Physician Selected Selinexor-based Therapy for Relapsed/Refractory Multiple Myeloma

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Clinical Study Protocol

Physician Selected Selinexor-based Therapy for Relapsed/Refractory Multiple Myeloma

Study Number:	20-2202
Study Phase:	2
Product Name(s):	Selinexor (KPT-330)
IND or EudraCT Number:	154562
IST Identifier:	336
Indication:	Relapsed/Refractory Multiple Myeloma
Sponsor:	University of Colorado, Anschutz Medical Campus
Sponsor-Investigator:	Daniel Sherbenou, MD PhD University of Colorado 1665 Aurora Court Aurora, CO 80045
Selinexor Supplier/Drug Supplier and Funding Source:	Karyopharm Therapeutics, Inc. Newton, MA 02459 USA
Protocol Version and Date:	V5, 02JAN2025

INVESTIGATORS' AGREEMENT

STATEMENT OF COMPLIANCE

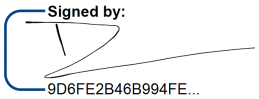
This is an investigator-initiated study. The principal investigator (PI), Daniel Sherbenou, MD PhD, is conducting the study and the University of Colorado is acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

In accordance with 21 CFR 25.30/25.31, this protocol qualifies for a categorical exclusion from the requirement for an environmental assessment for the manufacture and formulation for use in human clinical trials. All waste from the investigational drug(s) will be properly controlled. The amount of waste expected to enter the environment may reasonably be expected to be nontoxic. To the Sponsor-Investigator's knowledge, no extraordinary circumstances exist.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Investigator Signature:	
Investigator's Name:	Daniel Sherbenou, MD PhD
Institution:	**University of Colorado**
Date:	February 5, 2025 | 5:11:53 PM MST

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Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase (SGOT)
AUC_{last}	area under the curve, first-last measurement
$AUC_{(0-\infty)}$	area under the curve, time zero to last
BIW	twice weekly
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
°C	degrees Celsius
CBC	complete blood count
CBR	clinical benefit response rate
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence Interval
cm	centimeter
C_{max}	maximum serum concentration
CNS	central nervous system
CR	complete remission
CRA	clinical research associate
CrCl	creatinine clearance
CRM1	chromosomal region maintenance protein 1
CSF	cerebrospinal fluid
CSR	clinical study report
CST	Company-Sponsored Trial
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCR	disease control rate (CR, PR, SD ≥ 4 weeks)
Dex	dexamethasone
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMC	Data Safety Monitoring Committee
EC	ethics committee
ECG	electrocardiogram
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
F%	oral bioavailability

Abbreviation	Definition
°F	degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GRP	growth regulatory protein
GSH	glutathione
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr	Hour
IC_{50}	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
eIF4E	mRNA cap-binding protein eukaryotic translation factor 4E
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalization ratio
IPI	International Prognostic Index
IR	intermediate risk
IRB	Institutional Review Board
ISS	International Staging System
IST	Investigator-Sponsored Trial
IV	intravenous
kg	Kilogram
KM	Kaplan-Meier
LDH	lactic dehydrogenase
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	myocardial infarction
min	Minute
miRNA	microRNA
mL	Milliliter
mITT	modified Intent-to-Treat
MM	multiple myeloma
mmHg	millimeters of mercury
MTD	maximum tolerated dose
MR	minor response

Abbreviation	Definition
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition
My-DST	Myeloma drug sensitivity testing
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NK1R	neurokinin 1 receptor
NPC	nuclear pore complex
ORR	overall response rate (sCR + CR + VGPR + PR)
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamics
PE	physical examination
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QW	once weekly
RBC	red blood cell
RNA	ribonucleic acid
RR	Relapsed/Refractory
SAE	serious adverse event
SAM	S-adenosylmethionine
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SINE	selective inhibitor of nuclear export
SOC	standard of care
SOP	standard operating procedure
STD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
TRAE	treatment-related adverse event
TSP	tumor suppressor protein
TTP	time to progression
ULN	upper limit of normal
VGPR	very good partial response
WBC	white blood cell
XPO1	exportin 1

1 PROTOCOL SYNOPSIS

Sponsor-Investigator/Institution: University of Colorado, Anschutz Medical Campus	**Investigational Product (s):** Selinexor (KPT-330)	**Developmental Phase:** 2
Title of Study: Physician Selected Selinexor based Therapy for relapsed/refractory Multiple Myeloma		
Protocol Number: 20-2202		
IST Identifier: 336		
Indication: Relapsed and refractory multiple myeloma		

