase in DNA damage by melphalan and a decrease in both DNA repair enzymes and cell proliferation proteins by selinexor (KPT-330).

Sensitive myeloma cell cells (H929) were treated with various SINEs (at 100 or 300 nM) or leptomycin B (LMB, at 10 o r100 nM) for 20 hours, and intracellular localization and expression of p53, CRM1, and topo IIα were examined by immunofluorescence microscopy. Nuclei were counter-stained using DAPI (blue) (Figure 8).[27] CRM1 (green) nuclear localization in low-density log-phase cells (2 x 10^5/mL) was increased in unstained control, and KPT185-treated cells. Cells treated with KPT185, KPT249, selinexor (KPT330), and LMB had increased nuclear accumulation of p53 (Figure 8). When protein expression was assessed after treatment with SINEs, whole cell lysates assayed for p53 showed that total cellular p53 increased in cells treated with CRM1 inhibitors when compared to untreated and KPT185T-treated control samples (Figure 8).[27] 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 (KPT185, KPT249, and LMB).

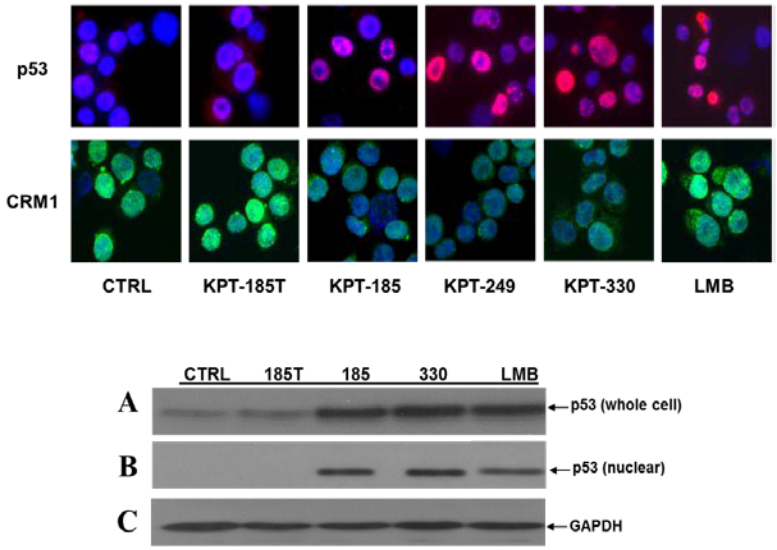


Figure 8: WT p53 and XPO1i's. XPO1 inhibitors increase total cellular and nuclear p53 as shown by immunofluorescence microscopy (red) and Western blot (Turner et al, J Cancer. 2013 Sep 10;4(8):614-25). Melphalan has been shown to kill cells through production of reactive oxygen species and activation of the p53 pathway. (Surget et al, Leuk, Lymphoma 2014 Sep;55(9):2165-73). Melphalan/selinexor (KPT-33)0 synergy may be due, in part, to an increase of nuclear p53 by selinexor (KPT-330), and the reported activation of p53 by melphalan.

TP53 is located at the chromosome 17p13.1 and encodes for p53 tumor suppressor protein. In multiple myeloma, p53 mutation is a rare occurrence at diagnosis (reported in approximately 3% of cases).[37] Deletion of chromosome 17p13 region is a recurrent cytogenetic abnormality and has been associated with unfavorable outcome.[38] p53 deletion has been reported as an important factor associated with resistance to chemotherapy.[39] Chemotherapeutic agents induce DNA damage in neoplastic cells and ultimately lead to cell death by activating p53 pathway.[40,41]

Our preclinical study finding of increased p53 after SINE treatment is intriguing as restoration of p53 in myeloma cells would potentially induce apoptosis in myeloma cells and enhance cell killing potential of alkylating agent, melphalan, while sparing toxicities to normal cells.

More recent experiments in the Sullivan lab have shown that when parental 8226 cells are exposed to melphalan (10-20 μM) for 20 h, 40-50% of the cells undergo apoptosis (Figure 9A)—if selinexor (KPT-330) or KOS-2464 are added concurrently then 100% of parental cells are apoptotic. Melphalan-resistant 8226/LR5 cells show < 8% apoptosis from the same melphalanconcentrations (they are about 8-fold resistant to melphalan). However, when 300 nM selinexor (KPT-330) or KOS-2464 is administered with melphalan there is a tremendous re-sensitization of the drug-resistant cells to melphalan. Melphalan-resistant U266/LR6 cells show a similar restoration of sensitivity to melphalan by the addition of selinexor (KPT-330) or KOS-2464 (Figure 9B).

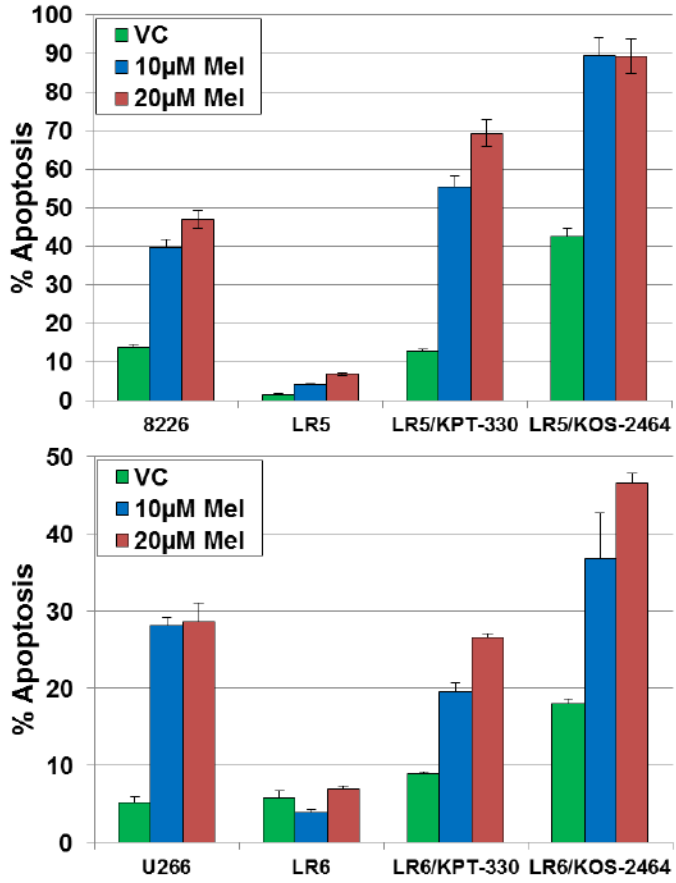


Figure 9. XPO1 inhibition sensitizes melphalan-resistant human myeloma cell lines to melphalan. Human 8226(**A**) and U266(**B**) drug-resistant (LR5 and LR6) and parental myeloma cell lines were treated concurrently for 20 hr with selinexor (KPT-330) (300 nM) or KOS-2464 (10 nM) +/- melphalan (10 or 20 μM) and assayed for apoptosis by flow cytometry (activated caspase 3). Resistant myeloma cell lines were 4.1 to 9.5-fold resistant to single agent melphalan when compared to parental cells. The addition of the XPO1i's selinexor (KPT-330) or KOS-2464 ($p = 0.015$ to 0.030) sensitized drug resistant LR5 cells to melphalan when compared to single agent melphalan. XPO1i's selinexor (KPT-330) or KOS-2464 ($p = 0.003$ to 0.0006) sensitized drug resistant LR6 cells to melphalan when compared to single agent melphalan. Parental cells treated with selinexor (KPT-330) or KOS-2462 + melphalan were 100% apoptotic/necrotic (data not shown).

Using a murine model (Figure 10), NSG mice were injected with parental U266 cells and the cells allowed to grow for 1 week. Mice (5/treatment group and 5 control mice) were then treated with melphalan alone (3 mg/kg IP Tues and Fri), selinexor (KPT-330) or KPT-8602 alone (twice weekly (Tue/Fri) by oral gavage at 10 mg/kg), or the combinations of melphalan with each XPO1i (given concurrently on Tues and Fri). Combination treatment by both melphalan/selinexor (KPT-330) and selinexor/KPT-8602 significantly improved control of tumor growth (measured by calipers (Figure 10A)) and bioluminescence (not shown)), with little toxicity as assessed by weight loss (Figure 10B).