Study Rationale: Given its unique mechanism of action, selinexor (KPT-330, Xpovio®) presents an attractive partner for commonly used therapeutic agents in relapsed/refractory multiple myeloma (RRMM). The ongoing phase Ib/II STOMP trial is evaluating selinexor as part of several multidrug regimens incorporating the most active currently available myeloma therapeutics. The STOMP trial includes dose finding and expansion cohorts to describe initial efficacy and safety for selinexor and dexamethasone in combination with the proteasome inhibitor carfilzomib, the immunomodulatory agent pomalidomide and the CD-38 targeting monoclonal antibody daratumumab, amongst other combinations. However, as with other therapeutic choices in the RRMM setting the decision for which of these partners to utilize with selinexor therapy is largely empiric. This trial will seek to evaluate the outcomes achieved with selinexor based combination in RRMM selected by physician's choice and compared prospectively to ex vivo drug sensitivity testing results.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the overall response rate achieved with physician's choice selinexor-based combination therapy	ORR by IMWG criteria (based on Kumar et al 2016) [appendix 5]
Secondary	
• To evaluate the minimal residual disease negative response rate achieved with physician's choice selinexor-based combination therapy	MRD negative response rate assessed via NGS or multiparametric flow cytometry with sensitivity of 10^{-5}
• To evaluate the duration of disease control and survival for patients treated with physician's choice selinexor-based combination therapy	PFS, DOR, OS, TTNT
	Occurrence, nature and severity of Adverse Events

Sponsor-Investigator/Institution: University of Colorado, Anschutz Medical Campus	**Investigational Product (s):** Selinexor (KPT-330)	**Developmental Phase:** 2

• To evaluate safety and tolerability of selinexor in combination with partner backbone agents	
Exploratory	
• Feasibility of My-DST testing to inform treatment choice • Evaluation of My-DST related predictors of response	Rate of assay failure; Rate of identification of preferred partner therapy or combination ORR in patients with concordance or discordance between MyDST results and physicians selected regimen

Overall Study Design:

This study will be a single institution, open-label phase II study to evaluate the overall response rate achieved with selinexor and dexamethasone based three drug combination therapy, selected by physician's choice, in patients with relapsed/refractory multiple myeloma.

Patients with RRMM will be eligible for enrollment. During screening, in addition to standard of care disease assessments, participant's bone marrow aspirate will be evaluated using a novel ex vivo Myeloma Drug Sensitivity Testing platform (My-DST). The following agents will be eligible for physician's choice, and in parallel evaluated for sample sensitivity in MyDST: pomalidomide, carfilzomib and daratumumab. Agents will be tested individually, in combination with selinexor and in combination with selinexor and dexamethasone. Results from MyDST will be not be available to investigators at time of treatment assignment, results from this test will be evaluated as part of exploratory analyses to better characterize test performance and relationship with treatment outcomes.

Investigators will assign patients to one of the following treatment combinations: Selinexor/Pomalidomide/Dexamethsone (SPd), Selinexor/Daratumumab/Dexamethasone (SDd) or Selinexor/Carfilzomib/Dexamethasone (SKd). Investigators will use patient specific considerations such as prior therapeutic exposures, response to / tolerance of prior therapies and comorbid conditions which may increase risk for toxicity with specific agents to guide expert judgement in selecting partner agent for selinexor and dexamethasone. Treatment will continue until progression of disease, unacceptable toxicity or death.

This study will evaluate if physician's choice partner drug selection for selinexor based combination therapy in RRMM will lead to an overall response rate of 75% or higher.

Oversight will be provided by the Data and Safety Monitoring Committee (DMSC) at the University of Colorado Cancer Center

Number of Patients (planned): 18

Study Population: Relapsed and refractory multiple myeloma

Sponsor-Investigator/Institution:	**Investigational Product (s):**	**Developmental Phase:**
University of Colorado, Anschutz Medical Campus	Selinexor (KPT-330)	2

Inclusion Criteria:

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

1. Age ≥ 18 years
2. Willing and able to provide written informed consent in accordance with federal, local, and institutional guidelines. The patient must provide informed consent prior to the first screening procedure.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤ 2
4. Histologically confirmed diagnosis, measurable disease and evidence of disease progression of MM after 1 or more prior lines of therapy with either of the following:
    a. Documented evidence of PD after achieving at least SD for ≥ 1 cycle during a previous MM regimen (i.e., relapsed MM)
    b. ≤ 25% response (i.e, patient never achieved ≥ MR) or PD during or within 60 days from end of the most recent MM regimen (i.e., refractory MM)
5. Patients must have measurable disease as defined by at least one of the following:
    a. Serum M-protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
    b. Urinary M-protein excretion at least 200 mg/24 hours
    c. Serum FLC ≥ 10 mg/dL, provided that FLC ratio is abnormal
    d. If no measurable disease by serum or urine, then the presence of a plasmacytoma of ≥2cm in one dimension prior to start of study can be used to follow response via radiologic imaging.
6. Adequate hepatic function:
    a. Total bilirubin < 1.5 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 × ULN), and
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) normal to <2.5 × ULN.
7. Adequate renal function as determined by serum creatinine of ≤2 mg/dL OR estimated creatinine clearance of ≥ 20 mL/min, calculated using the Cockcroft and Gault formula (140 – Age) • Mass (kg)/ (72 • creatinine mg/dL); multiply by 0.85 if female (Cockcroft 1976).
8. Adequate hematopoietic function within 28 days prior to C1D1: absolute neutrophil count ≥1000/mm^3, hemoglobin ≥8 g/dL and platelet count ≥100,000/mm^3 (patients for whom <50% of bone marrow nucleated cells are plasma cells) or ≥50,000/mm^3 (patients for whom ≥50% of bone marrow nucleated cells are plasma cells).
    a. Patients may receive hematopoietic growth factor support, including erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and platelet stimulators (eg, eltrombopag, romiplostim, or interleukin-11) at any time.
    b. Patients may receive RBC and/or platelet transfusions as clinically indicated per institutional guidelines during the study.
9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of

Sponsor-Investigator/Institution:	Investigational Product (s):	Developmental Phase:
University of Colorado, Anschutz Medical Campus	Selinexor (KPT-330)	2

contraception throughout the study and for 3 months following the last dose of protocol required therapies.

Exclusion Criteria:

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

1. Has received selinexor or another SINE (Specific Inhibitor of Nuclear Export) compound in a previous line of therapy.
2. Has any concurrent medical condition or disease (eg, uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.
3. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to Cycle 1 Day 1 (C1D1). Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
4. Known intolerance, hypersensitivity, or contraindication to study drugs.
5. Pregnant or breastfeeding females.
6. Major surgery within 4 weeks prior to C1D1.
7. Active, unstable cardiovascular function, as indicated by the presence of:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on anti-arrhythmics are excluded; patients with first degree atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or
    c. Congestive heart failure of New York Heart Association Class ≥3 or known left ventricular ejection fraction <40%, or
    d. Myocardial infarction within 3 months prior to C1D1.
8. Subjects with active hepatitis B virus (Hep B) are allowed if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/ml prior to first dose of trial treatment. Subjects with untreated hepatitis C virus (HCV) are allowed. Subjects with Human Immunodeficiency Virus (HIV) who have CD4+ T-cell counts ≥ 350 cells/µL and no history of AIDS-defining opportunistic infections in the last year are allowed.
9. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment, including prior gastric bypass or bowel resection procedures.
10. Inability or unwillingness to take supportive medications such as anti-nausea and anti-anorexia agents as recommended by the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (CPGO) (NCCN CPGO) for antiemesis and anorexia/cachexia (palliative care).
11. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent.
12. Contraindication to any of the required concomitant drugs or supportive treatments.
13. Patients unwilling or unable to comply with the protocol, including providing 24-hour urine samples for urine protein electrophoresis at the required time points.

Sponsor-Investigator/Institution:	**Investigational Product (s):**	**Developmental Phase:**
University of Colorado, Anschutz Medical Campus	Selinexor (KPT-330)	2

Study Treatment/Treatment Groups, Dose, and Mode of Administration:

Arm 1 SPd
- Selinexor 60 mg PO days 1, 8, 15
- Pomalidomide 4 mg PO on days 1-21
- Dexamethasone 40 mg PO or IV on days 1, 8, 15, 22
- 28-day treatment cycles

Arm 2 SDd
- Selinexor 80 mg PO days 1, 8, 15
- Daratumumab 1,800mg/30,000 units subcutaneous injection on days 1, 8, 15, 22 of cycles 1 and 2, days 1, 15 of cycles 3-6, day 1 of cycles >6 (may be substituted with IV Dara, if directed by Investigator)
- Dexamethasone 40 mg PO or IV days 1, 8, 15, 22
- 28-day treatment cycle

Arm 3 SKd
- Selinexor 80 mg PO days 1, 8, 15
- Carfilzomib IV infusion 20 mg/m2 cycle 1, day 1, 56 mg/m2 cycle 1 day 8, 15. Cycle 2+ days 1, 8, 15.
- Dexamethasone 40 mg IV or PO days 1, 8, 15, 22
- 28-day treatment cycle

Duration of Treatment and Follow-up:
There is no maximum treatment duration. Patients will continue to receive treatment during the study until progression, death, toxicity or withdrawal from study.

Following completion of therapy, patients will be monitored for survival and subsequent therapies annually for2 years.

Statistical Methods:
Efficacy will be assessed using the proportion of patients who achieve at least a partial response, as defined by IMWG criteria. The complementary failure rate—the rate of patients who do not achieve at least a partial response—will be assessed throughout the study. If at any time in the study the upper bound of the one-sided 90% confidence interval for the failure rate exceeds 51%, then the study will be stopped for efficacy. At study completion, the proportion of patients achieving at least a partial response will be calculated, along with one-sided 90% confidence intervals for this proportion. Assuming power of 80% and a one-sided type I error rate of 10%, then for a difference in proportion test using a normal approximation and assuming a null hypothesis of a 51% response rate and an alternative hypothesis of a 75% response rate, 18 patients are needed for this study.