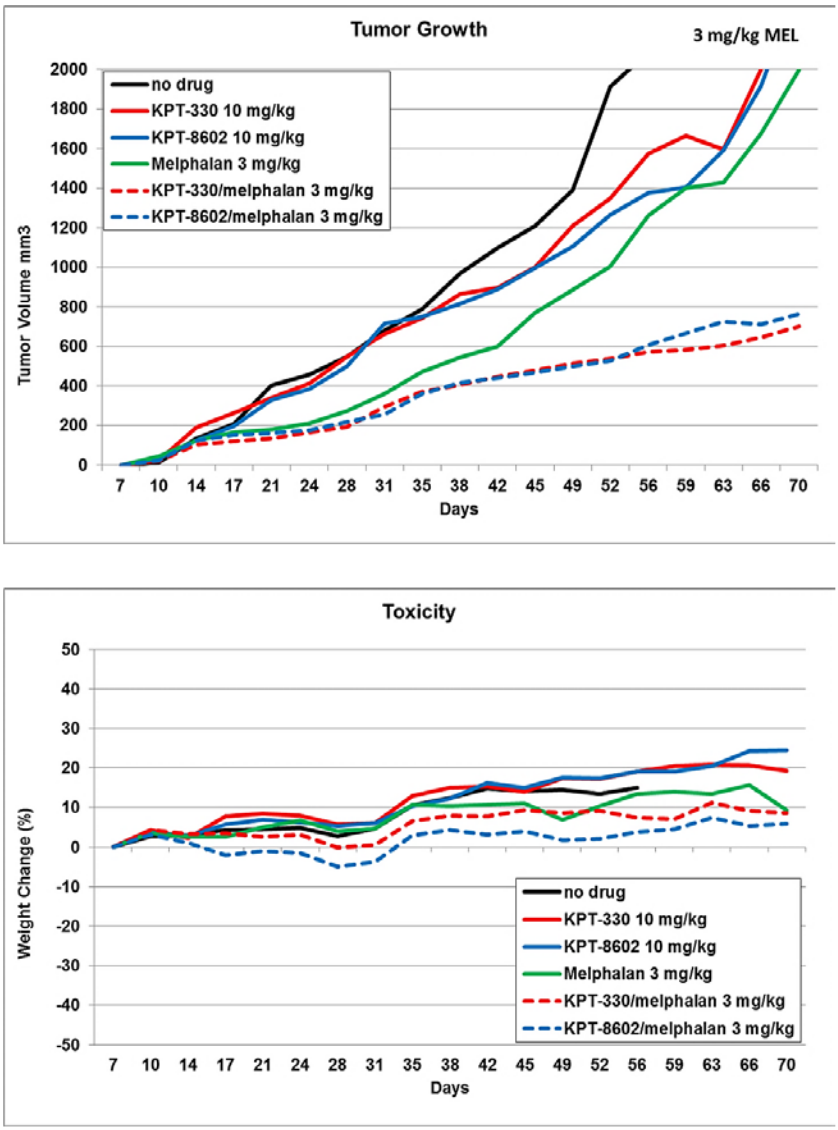


Figure 10. NSG mouse *in vivo* studies. A) Tumor growth with XPO1i's and melphalan. Melphalan/selinexor (KPT-330) or MEL/KPT-8602 treatment reduced human myeloma U266 tumor growth when compared to single-agent melphalan (P = 0.0024 and 0.0030, respectively). Tumor volumes were plotted versus time. Mice were euthanized when tumor volumes reached 2000 mm^3. **B) Toxicity**, as assessed by weight loss was minimal in all treatment groups. Melphalan (intraperitoneal injection) and the XPO1i's (oral gavage) were both administered twice weekly (Tues, Fri), and when given in combination were on the same day and concurrently.

2.5. Bone marrow microenvironment and drug-resistance in multiple myeloma

Multiple myeloma progression/relapse remains unavoidable as a consequence of minimal residual disease due at least in part to pro-survival niche afforded bone marrow resident cells.[42] The bone marrow niche affords sanctuary to resident multiple myeloma cells via networks of cytokines, chemokines, growth factors, and adhesive matrices that facilitate multiple myeloma cell homing and expansion.[43-47]

Environmental mediated drug resistance (EMDR) is linked to signaling from numerous soluble factors as well as adhesion to extracellular matrix components or to adjacent bone marrow stromal cells via specific cell surface receptors including VLA (very late antigen)-4/α4β1 integrins and Notch-1.[45,48-50] Although soluble effectors of the microenvironment confer a protective advantage to stimulated multiple myeloma cells, physical interactions between multiple myeloma cells and extracellular matrix such as fibronectin or bone marrow stromal cells appear to portend a greater degree of protection.[51-53] These results suggest that disruption of multiple myeloma adhesive dynamics within the bone marrow niche will reverse the EMDR phenotype. Specifically, adhesion of multiple myeloma cells to fibronectin/environmental determinants confer resistance to melphalan via alterations in expression of the Bcl-2 family members Bim and Noxa, following β1 integrin (VLA-4/5) and Notch-1 mediated adhesion, respectively.[53,54] Moreover, as demonstrated in Figure 6A a progressive resistance to melphalan is observed when comparing melphalan induced apoptosis in RPMI cells maintained in suspension, or co-cultured with bone marrow stromal cells separated by a semi-permeable membrane (without direct contact) and co-cultured with bone marrow stromal cells in direct contact.

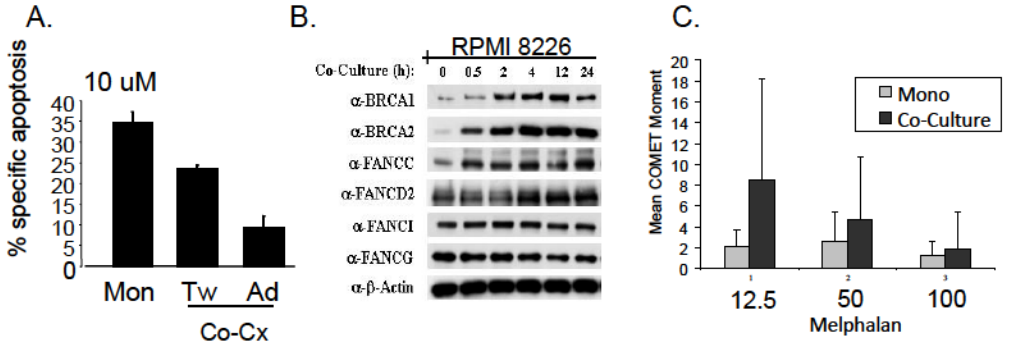


Figure 11. Direct contact of co-cultured RPMI8226 multiple myeloma cells with bone marrow stromal cells (HS-5) inhibits melphalan-mediated apoptosis correlating with increased FA/BRCA DNA repair pathway expression and reduced DNA damage. A) Co-culture of multiple myeloma cells with the HS-5 bone marrow stromal cell line inhibits melphalan induced caspase-3-PE labeling by flow cytometry. **B)** Western blot analysis of components of FA/BRCA pathway with time. **C)** Analysis of melphalan induced interstrand crosslinks by alkaline COMET assay. Multiple myeloma cells in **mono-culture demonstrated large amounts of DNA damage shown as decreased mean COMET moments relative to multiple myeloma cells in co-culture.**

Furthermore, preliminary data suggests that the melphalan resistance observed following co-culture of human bone marrow stromal cells and multiple myeloma cells may involve an enhanced expression of the FA/BRCA pathway and decreased DNA damage (Figure 11A-C). The FA/BRCA pathway has been shown to be an important mediator of resistance to melphalan in myeloma cells. These DNA repair determinants were initially identified in Fanconi Anemia (FA), a heritable DNA repair disorder characterized by bone marrow failure and cancer predisposition.[55] The FA pathway includes 13 FA proteins (FANCA, B, C, D1/BRCA2, D2, E, F, G, I, J/BRIP, L, M, and N/PALB2) that facilitate DNA repair via homologous recombination (HR) and translesion synthesis.[55,56]

In myeloma cell lines we demonstrated that NF-κB signaling was critical in FANCD2 and FA/BRCA pathway overexpression and survival in models of acquired melphalan resistance.[57] The bone marrow environment has also been shown to involve altered response to DNA damage and melphalan resistance via β1-integrins and Notch1 (EMDR).[54,58,59] RelB/p50 (NF-κB) DNA binding has been linked to multiple myeloma cell adhesion mediated drug resistance (CAM-DR).[60] Moreover, bone marrow stromal cells have been shown to afford melphalan resistance, stimulate FA/BRCA pathway gene expression, NF-κB DNA binding activity and reduced melphalan interstrand crosslinks (Figure 11A-C).[53] These studies suggest that the FA/BRCA and NFκB axis may also be important for melphalan resistance conferred by the bone marrow microenvironment. Taken together, the disruption of multiple myeloma-bone marrow microenvironment adhesive dynamics to abrogate EMDR appears to be important in targeting minimal residual disease and improving disease control in multiple myeloma.

2.6 Selinexor plus dexamethasone combination studies

Selinexor and dexamethasone in combination were found to have a synergistic effect on reducing MM1.S human MM cell viability relative to either drug alone.[61] Increased glucocorticoid receptor (GR) nuclear localization and concomitantly activated GR-mediated transcription in the presence of glucocorticoids were at least partly responsible for the synergistic cytotoxicity of the selinexor/dexamethasone combination in MM1.S cells (Gao 2014).
Enhanced activity of the selinexor/dexamethasone combination was also observed in two xenograft models of human multiple myeloma. The addition of dexamethasone to selinexor enhanced activity (86%) relative to selinexor alone.

In summary, the combination of selinexor and dexamethasone is synergistic *in vitro* and *in vivo* in multiple myeloma cell cytotoxicity assays through increased nuclear localization of GR and amplified GR transcriptional activity. Selinexor has also shown additive or synergistic activity when combined with other multiple myeloma drugs including proteasome inhibitors (Turner 2014; Tai 2014),[27] topoisomerase II inhibitors,[27] and lenalidomide (data on file). Taken together, these studies demonstrate that SINE compounds are active anti-myeloma compounds that cause decreased cell viability, increased apoptosis, and cell cycle arrest in vitro and potent inhibition of multiple myeloma tumor growth *in vivo*, and that the addition of dexamethasone can augment these effects.

Based on the activity and tolerability of selinexor as well as preclinical synergy with melphalan, we hypothesize that **addition of selinexor to high-dose melphalan before autologous HCT for multiple myeloma will improve outcomes.**

3.0 Objectives

3.1 Primary Objectives

3.1.1 Primary objective for phase 1

To determine the RPh2D/maximum tolerated dose (MTD) of conditioning regimen of selinexor plus high-dose melphalan for autologous HCT

3.1.2 Primary objective for phase 2

To assess complete response (CR) conversion rate at 3 months post autologous HCT.