2 SCHEDULE OF ASSESSMENTS AND STUDY SCHEMATICS

Table 1 Schedule of Study Activities and Assessments – ARM 1(SPd)

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X		X	X		X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if	X						X		X		X	

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
applicable)[i]									(even cycles only)			
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Pomalidomide (PO)		X (days 1 – 21)					X (days 1 – 21)		X (days 1 – 21)			
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]	*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*											
Concomitant medication recording	*Continuous*											

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

a Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

b After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

c Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

d ICF must be signed before any study-specific procedures are performed.

e BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

f Patients must rest for at least 5 minutes prior to the ECG recording.

g Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

h Details for clinical laboratory tests are provided in Table .

i For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

j Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

k Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

l Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening

should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

m If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

n Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis
b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

o After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

p Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

q SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

r Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

s Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

t These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

Table 2 Schedule of Study Activities and Assessments – ARM 2(SDd)

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Daratumumab (SQ/IV)		X		X	X	X	X	X	X	X (day 15. Stop this dose at cycle 7+)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]		*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*										
Concomitant medication recording	*Continuous*											

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

a Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

b After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

c Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

d ICF must be signed before any study-specific procedures are performed.

e BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

f Patients must rest for at least 5 minutes prior to the ECG recording.

g Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

h Details for clinical laboratory tests are provided in Table .

i For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

j Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

k Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

l Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

m If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

n Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis

b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

o After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

p Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

q SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

r Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

s Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

t These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

Table 3 Schedule of Study Activities and Assessments – ARM 3 (SKd)

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
		-1 day[s]	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Carfilzomib (SQ/IV)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]	*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*											
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									

Activity/Assessment	Screening [a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
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		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

a Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

b After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

c Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

d ICF must be signed before any study-specific procedures are performed.

e BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

f Patients must rest for at least 5 minutes prior to the ECG recording.

g Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

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j Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

k Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

l Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as

determined by the Investigator.

m If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

n Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis

b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

o After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

p Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

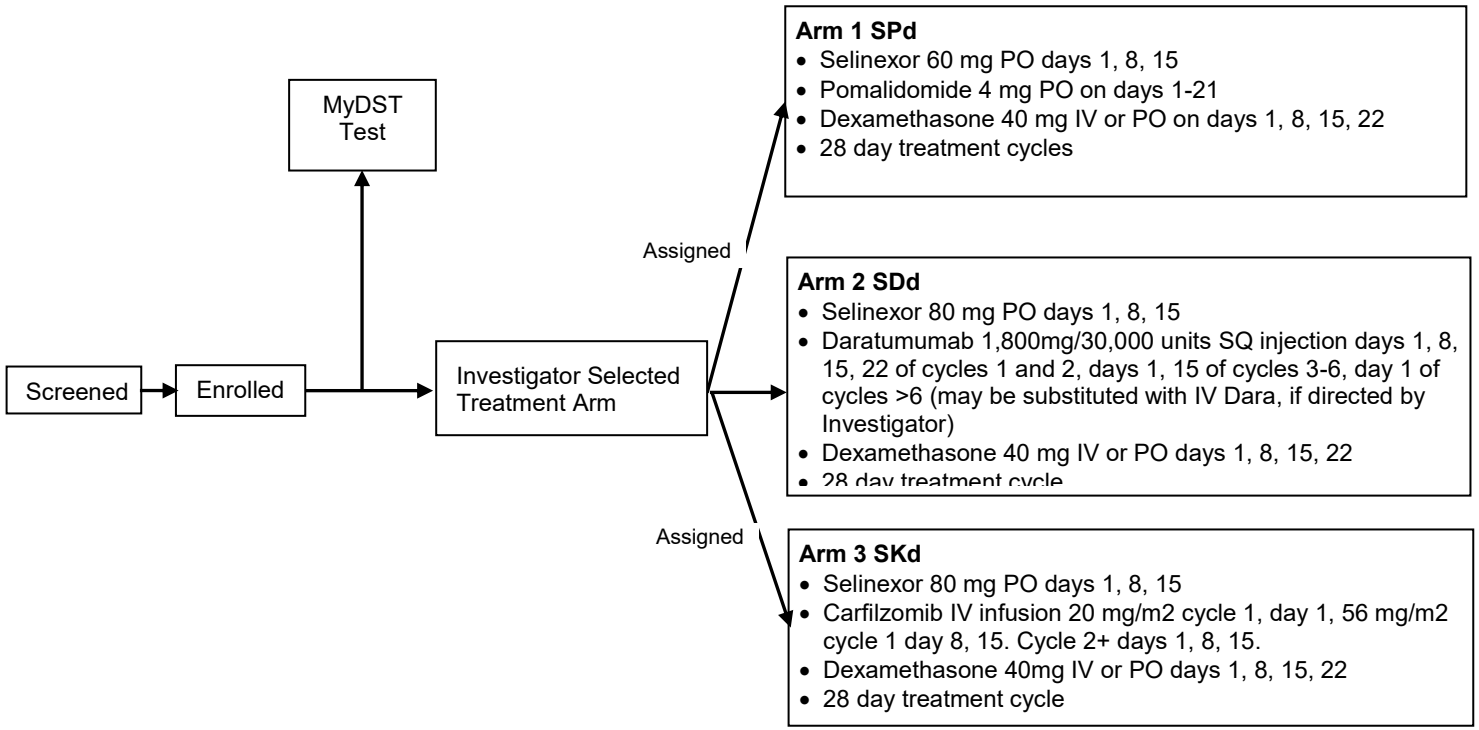
q SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

r Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

s Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

t These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

Figure 1 Study Flow Chart



Abbreviations: SPd= selinexor + pomalidomide + dexamethasone; SDd = selinexor + daratumumab + dexamethasone; SKd = selinexor + carfilzomib + dexamethasone
Patients will continue on therapy until progression or unacceptable toxicity