3.2 Secondary Objectives

- To estimate overall response rate (ORR) at 3 months post autologous HCT
- To estimate progression-free survival (PFS) at 2 years
- To estimate overall survival (OS) at 2 years
- To evaluate the cumulative incidence of engraftment post autologous HCT
- To assess minimal residual disease (MRD) with PET scan, bone marrow flow cytometry and/or immunoglobulin gene sequencing at 3 months after autologous HCT (exploratory endpoint)

4.0 Study Population

4.1 Inclusion Criteria

- Patients 18 years of age or older with histologically confirmed multiple myeloma
- Achieving partial response (PR) or very good partial response (VGPR) with systemic chemotherapy
- Received less than 4 lines of anti-myeloma therapy.
- Karnofsky performance status of $\geq$70%
- Organ function:
    a) Pulmonary: adjusted DLCO, forced expiratory volume in 1 second (FEV1), and forced vital capacity (FVC) $\geq$50% of predicted value (corrected for hemoglobin)
    β) Cardiac: left ventricular ejection fraction (LVEF) $\geq$45%
    c) Hepatic: total bilirubin ≤ 2 mg/dL; serum transaminases less than two times the institutional upper limit of normal (< 2 x ULN)
    d) Renal: creatinine clearance $\geq$40 mL/min, estimated or calculated
- Signed informed consent form in accordance with institutional policies prior to the initiation of high-dose therapy

4.2 Exclusion Criteria

- Non-secretory multiple myeloma
- Patients who achieved complete response (CR) prior to autologous HCT
- Central nervous system (CNS) involvement
- Patients with uncontrolled bacterial, viral or fungal infections

- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Patients with prior malignancies within the last 5 years except resected basal cell carcinoma or treated cervical carcinoma *in situ*.
- Female patients who are pregnant (positive β-HCG) or breastfeeding
- Patients who have received other investigational drugs within 14 days prior to screening
- Prior autologous or allogeneic HCT
- Prior organ transplant or autoimmune disease requiring immunosuppressive therapy

5.0 Research Design

5.0.1 Phase 1 study

A phase 1 study of selinexor+ high-dose melphalan will be conducted in patients with multiple myeloma who undergo autologous HCT. The trial aims to determine the RPh2D/maximum tolerated dose (MTD) of 3 dose levels of selinexor given in combination with high-dose melphalan.

Eligible multiple myeloma patients will receive high-dose melphalan plus selinexor followed by autologous hematopoietic cell transplantation (see Table 5). A cohort of 3-6 patients will be enrolled to each dose of selinexor, at 40 mg, 60 mg and 80 mg dose levels. Based on the half-life of selinexor (approximately 5 to 7 hours), selinexor will be given orally 2 to 3 hours prior to melphalan IV infusion in order to achieve adequate concentration at the time of maximum melphalan exposure. Dexamethasone PO (or IV) daily (on days -3 (12 mg), -2 (12 mg) and -1 (20 mg)) and fosaprepitant at 150 mg IV on days -3 and -2 will be given to patients as an antiemetic. Patients will be enrolled sequentially to each dose cohort in a traditional 3+3 design.

Table 5. Selinexor plus high-dose melphalan

	Day -3	Day -2	Day -1	Day 0
Dexamethasone PO (or IV) daily (prior to selinexor)	(12 mg) X	(12 mg) X	(20 mg) X	
Selinexor PO daily x 2 days (given 2-3 hours prior to melphalan)	**X**	**X**		
Fosaprepitant 150 mg IV daily	X	X		
Melphalan 100 mg/m^2 IV over 30-45 minutes	X	X		
PBSC infusion				X

5.0.2 Dose escalation schema (Phase 1)

In prior clinical studies, selinexor was administered at between 3 mg/m^2 and 70 mg/m^2 twice weekly as single agent and 40 mg/m^2 weekly (starting dose) was explored in a combination

regimen. There are no available clinical data on combination with high-dose melphalan at this time. Based on tolerability of single agent up to 40 mg/m^2 twice weekly, we expect that the starting dose level of 40 mg PO flat dose (~25 mg/m^2) (daily for 2 days) will be acceptable for combination with high-dose melphalan.

Table 6. Dose escalation of selinexor

Dose level	Selinexor PO daily x 2 doses	Number of patients
1	40 mg	3-6
2	60 mg	3-6
3	80 mg	3-6

5.0.3 Phase 2 study

Based on the MTD dosing and examining the totality of available data from phase 1 portion of the study, RP2D will be determined. Once RP2D/MTD of selinexor with high-dose melphalan is established, patients will be sequentially enrolled to phase 2 study at the RP2D/MTD dose. The conditioning regimen schedule will be the same as phase 1 study (please refer to Table 5).

5.1 Pre-Transplant Evaluation

All patients will undergo a vital organ testing (VOT) per BMT standard to determine their eligibility for autologous HCT and subsequent study eligibility. The subject's multiple myeloma diagnosis and stage at original diagnosis according to the criteria of Durie and Salmon and/or International Staging System when available. Subjects who meet eligibility criteria will be enrolled into the study, and will be assigned an identification number. VOT and myeloma disease assessment will be performed within 30 days from the scheduled autologous hematopoietic cell collection per BMT standard (Table 4).

5.2 Stem Cell Mobilization and Collection

Patients will receive granulocyte colony-stimulating factor (G-CSF) and have collection of CD34$^+$ peripheral blood stem cells per BMT standard. Administration of plerixafor will be performed based on institutional standards in applicable patients. A minimum of 2 x 10^6 CD34$^+$ peripheral blood stem cells per kilogram of patient's body weight must be collected in order to proceed with autologous transplant. The stem cells will be cryopreserved and stored in the Cell Core Facility until the day of transplant.

5.3 High-Dose Chemotherapy Followed by Autologous HCT

Patients will receive the following pre-transplant conditioning regimen:

Day -3 Selinexor orally
Melphalan 100 mg/m^2 intravenously over 30-45 minutes
Dexamethasone 12 mg PO or IV

Day -2 Selinexor orally
Melphalan 100 mg/m^2 intravenously over 30-45 minutes
Dexamethasone 12 mg PO or IV

Day -1	Dexamethasone 20 mg PO or IV
Day 0	Autologous peripheral blood hematopoietic cells rescue with a minimum of 2 million $CD34^+$ cells per kilogram of body weight

5.4 Supportive Care

Patients will receive prophylactic antibiotics and antiemetics following the institutional standards. All patients will receive 5-HT3 antagonists (ondansetron 8 mg or equivalent) daily from day -3 to day -1. Fosaprepitant will be given at 150 mg IV on days -3 and -2. If fosaprepitant cannot be used, aprepitant may be used at 125 mg PO on day -3, 80 mg PO on day -2 and -1. Standard appetite stimulants including megestrol acetate (Megace™) 160 – 400 mg PO daily and as recommended by institutional and/or National Comprehensive Cancer Network [NCCN] guidelines are allowed. Dronabinol (Marinol™) may be considered. Granulocyte colony-stimulating factor (G-CSF) will be given at 5 μ/kg subcutaneously daily from day +7 until absolute neutrophil count (ANC) > 1500 per the institutional standards. For specific guidance on supportive care and dose modifications for selinexor-related adverse events, including citations for NCCN fatigue, antiemesis and anorexia/cachexia guidelines, please see Appendix IX.

5.5 Post-Transplant Monitoring

Patients will be followed as per the institutional protocol for autologous transplant. During the peri-transplant period, CBC will be performed daily (until engraftment) to assess engraftment and potential graft failure. Chemistry profile will be obtained at least twice weekly for toxicity assessment (for the first 2 weeks). Approximately 90 days following the autologous transplant, a full history and physical examination, SPEP with immunofixation, serum quantitative immunoglobulin, 24-hour UPEP with immunofixation, serum free light chains, and complete skeletal survey (X-ray) will be performed. Bone marrow aspirate and biopsy will be repeated at day +90 to assess marrow involvement by multiple myeloma. Beyond 3 months from the time of transplant, patients will be followed under the long-term follow up study, MCC12567 ("A long-term follow-up study for subjects previously treated with high-dose chemotherapy (+/- radiotherapy) followed by a blood-forming cell transplant and/or cellular therapies").

5.6 Toxicity Assessment

Toxicity data will be collected at least weekly until day +28 (± 3 days), then at day +90 (± 3 days). Toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

5.6.1 Ophthalmologic examination

A complete ophthalmologic assessment will be conducted on all patients by an optometrist or ophthalmologist at screening and if clinically indicated during the study. The full ophthalmologic assessment at Screening Visit #1 and Final Study Visit includes

- *Prior to dilation:* best corrected visual acuity (Snellen chart or ETDRS chart) and slit lamp examination including tonometry

- *Following dilation:* fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the exam, cataract will be graded using a Grade 1-4 scale (Appendix IX).

5.6.2 Definitions of Dose-limiting toxicity (DLT)

In the phase 1 portion of the study, dose-limiting toxicity (DLT) observation period is defined as until day +28 (see section 7.01). The definition of DLT includes any treatment-related death and grade 3-5 non-hematologic toxicity (graded based on the CTCAE version 5.0) not clearly resulting from the underlying malignancy (i.e., myeloma) during the DLT window of until day +28. Grade 3 or 4 hematological toxicities are considered expected due to autologous HCT and will not be considered DLT.