3 INTRODUCTION

3.1 Multiple Myeloma

Multiple Myeloma (MM) is the second most common hematologic malignancy and is increasing in frequency. In 2017 there were approximately 30,000 new cases of MM diagnosed in the United States and 12,600 MM related deaths (Siegel, Miller, & Jemal, 2019). The past 2 decades have seen 11 new drug approvals in multiple myeloma (MM) which have dramatically altered treatment approaches in this disease and led to improved patient outcomes (Kumar, Dimopoulos, et al., 2017). Despite these improvements MM remains an incurable blood cancer with nearly all patients experiencing relapse after initial therapy and often requiring several salvage treatment approaches (Laubach et al., 2016). Drug classes which are regularly used in relapsed multiple myeloma include immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, conventional chemotherapeutics and corticosteroids. Recently the field has expanded with the approval of Selinexor (Xpovio), the first in class selective inhibitor of nuclear export.

Current National Comprehensive Cancer Network (NCCN) guidelines for management of patient with previously treated multiple myeloma include 8 preferred regimen options and 23 “Other Recommended Regimens” (Kumar, Callander, et al., 2017). This diversity of treatment options in RRMM leads to challenges in therapeutic decision-making. There is limited direct data to guide clinicians in choosing between available treatment options. The large majority of available regimens have not been compared directly to one other in controlled trials. Furthermore, although risk stratification in multiple myeloma exists and can help predict overall disease aggressiveness, to date there has not been identification of myeloma related biomarkers that may help to predict relative efficacy of different active agents or development of validated risk adapted therapeutic recommendations for management of RRMM (Fonseca et al., 2009; Sonneveld et al., 2016).

3.2 Selinexor

Selinexor is being evaluated for the treatment of hematologic and solid tumor indications, including multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), and advanced unresectable dedifferentiated liposarcoma (DDLS). On July 3, 2019 selinexor was granted accelerated approved by the Food and Drug Administration (FDA) in combination with dexamethasone for patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents and an anti-CD38 monoclonal antibody. On June 22, 2020 granted selinexor it’s second approval this time in patients with relapsed or refractory DLBCL after at least 2 lines of systemic therapy.

To date, more than 3,000 patients with hematologic or solid tumors have received selinexor in clinical studies, including Company-sponsored Trial (CSTs), Investigator-Sponsored Trials (ISTs), and the Selinexor Expanded Access Program (EAP), in >10 disease indications. The majority of patients were treated with selinexor as a single agent but >700 patients received selinexor in combination with a diverse array of other anticancer agents. Single-agent Phase 1 studies with oral selinexor have been conducted in advanced hematological malignancies including MM, acute myeloid leukemia (AML), NHL, and chronic lymphocytic leukemia; in solid tumors; and in soft tissue and bone sarcomas. Broad antitumor activity has been observed in all of these studies. In addition, Phase 2 studies have been conducted in Richter’s transformation and AML and are ongoing in MM, DLBCL, glioblastoma, gynecological

malignancies, and dedifferentiated liposarcoma (Phase 2 and 3). A separate Phase 3 study is ongoing in MM. Additional information about clinical studies of selinexor is available in the Selinexor Investigator's Brochure (IB), version 9, dated August 13, 2019.

The current study will evaluate selinexor combined with dexamethasone and common backbone agents daratumumab, pomalidomide or carfilzomib for the treatment of RRMM.

3.2.1 Selinexor Mechanism of Action

Selinexor is an oral, first-in-class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1).

XPO1 is overexpressed in a large variety of malignancies including multiple myeloma (MM), osteosarcoma, pancreatic cancer, ovarian cancer, glioma, leukemia, and lymphoma and correlates with advanced disease, resistance to therapy, and poor survival. XPO1 exports tumor suppressor proteins (TSPs; eg, p53, p73, pRb, FOXOs, APC, PTEN) and growth regulatory proteins (GRPs; eg, IκB, p21, p27, Survivin) out of the nucleus. These protein cargos mediate their cell cycle checkpoint/tumor suppression functions within the nucleus. Therefore, nuclear to cytoplasmic transport of these proteins by XPO1 leads to their functional inactivation. XPO1 also regulates the cytoplasmic localization and, in turn, translation of key proto oncogenic mRNAs (eg, MYC, BCL2, BCL6 and cyclin D) that complex with the XPO1 cargo protein, eukaryotic initiation factor 4E (eIF4E). In addition, XPO1 is involved in regulating nuclear levels of the glucocorticoid receptor (GR).

Inhibition of XPO1 by selinexor promotes apoptosis in malignant cells by blocking each of the above XPO1-mediated mechanisms. Because these mechanisms are relevant to any neoplastic cell, selinexor has the potential to effectively treat a range of malignancies. Normal cells undergo reversible cell cycle arrest following inhibition of XPO1 and recover when the block is removed.