Following toxicities are excluded from DLT definition.

a. Alopecia
b. Grade 3 fatigue, asthenia, fever, anorexia, or constipation
c. Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
d. Grade 3 mucositis
e. Infection, bleeding, or other expected direct complication of cytopenias due to active underlying disease (i.e., myeloma) and autologous HCT
f. Grade 3 or 4 isolated electrolyte abnormalities (i.e., those occurring without clinical consequence) that resolve, with or without intervention, to < grade 2 levels in < 72 hours will not be considered DLT.

Though it is beyond the specified DLT window, grade 4 neutropenia, anemia or thrombocytopenia beyond day +42 (until day +90 (± 7 days) will be monitored and reported.

5.7 Response Assessment

Multiple myeloma response will be assessed prior to autologous HCT and post HCT at day +90 using the International Myeloma Working Group consensus criteria.[62] Multiple myeloma response beyond day +90 will be assessed periodically until disease progression per the institutional standards and under the long-term follow up study, MCC12567 ("A long-term follow-up study for subjects previously treated with high-dose chemotherapy (+/- radiotherapy) followed by a blood-forming cell transplant and/or cellular therapies").

Table 7. Study Calendar

Required Studies/Testing*	Prior to high-dose chemotherapy (within 30 days of scheduled stem cell collection)	Day -3	Day -2	Day -1	Day 0	Day +1 until engraftment[5] (daily)	Day +14 (± 3 days)	Day +21 (± 3 days)	Day +28 (± 3 days)	Every 2 weeks (± 4 days) until day +90	Day +90 after HCT (± 7 days)
History and Physical Examination	X[1]	X	X	X	X	X	X	X	X		X
Phone contact for toxicity assessment										X	
Informed consent	X										
Administration of high-dose melphalan and selinexor		X	X								
Administration of dexamethasone		X	X	X							
Adverse events (AEs)/toxicity assessment		X	X	X	X	X	X	X	X	X	X
Hematopoietic cell transplantation					X						
CBC with Differential,	X	X	X	X	X	X	X	X	X		X

PLT											
CMP	X	X[3]			X[3]	X[3]	X	X	X		X
BMP			X[3]	X[3]	X[3]	X[3]					
Serum Pregnancy Test[2]	X										
Karnofsky Performance Score	X										
Creatinine clearance assessment	X										
LV Ejection Fraction Assessment	X										
Pulmonary function test	X										
Skeletal Survey	X[9]										X[10]
Bone Marrow Aspirate and Biopsy (including flow cytometry[11], cytogenetics and FISH)	X[4]										X
Research bone marrow aspirate and biopsy [7]	X[6]										
Serum Immunoglobulin Levels, SPEP/IFE, UPEP/IFE, serum free light chains, beta-2 microglobulin	X										X
Ophthalmologic exam[8]	X										
Body surface area	X										
Concomitant medications	X										

[1]Height and weight
[2]Female of childbearing potential defined as a sexually mature female who: (1) has not undergone a hysterectomy or bilateral oophorectomy; or (2) has not been naturally postmenopausal for at least 24 months (i.e., has had menses at any time in the preceding 24 consecutive months).
[3]CMP will be obtained twice weekly from day -3 until engraftment. BMP will be obtained on other days.

[4]Commercially available bone marrow aspirate gene expression profiling (MyPRS™ by Signal Genetics) will be performed from the bone marrow aspirate.
[5]Median time for neutrophil engraftment is day+12.
[6]Obtained at the time of standard bone marrow biopsy/aspirate for pre-HCT disease assessment.
[7]Research bone marrow aspirate and core biopsy samples may be obtained at the time of myeloma relapse or progression after autologous HCT. Samples will be obtained at the same time with standard bone marrow aspirate and biopsy.
[8]Full ophthalmological exam will be conducted on all patients by an optometrist or an ophthalmologist at screening. If clinically indicated, it may be requested subsequently per the discretion of treating physician. The full ophthalmologic examination includes:

- *prior to dilation:* best corrected visual acuity (Snellen chart or Early Treatment Diabetic Retinopathy Study (ETDRS) chart) and slit lamp examination including tonometry
- *following dilation:* fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the exam, cataract will be graded using a Grade 1-4 scale (Appendix IX).

[9]Consider positron emission tomography (PET) scan as disease staging if clinically indicated
[10]PET scan for disease assessment and minimal residual disease (MRD) assessment may be considered if it was positive prior to autologous HCT.[11]Minimal residual disease (MRD) assessment with flow cytometry and/or immunoglobulin gene high-throughput sequencing will be performed as part of the standard of care.

6.0 Correlative Studies

Correlative studies will be performed using patient bone marrow aspirates and bone marrow biopsies collected at the time of pre-HCT evaluation (< 6 weeks prior to the initiation of high-dose chemotherapy), and at the time of progression in all patients. The number of patients for the bone marrow correlative studies could be up to 40. Buffy coat fractions from bone marrow aspirates (20-30 mL in 50 cc heparinized syringe) will be isolated by CPT tube centrifugation. CD138/light chain antibody staining and flow cytometry will be used to determine the percent plasma cell population. Samples containing approximately 5% or more plasma cells (~7.5 $x10^6$ plasma cells in a 30 mL aspirate) will be necessary to perform all correlative studies.

Due to the anticipated low number of plasma cells (patients must be a PR or VGPR to enter the trial), experiments will be prioritized to first look at specific protein biomarkers by intracellular staining, second, to examine apoptosis (EC50 data) as a biomarker for response to therapy, and third, any remaining samples will be used for RNA-Seq and whole exome sequencing. Based on the preliminary observation, microscopic analysis for intracellular localization and EC50 will be performed at the time of relapse or progression due to limited number of plasma cells prior to HCT.

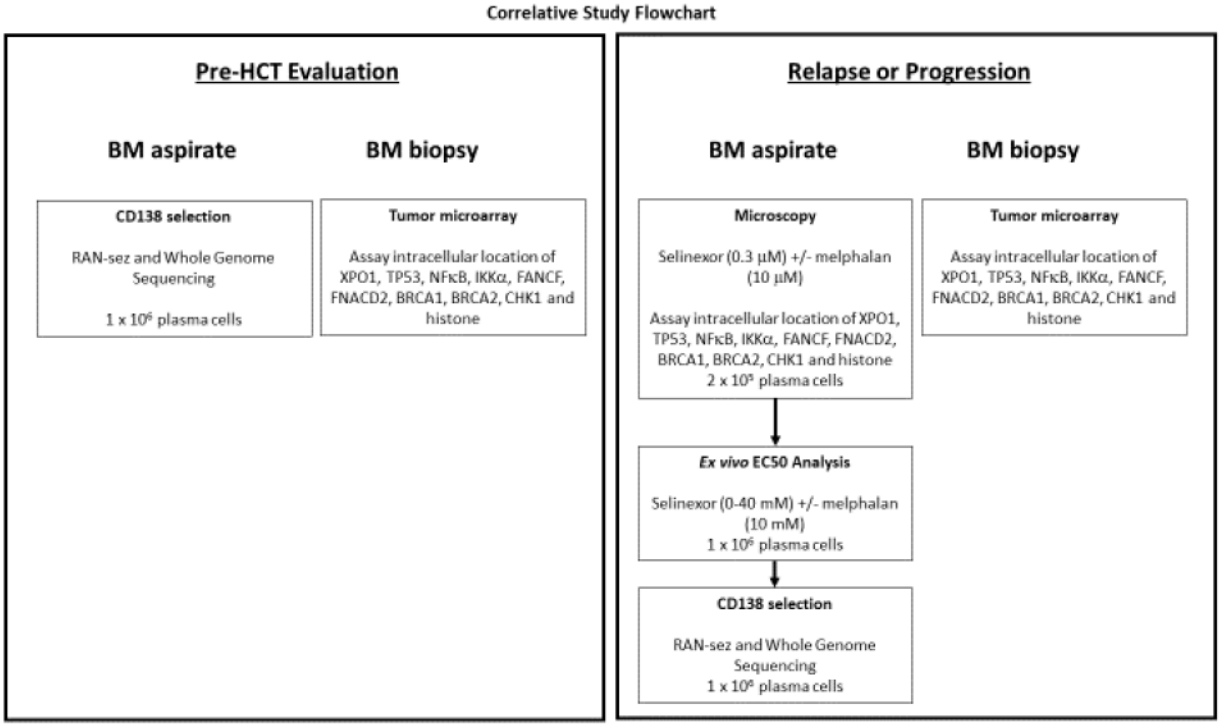
Assays for protein biomarker expression and intracellular location will be done using immunofluorescence microscopy. Biomarkers assayed include XPO1, TP53, IKKα, FANCF, FANCD2, FANCD1, BRCA1, BRAC2 and CHK1. Additional biomarkers may be added during the study. Data analysis will be performed using Tissue Studio® 4.0 for qualitative digital pathology (Definiens, Inc).These analyses will require 3.75 x 10^6 mononuclear cells (need a minimum of 2 $x10^5$ plasma cells).

EC50 data will be generated by treating patient mononuclear cells *ex vivo* with serial diluted selinexor (0, 0.156, 0.625, 2.5, 10, 40 μM) +/- melphalan (10 μM) for 20 hours and apoptosis assayed by activated-caspase 3 in the CD138/light chain double positive myeloma cell population by flow cytometry. EC50 data will be generated from the apoptosis values for selinexor alone and if there is sufficient sample, selinexor + melphalan. Approximately 2 $x10^7$ mononuclear cells are required for the EC50 assay (need a minimum of 1 x 10^6 plasma cells).

If there is sufficient patient bone marrow aspirate remaining, plasma cells will be isolated by CD138 magnetic bead columns and the plasma cells assayed by RNA-Seq and whole exome sequencing. A minimum of 1 x 10^6 plasma cells will be required for these assays.

Tissue microarrays will be made from patient core biopsies, plasma cells identified by light-chain antigen staining and assayed by immunofluorescence microscopy for expression and intracellular location or XPO1, TP53, NFkB, IKKα, FANCF, FAND2, BRCA1, BRCA2 and CHK1. Additional biomarkers may be added during the study.

In addition, we will attempt to obtain bone marrow aspirates and biopsies at the time of relapse or progression of myeloma after autologous HCT to evaluate aforementioned correlative studies. The samples will help to evaluate the changes in protein expression relative to the pre-HCT and during the treatment that may be related to drug resistant to melphalan plus selinexor.



7.0 Statistical Considerations

7.01 Dose escalation rule (3+3 for phase 1 design)

The study will utilize typical 3+3 phase 1 design. Patients will be enrolled in cohorts of 3 patients to each dose level. Grade 4 oral mucositis, grade 4 diarrhea, and ANY grade 4 non-hematologic toxicities per CTCAE version 5.0 would be considered DLT for high-dose melphalan followed by autologous HCT (please see section 5.6.2 for detailed DLT definitions). Grade 3 or 4 hematological toxicities are considered expected due to autologous HCT. If no DLT events are noted within a cohort by day +28 after autologous HCT, then the next cohort of 3 patients will be enrolled at the next dose level. Dose escalation will be stopped if ≥ 2 DLT events occur at a selinexor dose level, with that dose being declared as the maximum administered dose. If a single DLT event is noted, then 3 additional patients will be entered at that selinexor dose level, and dose escalation will proceed only if no additional DLT events (i.e., 1 of 6) are noted. If 1 or more of these 3 additional patients have DLT, then the dose escalation will be stopped, and this selinexor dose will be declared the maximally administered dose. The maximum tolerated dose (MTD) is defined as the highest dose level in which 1 or less of 6 patients experiences a DLT. If a full cohort of 3 patients is entered at a given selinexor level without the observation of DLT, then dose escalation to the next level will be permitted.

7.02 Toxicity assessment

Patients will be followed prospectively for adverse events from the start of conditioning regimen (day -3) through day +21, and then at day +90 from autologous HCT. Toxicities will be assessed on a daily basis starting from day -3 until engraftment; thereafter, toxicities will be assessed weekly until day +21 (± 3 days), then at day +90 (± 7 day). After day +28, patients will be followed by phone every 2 weeks to monitor toxicities (until day +90 for on-site evaluation). Toxicities will be graded according to the National Cancer Institute CTCAE version 5.0.

7.1 Endpoint Definitions

Hematologic engraftment

- Neutrophil engraftment will be defined as the first day the absolute neutrophil count (ANC) is ≥ 500/μL for 3 consecutive days.
- Platelet engraftment will be defined as the first day the platelet count is ≥ 20,000/μL for 7 consecutive days without transfusion.
- Engraftment will be considered successful (not delayed) if the time to neutrophil recovery is ≤ 14 days and the time to platelet recovery is ≤ 30 days.

7.2 Toxicity/Early Stopping Rule

Toxicity will be graded using CTCAE v5.0. The patients will be enrolled sequential to each dose level. Based on the expectedly low transplant related mortality with high-dose melphalan, there will be a stopping rule in place to carefully examine the association between the toxicities and study drug. If there are greater than or equal to 2 patients experiencing non-hematologic grade 4 and/or 5 toxicity at any stage of the trial, we will thoroughly examine the events while the trial is halted for accrual. If no associations are found by PMC, then the study will be resumed.

Of note, higher doses of melphalan followed by autologous HCT have been investigated in conjunction with other agents. High-dose melphalan at 280 mg/m^2 with either amifostine (cytoprotective agent) or palifermin (recombinant keratinocyte growth factor) resulted in severe cardiac toxicities.[63,64] The current study will use widely accepted standard high-dose melphalan at 200 mg/m^2. In the Intergroupe Francophone du Myélome (IFM) 9502 study, the following grade 3-4 toxicities were reported with high-dose melphalan at 200 mg/m^2 in 142 patients: grades 3-4 cardiac toxicity 0.7%; grades 3-4 mucositis 30%; grades 3-4 pulmonary toxicity 1.4%; grades 3-4 renal toxicity 2.1%; grades 3-4 liver toxicity 0.7%.[65] Transplant-related mortality at day +100 for high-dose melphalan is generally considered to be at 1% in 2005 to 2010.[66]

7.3 Sample Size Justification

7.3.1 Phase 1 portion

Maximum of 3 dose levels will be evaluated in this portion, and up to 18 patients may be enrolled to phase 1 portion of the study. Patients with either PR or VGPR will be eligible for phase 1 portion and actual number of patients may depend on the toxicity of the regimen.

7.3.2 Phase 2 portion

From 2010 to 2011, 175 patients received high-dose melphalan at 200 mg/m^2 followed by autologous HCT at Moffitt Cancer Center. Based on the number of CR at 3 months after autologous HCT (Table 8), we expect that the baseline CR conversion rate for patients in PR and VGPR at 3 months would be 9% and 29%, respectively, as illustrated in Table 8. The overall conversion rate for VGPR or PR patients is 16% when ~35% of those (42/119) are VGPR. The efficacy of the combination therapy will be evaluated by using Simon's minimax design. We will consider 16% not warranting further study and 36% CR conversion rate as the alternative hypothesis of the study. With 10% one-sided type I and II error rate, 17 evaluable patients will be investigated in the first phase (including the MTD cohort from phase 1 (n=6)). If 2 or less patient achieves CR at 3 months, the study will be terminated early. Otherwise, 17 additional evaluable patients (a total of 34 evaluable patients) will be enrolled. If 9 or more of 34 patients (26%) achieve CR at 3 months post-HCT, then the null hypothesis is rejected and the regimen will be considered promising for further study. If the drug combination is actually not effective, there is a 0.079 probability of concluding that it is. If the drug combination is actually effective, there is a 0.098 probability of concluding that it is not. Note that 6 VGPR and 11 PR patients (17 evaluable) at each stage should be enrolled to meet the proportion of VGPR patients in Table 8. A total of 38 patients (including the MTD cohort of phase 1 patients (n=6)) will be accrued in phase 2 to account for 10% of (potential) non-evaluable patients. A patient who does not receive the conditioning regimen as specified in the protocol, or comes off study due to non-treatment related death, or withdraws consent due to any reason other than toxicity is defined as non-evaluable for the efficacy of the regimen and will be replaced. Per intention-to-treat (ITT) approach, a patient who dies of disease progression or experiences a DLT (prior to day +90) is evaluable and considered a failure to conversion to CR. As noted above, MTD cohort from phase 1 will be included in the efficacy analysis.

Table 8. Myeloma responses before and after autologous HCT (from MCC experience, see text)

Disease status at HCT	Number at HCT	Number of patients in CR at 3 months	CR conversion rate (All)	CR conversion rate for VGPR/PR
CR	26	26	-	-
VGPR	42	12	29%	16%
PR	77	7	9%	
SD	25	1	4%	-
Progression/relapse	5	1	(20%)	-

7.4 Statistical Analysis Plan

7.4.1 Primary endpoints

The primary endpoint of the phase 1 portion is to determine the MTD which is the highest dose level at which 1 or less of 6 patients experience a DLT. In phase 2, the CR conversion rate will be estimated and the lower limit of one-sided 90% confidence interval will be computed using Atkinson and Brown method, which accounts for the nature of two-stage design.[67]

7.4.2 Secondary endpoints

Time-to-event data such as OS, PFS, and cumulative incidence of relapse/progression, non-relapse mortality, and cumulative incidence of engraftment will be measured from Day 0. OS and PFS will be estimated using the Kaplan-Meier method[68] and time-to-event data with competing risks will be computed using Gray's method.[69] Relapse/progression is considered as competing risk of non-relapse mortality, and relapse/progression and death are the competing risks of engraftment. The association between potential predictors and time-to-event data with or without competing risks will be explored by the Cox proportional hazards regression model and Fine and Gray method,[70] respectively.
We anticipate that VGPR patients have limited number of plasma cells in the marrow and that at least 22 PR patients' samples will be used for correlative studies. In general, 50% of myeloma patients progress after autologous HCT at approximately 3.5 years. Assuming that 40% to 60% of patients progress when the final data analysis is conducted, 9-13 paired samples will achieve 82-95% power to detect an effect size (mean difference divided by standard deviation) of 1.1 with a two-sided significance level of 5%.
No multiplicity adjustment is planned for secondary endpoints. A two-sided p-value of < 0.05 will be considered significant. Beyond 3 months from the time of transplant, patients will be followed under the long-term follow up study, MCC12567 ("A long-term follow-up study for subjects previously treated with high-dose chemotherapy (+/- radiotherapy) followed by a blood-forming cell transplant and/or cellular therapies").

Correlative study:
Bone marrow aspirates and biopsies will be obtained at the pre-HSCT evaluation (T1) and at disease progression (T2). The change of each biomarker (e.g., XPO1, topo IIβ, Fanconi pathway, homologous recombination, CHK1, p53, CRM1, NFκB, etc.) from T1 to relapse/progression (T2) will be examined by the paired t-test. An appropriate data transformation such as log-transformation may be considered to apply parametric analytic methods. In addition, we will also examine if the time-to-event endpoints are associated with the change in each biomarker using Cox regression and Fine and Gray method.