Further information regarding the mechanism of action can be found in the Selinexor IB.

3.2.2 Selinexor Nonclinical Studies

Tumor reduction and increased survival was observed at doses of selinexor 15 through 60 mg/m^2 (5 through 20 mg/kg) in mouse models of hematological and solid tumors. In addition, marked synergy was observed when selinexor was combined with a variety of chemotherapies and targeted therapies.

The major side effects across all animal models studied were reduced appetite with anorexia induced weight loss or reduction in weight gain. Cachexia (loss of muscle mass) was not observed. Similar effects are observed in humans, where high caloric foods and appetite stimulants, including glucocorticoids, are known to improve appetite and mitigate weight loss.

Further information regarding selinexor nonclinical studies can be found in the Selinexor IB.

3.2.3 Overall Clinical Experience with Selinexor

3.2.3.1 Pharmacokinetics

Selinexor is orally bioavailable and exhibits dose-proportional exposure with moderate to high interpatient variability across a wide dose range of doses in patients with advanced hematologic

malignancies or solid tumors. The elimination (terminal) half-life of selinexor is approximately 5 to 8 hours. Additional details are available in the Selinexor IB.

3.2.3.2 Safety and Efficacy

Over 3,366 patients with hematologic or solid-tumor malignancies have been treated with selinexor in CSTs, ISTs, and the Selinexor EAP.

The most commonly reported treatment-emergent adverse events (TEAEs) in CSTs have been generally low-grade and reversible nausea, fatigue, anorexia (including decreased appetite), vomiting, and diarrhea. TEAEs of thrombocytopenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies.

The most frequently reported non-hematologic treatment-related adverse events (TRAEs) reported in CSTs have been fatigue, GI disorders, and anorexia. These TRAEs respond to supportive care measures and/or dose interruption/reduction. Careful attention to these side effects, particularly in the first 4 to 6 weeks of dosing, is critical. Additional non-hematologic TRAEs that have occurred in ≥10% of patients in CSTs include hyponatremia, blurred vision and increased risk of cataracts in patients with prolonged exposure to selinexor with dexamethasone and dizziness. Hematologic toxicities, including thrombocytopenia, anemia, and neutropenia, have been observed and typically respond to dose modifications, growth factors, and/or transfusions.

Although some patients with rapid tumor responses experience significant fatigue, nausea, malaise and/or asthenia after 1 or more doses of selinexor, this effect has not been associated with typical markers of tumor lysis syndrome (TLS). Eight TLS cases have been reported (as of 31 March 2019), including 4 patients in CSTs, 2 patients in ISTs, and 2 patients in the selinexor EAP. If TLS is suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

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

More information about the safety and efficacy of selinexor is available in the current Selinexor IB.

3.2.4 Treatments That Will Be Used in Combination with Selinexor

3.2.4.1 Pomalidomide (Pomalyst®)

Pomalidomide (Pomalyst®) is an immunomodulatory agent, IMiD, which was developed as a thalidomide analogue. Derived as a dramatically more potent inhibitor of tumor necrosis factor than its parent compound, pomalidomide was more subsequently found to exert its anti-tumoral activity by altering the activity of Cereblon, a component of an E3 ubiquitination ligase complex, to increase degradation of the cellular proteins Ikaros and Aiolos (Hideshima et al., 2000; Kronke, Hurst, & Ebert, 2014; Lu et al., 2014). As pomalidomide is structurally and pharmacologically related to thalidomide, a known teratogen, it is contraindicated in pregnant women and women who have a possibility of becoming pregnant. The

pomalidomide product monographs/labeling contain the following boxed-text warning:

> WARNING: EMBRYO-FETAL TOXICITY (and VENOUS THROMBOEMBOLISM)
>
> *See full prescribing information for complete boxed warning*
>
> EMBRYO-FETAL TOXICITY
>
> Pomalidomide is contraindicated in pregnancy.
>
> Pomalidomide is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life-threatening birth defects.
>
> For females of reproductive potential: Exclude pregnancy before start of treatment. Prevent pregnancy during treatment by the use of 2 reliable methods of contraception.
>
> Pomalidomide is available only through a restricted program called POMALYST REMS
>
> In order to prevent pregnant women from being exposed to pomalidomide, a Risk Evaluation and Mitigation Strategy (REMS) called POMALYST REMS in the EU and US, and RevAid® in Canada, has been established by the manufacturer of both products. In order to participate in Arm 1 of this study, investigators and patients must agree to comply with the requirements of the plans.

Initial phase I testing identified myelosuppression as the dose limiting toxicity of IMiD therapy in MM, subsequent clinical trial experience also demonstrated the risk of treatment related thromboembolic events and the need for and efficacy of prophylactic anticoagulation during therapy (Palumbo et al., 2008; Richardson et al., 2002). The activity of pomalidomide in RRMM was described in the landmark phase III MM-003 study which demonstrated markedly increased ORR, increased PFS and OS for pomalidomide and dexamethasone therapy in comparison to the high dose dexamethasone alone control arm (San Miguel et al., 2013).

Pomalidomide has subsequently been evaluated in numerous phase II and III studies in relapsed multiple myeloma as a 2-drug combination with dexamethasone or as part of 3-drug combinations with dexamethasone and additional partners including bortezomib, carfilzomib, daratumumab, elotuzumab, cyclophosphamide and clarithromycin (Mark et al., 2019). Full prescribing information is available for reference for the most current clinical experience and safety and reproductive risk information for pomalidomide (available at https://media.celgene.com/content/uploads/pomalyst-pi.pdf).

3.2.4.2 **Daratumumab**

Daratumumab (Darzalex) is a monoclonal antibody targeting the CD38 glycoprotein which has near uniform expression on malignant plasma cells from patients with MM (de Weers et al., 2011). Daratumumab has been shown to exert an anti-myeloma effect through several mechanisms including complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, macrophage-mediated phagocytosis, the induction of programmed cell death and apoptosis as well as blocking the enzymatic activity of CD38 (de Weers et al., 2011; Overdijk et

al., 2016; Overdijk et al., 2015; van Bueren et al., 2014). Daratumumab activity in the RRMM setting was first demonstrated in 2 phase I/II trials using daratumumab monotherapy in heavily pretreated patients (Lokhorst et al., 2015; Lonial et al., 2016). These demonstrated overall response rates of approximately 30% with limited toxicities aside from infusion related reactions with initial dosing and low-grade myelosuppression, leading to initial FDA approval. The landmark phase III CASTOR and POLLUX trials evaluated daratumumab in patients with less prior treatment exposure (1-3 prior lines of therapy) in combination with either a PI (CASTOR: daratumumab/bortezomib/Dex vs bortezomib/dex) or an IMiD (POLLUX: daratumumab/lenalidomide/Dex vs lenalidomide/Dex) (Dimopoulos, Oriol, et al., 2016; Palumbo et al., 2016). These studies both demonstrated significant improvements in PFS and response rates at all levels evaluated for the patients that received daratumumab in comparison to the control arm with very manageable additive toxicities. Full prescribing information is available for reference from the most current clinical experience and safety and reproductive risk information for daratumumab (available at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf).

3.2.4.3 **Carfilzomib**

Carfilzomib (Kyprolis) is an irreversible, second generation proteasome inhibitor (PI) with increased inhibition of the chymotrypsin-like subunit of the proteasome, compared to bortezomib (Kuhn et al., 2007; Parlati et al., 2009). Preclinical and early phase I studies established a twice weekly dosing schema, days 1, 2, 8, 9, 15 and 16 of 28, for carfilzomib which was instituted for clinical development (O'Connor et al., 2009). Use of an initial 20 mg/m^2 dosing for days 1 and 2 of cycle one with subsequent escalation to 27 mg/m^2 was established as the MTD for carfilzomib with dexamethasone in the phase I/II studies using an administration time of 2-10 minutes. Carfilzomib 20/27 with dexamethasone was found to have significant activity in RRMM and was approved by the FDA for use in this setting based on the strong results from phase II testing, particularly the PX-171-004 study (Vij et al., 2012). Subsequent evaluations demonstrated a significant decrease in peak plasma levels and diminished toxicity profile with slower administration and further phase I testing established the safety of carfilzomib doses up to 56 mg/m^2 when administered over 30-minutes on the same twice weekly schema with initial dosing (Papadopoulos et al., 2015). Recently studies have demonstrated the safety and efficacy of weekly dosing. The phase I/II CHAMPION demonstrated the safety and efficacy of once-weekly carfilzomib with a target dose of 70mg/m^2(Berenson et al., 2016). Recently reported results from the phase III ARROW study compared twice weekly carfilzomib at a dosing of 27 mg/m^2 versus weekly dosing of 70 m^2 in 478 patients with RRMM and demonstrated longer PFS in the weekly dosing arm, 11.2 months vs 7.6, HR=0.69 (95% CI 0.54-0.88).

Carfilzomib activity was further established in the phase III ENDEAVOR trial which compared carfilzomib and Dex (Kd) with bortezomib and Dex (Vd) for treatment of RRMM (Dimopoulos, Moreau, et al., 2016). This study used a dosing of carfilzomib of 56 mg/m^2 and did include a significant portion of patients with prior bortezomib exposure. Median progression free survival for the Kd cohort was 18.7 months versus 9.4 months for Vd (HR 0.53, CI 0.44-0.65; p<0.0001). Planned subgroup analysis for patients with prior bortezomib exposure demonstrated a similar benefit for Kd, median PFS 15.6 vs 8.1 month (HR 0.56, CI 0.44-0.73). Recently overall survival data was presented which demonstrated that patients in the Kd arm had longer median overall survival, 47.6 months, then patients treated with Vd, 40 months (HR 0.79, 95% CI 0.65-0.96; p-0.01).

Full prescribing information is available for reference for the most current clinical experience and safety and reproductive risk information for carfilzomib (available at https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/kyprolis/kyprolis_pi.pdf).