8.0 Reporting of Serious/Unexpected Adverse Events

8.1 Adverse Event Definition

8.1.1 Adverse event definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

8.1.2 Serious adverse event definition

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.

- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events 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 outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Hospitalization that do not meet this criteria are:

- reasons described in the protocol, e.g., drug administration, protocol-required testing
- social reason in the absence of an AE
- surgery or procedure planned prior to entry into the trial

8.2 Procedures for AE and SAE Reporting /Serious Adverse Event (SAE)

Grade 1 and 2 events do not need to be recorded unless corrective action is required or the event is deemed clinically significant by the treating physician. Non-hematologic grade 3 and grade 4 events must always be recorded as adverse events regardless of corrective action or whether or not the investigator deems them clinically significant. All serious adverse events must be reported to IRB. This includes any event that occurs during the participation of the trial regardless of associated therapy, severity or relationship.

8.2.1 Adverse drug reaction reporting

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. All appropriate treatment areas have access to a copy of the CTCAE Version 5.0. All serious 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 serious adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all grade 4 non-hematologic 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.

8.2.2 Investigator reporting responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (unrelated, unlikely, possible, probable and definite), 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.

8.2.3 Report of adverse events to the Institutional Review Board

The Principal Investigator is required to notify the Institutional Review Board (IRB) of a serious adverse event according to institutional and IRB policies. All serious, related adverse events (and unanticipated) will be reported and documented on forms as required and submitted according to institutional and IRB policies.

8.2.4 Investigator reporting to the FDA

All SAEs must also be reported to Moffitt Cancer Center in order for them to comply with their responsibility for oversight of the project and reporting to the FDA as needed.

Moffitt Cancer Center will be responsible for all communication with the FDA. ALL SAEs that require reporting to the FDA, regardless of the site of occurrence, will be reported by Moffitt Cancer Center. 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 Moffitt Cancer Center. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Moffitt Cancer Center 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.

The Investigator must keep copies of all AE information, including correspondence with the FDA and the IRB on file.

8.2.5 Reporting to Karyopharm (company holding cross-referenced IND)

In addition to reporting to the FDA and IRB, Sponsor-Investigator (Moffitt) will forward completed SAE and pregnancy forms to representatives of the Karyopharm Therapeutics. All serious unexpected suspected adverse reactions (SUSARs) will be reported to Karyopharm to the following email address (PVG@karyopharm.com) no later than 15 days from becoming aware of the event.

8.2.6 Monitoring of adverse events and period of observation

All serious adverse events and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until 30 days after the event.

9.0 Administrative Requirements

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at Moffitt Cancer Center after IRB approval has been obtained. The protocol, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

9.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

9.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from FDA, or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records

and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from IRB prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB. The investigator will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

9.6 Protocol Monitoring Plan

The monitoring of the study will be conducted by the Institutional Protocol Monitoring Committee (PMC). The PMC monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

The PI shall provide a statistical report of the study's progress and summary of adverse events and deviations of the study and the associated risk of the study.

The PI is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

The PI will have primary responsibility for ensuring that the protocol is conducted as approved by the Scientific Review Committee (SRC) and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

The Corporate Compliance Office will coordinate the internal audits of the trial. The audit procedure is a formal, comprehensive, source document review of all clinical trials.

Corporate compliance shall provide a report to the PMC of internal audit findings for PMC action. For cause audits will be discussed during an executive session of the PMC. Only members (voting and ex-officio) may attend this session.

9.6.1 Internal monitoring

Data will be captured in Oncore, Moffitt's Clinical Trial Database. Regulatory documents and case report forms will be reviewed routinely by the Moffitt Cancer Center Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to Moffitt Cancer Center Monitoring Policies.

9.6.2 Institutional Review Board (IRB)

The trial will not be initiated without approval of the IRB. All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration (FDA). A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

9.6.3 Monitoring of the study and regulatory compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is the database of record for all CRF entries and will be verified with source documentation. The review of medical records within PowerChart will be done in a manner to assure that patient confidentiality is maintained.

9.6.4 Protocol modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require IRB approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the case report form and the source documentation.

9.6.5 Patient privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. The FDA may also request access to all study records, including source documentation for inspection.

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Appendix I

Karfnosky Performance Score

Percentage	
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent
20	Very sick, hospitalization necessary, active supportive treatment necessary
10	Moribund, fatal processes, progressing rapidly
0	Dead

Reference:

Karnofsky DA: Meaningful clinical classification of therapeutic responses to anti-cancer drugs. Editorial: *Clin Pharmacol Ther* 2:709-712, 1961.

Appendix II

IMWG uniform response criteria by response subcategory for multiple myeloma

Response subcategory	*Response Criteria*
Stringent CR	• CR as defined below plus normal FLC ratio and absence of clonal plasma cells in bone marrow by immunohistochemistry or 2- to 4-color flow cytometry
CR	• Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and ≤ 5% plasma cells in bone marrow
VGPR*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 hours
PR	• ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours • If the serum and urine M-protein are not measurable, a decreased ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, or PD
PD[+]	• Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), and/or • Urine M-component (absolute increase must be ≥ 200 mg/24 hours), and/or • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing 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 proliferative disorder

*Clarifications to IMWG criteria for coding CR and VGPR in patients whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

[+]Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

Reference:

Rajkumar SV, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1.*Blood* 2011;117:4691-4695

Appendix III

Criteria for Symptomatic Multiple Myeloma

All three required:

1. Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma
2. Monoclonal protein present in the serum and/or urine[a]
3. Myeloma-related organ dysfunction (1 or more)[b]
    - (C) Calcium elevation in the blood (serum calcium > 10.5 mg/L or upper limit of normal)
    - (R) Renal insufficiency (serum creatinine > 2 mg/dL)
    - (A) Anemia (hemoglobin < 10 g/dL)
    - (B) Lytic bone lesions or osteoporosis[c]

*Note: These criteria identify Stage IB and Stages II and III A/B myeloma by Durie-Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[a]If no monoclonal protein is detected (nonsecretory disease), then ≥30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
[b]A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma-related.
[c]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then ≥30% plasma cells are required in the bone marrow.

Reference:

*Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *The Hematology Journal* 2003;4:379-398

Appendix IV

Toxicities and adverse events will be scored using **Common Terminology Criteria for Adverse Events (CTCAE)** Version 5.0 by U.S. Department of Health and Human Services which was published on November 27, 2017.
A copy of the CTCAE version 5.0 can be downloaded in PDF format from the following NCI websites. All appropriate treatment areas have access to a copy of the CTCAE version 5.0.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Appendix V

New York Heart Association (NYHA) Classification

A functional and therapeutic classification for prescription of physical activity for cardiac patients.

Class I:	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV:	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Appendix VI

Body Surface Area Calculation

Body surface area (BSA) should be calculated using the DuBois formula that yields the following result in meters squared (m^2):[1]

$$BSA\ (m^2) = Wt\ (kg)^{0.425} \times Ht\ (cm)^{0.725} \times 0.007184$$

Reference:

1. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Medicine*. 1916;17:863-871.

Appendix VII

Drug Formulation, Preparation and Administration

Product: Selinexor (KPT330)

Classification: cell biological modifier: apoptosis inducing agent

Mechanism of action: selinexor is a selective inhibitor of nuclear export (SINE) that specifically blocks nuclear export by slowly-reversible covalent binding to XPO1 (also called CRM1) protein.

Formulation:
Selinexor study medication will be in the form of a coated, immediate release tablet for oral administration. Selinexor tablets will be supplied in either bottles or blister packs. Tablets will be provided in two coated tablet strengths: 10 and 25 mg. When available, 20 mg strength tablets will be provided in

Labeling:
Selinexor tablets will be labeled in accordance with current ICH, GCP, FDA and specific national requirements.

Storage:
Selinexor tablets will be stored at room or refrigerated temperatures between 41° to 86°F or 5° to 30°C (room temperature is preferred) in a secured area with access restricted to the site staff pharmacist or designee(s). The tablets should not be stored at freezer temperatures or frozen. The 10 and 25 mg tablets will be supplied in 50 count bottles. The 20 mg tablets will be supplied in blister packs.

Drug Accountability:
Study drugs 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 medications 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.

Selinexor drug information:
Selinexor will be taken within 30-minutes of solid food consumption together with ≥ 120 mL (8 ounces) of water.

Potential Risks:
Selinexor is currently in clinical development and has not been approved by the FDA for commercial use. Human experience with selinexor has been evaluated in > 550 patients (as of December 15th, 2014) 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.

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

In the ongoing clinical study, the most common AEs suspected to be related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and thrombocytopenia. Virtually all 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 thrombocytopenia, hyponatremia, and a decrease in red blood cells. The majority of these have been mild to moderate. Please refer to the current Selinexor/KPT-330 Investigator's Brochure for the most current information.

One patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 4 doses of selinexor at 85 mg/m^2 BSA twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Since the time of the initial reported event, this patient is recovering and both her speech and mobility have recovered to near baseline over ~6 weeks. No other patients have reported such symptoms to date.

Reproductive Risks:
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 that patients understand the need to use birth control while on this study. 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.

Side effects of selinexor (KPT-330 based on Investigator's Brochure version 9.0 dated 8/13/2019:

Very common side effects (≥ 10%):

- Nausea
- Fatigue and asthenia – loss of energy; weakness
- Anorexia
- Vomiting
- Diarrhea
- Dizziness
- Hyponatremia
- Dehydration
- Blurred vision
- Weight loss
- Dysgeusia
- Leukopenia/Neutropenia
- Thrombocytopenia
- Anemia
- Constipation
- Decreased appetite
- Abdominal pain
- Shortness of breath
- Cough
- Headache
- Difficulty falling sleep
- Pneumonia
- Low potassium
- Peripheral edema
- High blood sugar

Common side effects (≥ 1-10%):

- Dry mouth
- Creatinine increased
- Febrile neutropenia
- Syncope
- Confusion
- Sepsis
- Rash
- Eye disorders including cataract, dry eye, visual impairment, seeing flashes of light
- Night sweats
- Stomatitis
- Dyspepsia
- Chills
- Hypotension
- Hypertension

- Tachycardia
- Nosebleed
- Electrolyte imbalances (low phosphate; low magnesium; low calcium; high potassium)
- Low albumin
- Peripheral neuropathy
- Decrease in lymphocytes
- Elevated liver enzymes
- Elevated pancreatic znzymes
- Muscle weakness
- Respiratory tract infection
- Pain in joints and muscles
- Malaise
- Muscle spasms
- Gait disturbance
- Hair loss
- Itching
- Depression
- Cognitive disorder
- Mental status changes

Uncommon side effects (> 0.1 – 1%):

- Cognitive disturbance
- Altered balance
- Tumor lysis syndrome
- Enterocolitis infectious
- Gastroenteritis
- Rhinovirus infection

Rare side effects (> 0.01 – 0.1%):

- Acute cerebellar syndrome – symptoms can include a sudden loss of coordination, balance, or slurred speech

Appendix VIII

Drug Formulation and Procurement

Melphalan Hydrochloride

Description and Pharmacology:

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-[bis(2-chloroethyl)amino]-*L*-phenylalanine. The molecular formula is C13H18Cl2N2O2 and the molecular weight is 305.20. The structural formula is: Melphalan is the active L-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the L-isomer. The racemic (DL-) form is known as merphalan or sarcolysin. Melphalan is practically insoluble in water and has a pKa_1 of approximately 2.5.

Melphalan for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. Melphalan for Injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and Water for Injection to a total of 10 mL. Melphalan for Injection is administered intravenously.

Clinical Pharmacology

Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicit appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

Pharmacokinetics: The pharmacokinetics of melphalan after IV administration has been extensively studied in adult patients. Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m^2) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 mL/min/kg after the first course, to 5.5 mL/min/kg after the third course, but did not decrease appreciably after the third course. Mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 mcg/mL, respectively. The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Serum albumin is the major binding protein, while α1-acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no

other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.

Formulation and Stability:
1. Melphalan for Injection must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5-mg/mL solution of melphalan. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.

2. **Immediately** dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45 mg/mL.

3. Administer the diluted product over a minimum of 15 minutes.

4. Complete administration within 60 minutes of reconstitution.
The time between reconstitution/dilution and administration of Melphalan should be kept to a minimum because reconstituted and diluted solutions of Melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of melphalanwith Sterile Diluent for melphalan. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolyzes every 10 minutes.

A precipitate forms if the reconstituted solution is stored at 5°C. DO NOT REFRIGERATE THE RECONSTITUTED PRODUCT.

Administration Precautions: As with other toxic compounds, caution should be exercised in handling and preparing the solution of melphalan. Skin reactions associated with accidental exposure may occur. The use of gloves is recommended. If the solution of melphalan contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product.

How Supplied:
Melphalan for Injection is supplied in a carton containing one single-use clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10-mL clear glass vial of sterile diluent (NDC 0173-0130-93).

Store at controlled room temperature 15° to 30°C (59° to 86°F) and protect from light.

Contraindications:

Melphalan should not be used in patients whose disease has demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.

Warnings:

Melphalan should be administered in carefully adjusted dosage by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use.

As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with Melphalan for Injection in most patients. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent dose of melphalan: platelet count, hemoglobin, white blood cell count, and differential. Thrombocytopenia and/or leukopenia are indications to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity. Dose adjustment on the basis of blood counts at the nadir and day of treatment should be considered.

Hypersensitivity reactions including anaphylaxis have occurred in approximately 2% of patients who received the IV formulation (see ADVERSE REACTIONS). These reactions usually occur after multiple courses of treatment. Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of volume expanders, pressor agents, corticosteroids, or antihistamines at the discretion of the physician. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

Carcinogenesis: Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was 19.5% for cumulative doses ranging from 730 to 9,652 mg. In this same study, as well as in an additional study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However, intraperitoneal (IP) administration of melphalan in rats (5.4 to 10.8 mg/m2) and in mice (2.25 to 4.5 mg/m^2) 3 times per week for 6 months followed by 12 months post-dose observation produced peritoneal sarcoma and lung tumors, respectively.

Mutagenesis: Melphalan has been shown to cause chromatid or chromosome damage in humans. Intramuscular administration of melphalan at 6 and 60 mg/m^2 produced structural aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

Impairment of Fertility: Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported.

Pregnancy: Pregnancy Category D. Melphalan may cause fetal harm when administered to a pregnant woman. While adequate animal studies have not been conducted with IV melphalan, oral (6 to 18 mg/m2/day for 10 days) and IP (18 mg/m2) administration in rats was embryolethal and teratogenic. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Precautions:
General: In all instances where the use of melphalan for Injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy or whose marrow function is recovering from previous cytotoxic therapy.

Dose reduction should be considered in patients with renal insufficiency receiving IV melphalan. In one trial, increased bone marrow suppression was observed in patients with BUN levels ≥30 mg/dL. A 50% reduction in the IV melphalan dose decreased the incidence of severe bone marrow suppression in the latter portion of this study.

Laboratory Tests: Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. At least 1 determination should be obtained prior to each dose. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anemia (see WARNINGS).

Adverse reactions (see Overdosage):
The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic: The most common side effect is bone marrow suppression. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported.

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive disease has been reported.

Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for Injection for myeloma (see WARNINGS). These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

Miscellaneous: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, allergic reaction, pulmonary fibrosis, and interstitial pneumonitis.

Overdosage

Overdoses resulting in death have been reported. Overdoses, including doses up to 290 mg/m^2, have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions, muscular paralysis, and cholinomimetic effects. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m^2). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Significant hyponatremia caused by an associated inappropriate secretion of ADH syndrome has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely. The principal toxic effect is bone marrow suppression. Hematologic parameters should be closely followed for 3 to 6 weeks. An uncontrolled study suggests that administration of autologous bone marrow or hematopoietic growth factors (i.e., sargramostim, filgrastim) may shorten the period of pancytopenia. General supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from plasma to any significant degree by hemodialysis or hemoperfusion. A pediatric patient survived a 254-mg/m^2 overdose treated with standard supportive care.

Drug Interactions:

The development of severe renal failure has been reported in patients treated with a single dose of IV melphalan followed by standard oral doses of cyclosporine. Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan may also reduce the threshold for BCNU lung toxicity. When nalidixic acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in pediatric patients.

Nursing Mothers: It is not known whether this drug is excreted in human milk. IV melphalan should not be given to nursing mothers.

Pediatric Use: The safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of melphalan for Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Appendix IX

Selinexor Dose Reduction and Supportive Care Guidelines

Toxicity will be graded according to NCI CTCAE, version 5.0; the therapy modifications described below are applied according to this severity grading.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay must be documented, including the respective reason.

Based on observations from the ongoing phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from ~6 mg/m^2 to ≥ 60 mg/m^2. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, if a patient experience selinexor related toxicities after the first dose (on day -3) and before the second dose (day -2), dose reductions will be allowed as described in Tables A1 and A2. Patients should also be treated aggressively with supportive care to reduce toxicities.

For all ≥ grade 3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Karyopharm Therapeutics Medical Monitor 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.

Table A1. Pre-specified Dose Modifications for Adverse Events Related to Selinexor

Dose Level	Dose of Selinexor
Dose level 1 (40 mg daily x2)	(1) Dose reduce to 20 mg on day -2 if grade 2 selinexor related AE* (2) Hold selinexor on day -2 if grade 3-4 selinexor related AE encountered
Dose level 2 (60 mg daily x2)	(1) Dose reduce to 30 mg on day -2 if grade 2 selinexor related AE* (2) Hold selinexor on day -2 if grade 3-4 selinexor related AE encountered
Dose level 3	1) Dose reduce to 40 mg on day -2 if grade 2 selinexor related AE* (2) Hold selinexor on day -2 if grade 3-4 selinexor related AE encountered

*Certain grade 2 selinexor related AEs may not require dose reduction. Additionally, some grade 3 selinexor related AEs allow continuation of treatment. Please refer to Table A2 for details.

Table A2 Supportive Care and Dose Adjustment Guidelines for Selinexor-Related Toxicities

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Fatigue (common)		
Grade 1	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status.	Maintain dose.
Grade 2	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. For additional support see NCCN guidelines[a].	Dose reduce for day -2 as described in Table A1.
Grade 3	See guidelines for Grade 2 fatigue.	Hold selinexor for day -2 as described in Table A1.
Anorexia or Weight loss		
Grade 1	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®).	Maintain dose.
Grade 2	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). For additional supportive care see NCCN guidelines[b].	Dose reduce for day -2 as described in Table A1
Grade 3	See guidelines for Grade 2 anorexia.	Hold selinexor for day -2 as described in Table A1.
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia.	Hold selinexor for day -2 as described in Table A1.
Nausea/ - acute (common)		
Grade 1	Insure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 2	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis[c].	Dose reduce for day -2 as described in Table A1
Grade 3	See guidelines for Grade 1 nausea For additional options see NCCN guidelines for antiemesis[c].	Hold selinexor for day -2 as described in Table A1.
Hyponatremia (common)		
Grade 1 (sodium levels <Normal to 130 nM)	Be certain sodium level is corrected for hyperglycemia (serum glucose >150 mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Consider salt supplementation one – two times per day.	Maintain dose.
Grade 3 (sodium levels 126-129nM) without Symptoms	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Consider immediate IV rehydration with appropriate saline solution. Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Initiate salt supplementation two-three times per day.	Consider administration of appropriate saline solution and remeasure serum sodium levels. If (corrected) sodium is Grade ≤1, then patient may receive standard dosing. If immediate sodium correction is not successful, hold selinexor for day -2 as described in Table A1.
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with Symptoms	Correct sodium as per institutional guidelines. Initiate salt supplementation two-three times per day.	Hold selinexor for day -2 as described in Table A1.
Diarrhea (common)		

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 1+2	Initiate institutional diarrheal workup and anti-diarrheal therapy.	For Grade 2 only, dose reduce selinexor for day -2 as described in Table A1
Grade 3	Institute IV fluids as appropriate. Initiate standard anti-diarrheal therapy.	Hold selinexor for day -2 as described in Table A1.
Grade 4	Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, Follow institutional guidelines for Grade 4 diarrhea.	Hold selinexor for day -2 as described in Table A1.
Thrombocytopenia		
Grade 1	Rule out other causes of thrombocytopenia.	Maintain dose.
Grade 2	Rule out other causes of thrombocytopenia.	Maintain dose.
Grade 3 Thrombocytopenia Without bleeding	Rule out other causes of thrombocytopenia.	Hold selinexor for day -2 as described in Table A1.
Grade 4 Thrombocytopenia Without bleeding	Follow guidelines for Grade 3 thrombocytopenia without bleeding. Transfuse as per institutional guidelines.	Hold selinexor for day -2 as described in Table A1.
≥ Grade 3 Thrombocytopenia associated with bleeding	Transfuse as per institutional guidelines. Follow guidelines for Grade 3 thrombocytopenia without bleeding.	Hold selinexor for day -2 as described in Table A1.
Neutropenia		
Grade 3 neutropenia without fever	Monitor neutrophil count.	Maintain dose.
Grade 4 neutropenia without fever	Monitor neutrophil count.	Dose reduce for day -2 as described in Table A1

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3 or 4 neutropenia with fever (febrile neutropenia)	Treat febrile neutropenia per institutional guidelines. Please note that selinexor has not been associated to date with any opportunistic infections.	Hold selinexor for day -2 as described in Table A1
Other selinexor-related adverse events*		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.
Grade 3	Initiate standard supportive care and follow institutional guidelines.	Dose reduce for day -2 as described in Table A1
Grade 4	Initiate standard supportive care and follow institutional guidelines.	Hold selinexor for day -2 as described in Table A1
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 gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed. Note: for combinations of Grade 1 or 2 adverse events (e.g., nausea, fatigue, anorexia) that significantly impair the patient's quality of life, dose reduction of selinexor on day -2 could be considered per investigator's discretion.		
[a]**National Comprehensive Cancer Network®.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. Available at http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf . [b]**National Comprehensive Cancer Network®.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 1.2014. Fort Washington, NY. April 2014. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf. [c]**National Comprehensive Cancer Network®.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 2.2014. Fort Washington, NY. April 2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. [d]Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.		

Selinexor Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. If dialysis is implemented during selinexor treatment, then

selinexor should always be given after dialysis. Selinexor should be given with, or within 30 minutes of, solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.).

Conditions Not Requiring Selinexor Dose Reduction

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

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions
-

Missed or Vomited Doses

Missed Doses

Due to the schedule of selinexor administration, missed doses will not be replaced.

Vomited Doses

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

Concomitant Treatments and Supportive Care

Required Supportive Care Medications

5-HT3 Antagonists

Patients will be on 5-HT3 antagonists for peri-transplant care per the institutional guidelines.

Recommended Supportive Care

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 560 adult patients treated with selinexor as of 01 February 2015, the main side effects are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding. All transplant patients are prescribed with additional anti-emetics and anti-acid medications per institutional guideliens. Additional supportive care may follow National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for antiemesis and anorexia/cachexia [palliative care]).

Infection

All transplant patients will receive prophylactic antibacterial, antiviral and antifungal agents starting the day of transplant (day 0). If febrile episodes are encountered, patients will be treated following the institutional guidelines for transplant patients including broad spectrum antibiotics in the case of febrile neutropenia. As of 01 February 2015 in over 560 patients with advanced malignancies, selinexor has not been associated with any opportunistic infections.

Concomitant Medication and Treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations. Patients may continue their baseline medication(s). Patients may continue their baseline medications. Patients may receive red blood cell or platelet transfusions, if clinically indicated, per institutional guidelines. Therapy with growth factors as specified herein is allowed.

All concomitant medication(s) within 30 days prior to enrollment to the study must be reported in the electronic case report form (eCRF). Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

Permitted Concomitant Medication

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

Prevention of pregnancy

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. Female patients of child-bearing potential must have a negative serum pregnancy test at screening and agree to use reliable methods of contraception for three months after their last dose of medication. Such methods include intrauterine devices, hormonal contraceptives [contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release], abstinence or sterilization of the partner. Male patients must use a reliable method of contraception (abstinence or contraception with one of the above-described methods for your partner) if sexually active with a female of child-bearing potential. 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.

Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted during the course of the trial but after the completion of autologous HCT (beyond day +30 of HCT).

Prohibited Medication

Transplant patients are not permitted to receive acetaminophen (paracetamol) or acetaminophen/paracetamol-containing products while undergoing autologous HCT (until day +30). Concurrent therapy with any other approved or investigative anticancer therapeutic is **not** allowed. Glutathione (GSH), S-adenosylmethionine (SAM), or N-acetylcystine (NAC) should not be taken while patients are taking selinexor. These agents may be used if liver toxicity occurs, but all natural products or supplements containing these should be avoided.
Use of any immunosuppressive agents during the study must be approved by the Medical Monitor prior to use. Other investigational agents for any condition should not be used during the study.

Appendix X Ophthalmological Exam

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

The examination is to include the following:
Prior to dilation:

- best corrected visual acuity
- slit lamp examination
- tonometry

Following dilation:

- fundoscopy
- slit lamp examination to document lens clarity

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

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

Appendix XI Ophthalmological Exam Form

Subject Initials:_____ Subject Number: -

Date of Exam:_____

Eyes assessed: ☐ Both ☐ Right ☐ Left

Visual acuity

Was a visual acuity exam performed? ☐ Yes ☐ No

Total visual acuity score (ETDRS)

Right Eye (OD) _____ ☐ Not assessed

Left Eye (OS) _____ ☐ Not assessed

Visual acuity Snellen's eqivalent?

Right Eye (OD) 20/_____ ☐ Not assessed

Left Eye (OS) 20/_____ ☐ Not assessed

Was there a >1 line worsening on the chart? ☐ Yes ☐ No ☐ N/A

Was intraocular pressure (tonometry) assessed? ☐ Yes ☐ No

Right Eye (OD)_____mmHg ☐ Not assessed

Left Eye (OS)_____mmHg ☐ Not assessed

Was slit lamp exam performed? ☐ Yes ☐ No

Location	EYE	Normal	Abnormal	Not Done	If abn., specify	
Conjunctiva	Right Eye (OD)					☐NCS ☐CS
Cornea	Right Eye (OD)					☐NCS ☐CS
Conjunctiva	Left Eye (OS)					☐NCS ☐CS
Cornea	Left Eye (OS)					☐NCS ☐CS

Was dilated fundoscopy performed? ☐ Yes ☐ No

Type of examination indirect? ☐ Yes ☐ No

Pupils dilated? ☐ Yes ☐ No

Right Eye (OD)						
Test	If other, specify	Normal	Abnormal	Not Done	If abn., specify	
Vitreous						☐NCS ☐CS
Optic nerve						☐NCS ☐CS
Optic nerve pallor						☐NCS ☐CS
Optic disc						☐NCS ☐CS
Macula						☐NCS ☐CS
Retina						☐NCS ☐CS
Periphery						☐NCS ☐CS
Other						☐NCS ☐CS
Left Eye (OS)						
Test	If other, specify	Normal	Abnormal	Not Done	If abn., specify	
Vitreous						☐NCS ☐CS
Optic nerve						☐NCS ☐CS
Optic nerve pallor						☐NCS ☐CS
Optic disc						☐NCS ☐CS
Macula						☐NCS ☐CS
Retina						☐NCS ☐CS
Periphery						☐NCS ☐CS
Other						☐NCS ☐CS

If optic disc cupping in seen, please describe:

Dilated slit lamp exam

Was a slit lamp exam performed to document lens clarity? ☐ Yes ☐ No

Cataract present? ☐ Both ☐ Right ☐ Left

Cataracts must be graded according to LOCSIII

Lens opacities classification system III

Right Eye (OD):

Nuclear opalescence: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Cortical: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Posterior subcapsular: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Left Eye (OS):

Nuclear opalescence: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Cortical: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Posterior subcapsular: ☐ 1 ☐ 1+ ☐ 2 ☐ 2+ ☐3 ☐3+ ☐4 ☐4+

Please complete and return to Michael Dumala by fax 813-449-8598 or by email michael.dumala@moffitt.org