3.2.5 Myeloma Drug Sensitivity Testing

To address the issue of rational drug selection for patients with myeloma, we have developed an ex vivo assay, termed My-DST (Myeloma Drug Sensitivity Testing) (Walker et al., 2020). For My-DST, primary patient bone marrow aspirates undergo Ficoll mononuclear cell separation and are then screened for plasma cell survival in a 96-well plate against a panel of anti-myeloma drugs in solution. This functional assay avoids CD138+ cell selection of bone marrow aspirates to optimize viability of plasma cells by maintaining their usual cellular support environment and also allows for the determination for monoclonal antibody response through cell-mediated cytotoxicity mechanisms.

In the development of the My-DST platform, dose response relationships were determined for clinically used agents, including pomalidomide, carfilzomib, daratumumab and dexamethasone. Concentrations that produced an reproducible decrease in MM cell viability in sensitive patients were selected for each drug individually for the screening format of the working platform. For high-throughput testing, the concentrations selected were 2.5 nM for PIs, 10 μM for IMiDs, 1 μM for dexamethasone and 20 nM for daratumumab. Ex vivo incubation is performed for 48 hours, followed by flow cytometry using widely accepted markers for MM cells: CD138, CD38, CD45 and CD19. Viability of the MM cell population is then measured by viability dye exclusion, and results reported with normalization compared to vehicle-treated controls. Drug treatments at these standardized single concentrations with <80% cell survival in My-DST are considered to be active agents.

Using this approach, retrospective evaluation of 55 MM patients' samples My-DST results was compared to the clinical outcomes of the patients. When patients received solely agents that were tested in My-DST, the ex vivo results were 96% sensitive and 88% specific for a clinical partial response (50% decrease in disease burden by IMWG criteria) to subsequent therapy (Walker et al., 2020). My-DST has demonstrated good reproducibility, and the sensitivities of PIs, IMiDs and daratumumab correlated inversely with the number of prior therapies, and the patients' prior drug exposures. Patient samples can be analyzed, and results interpreted in less than 96 hours allowing the test to inform subsequent treatment decision making without delaying care. For the next step in determining the predictiveness of My-DST, a stratified, prospective study of how well ex vivo results correspond to patients' clinical responses is necessary.

3.3 Study and Dose Rationale

3.3.1 Rationale for the Study and the Study Design

Given its unique mechanism of action selinexor presents an attractive partner for several commonly used therapeutic agents in RRMM. The ongoing phase Ib/II STOMP trial is evaluating selinexor as part of several multidrug regimens incorporating the most active currently available myeloma therapeutics. The STOMP trial includes dose finding and expansion cohorts to describe initial efficacy and toxicity for selinexor and dexamethasone in combination with the proteasome inhibitor carfilzomib, the immunomodulatory agent pomalidomide and the CD38

targeting monoclonal antibody daratumumab among other combinations. However, as with other therapeutic choices in relapsed and refractory multiple myeloma the decision for which of these partners to join with selinexor therapy is largely empiric.

Ex vivo drug sensitivity testing using the My-DST assay has the potential to use a functional assessment of each individual patient's multiple myeloma to help identify the optimal agents to increase likelihood of treatment response. We propose to evaluate the efficacy of physician's choice therapy for RRMM using selinexor based 3-drug combinations selected by investigators expert judgement. Patients will undergo concurrent My-DST testing prior to the start of therapy to characterize My-DST performance in a prospective manner. The My-DST results will be used for exploratory analyses only and will not be available to providers at time of treatment arm selection.

3.3.2 Dose Schedule Rationale

3.3.2.1 Selinexor Dosing

Based on the pharmacology, pharmacokinetics, pharmacodynamics (PD), tolerability, and efficacy observed in clinical studies, the recommended dose for the use of single-agent selinexor in most cancer indications is 60 mg twice weekly (BIW), administered on Days 1 and 3 of each week, continuously. In patients with heavily pretreated MM, the combination of 80 mg selinexor plus 20 mg dexamethasone BIW was identified as the RP2D (Karyopharm internal report: Selinexor Exposure-Response White Paper, 06 April 2017) and this dose has been shown to be active in penta-refractory MM. When selinexor is combined with other anti-neoplastic agents, it can often be given once weekly (QW) at doses of 60 to 100 mg each week.. Given potential for overlapping hematologic toxicities with pomalidomide 60 mg weekly dosing was selected as selinexor dose as part of SPd combination (arm 1). Hematologic toxicity is less prominent with daratumumab and carfilzomib so 80 mg weekly dosing for selinexor is planned for SDd and SKd combinations (Arms 2 and 3)

3.3.2.2 Pomalidomide Dosing

Pomalidomide is approved for administration as a 4 mg oral capsule on days 1 through 21 of 28 day treatment cycle.

3.3.2.3 Daratumumab Dosing

Daratumumab is approved for administration at a dose of 1,800mg/30,000 units subcutaneously (may be substituted with IV Dara, if directed by Investigator). It is administered on days 1, 8, 15, 22 of cycles 1 and 2, days 1, 15 of cycles 3-6 and day 1 of cycle >6.

3.3.2.4 Carfilzomib Dosing

Carfilzomib is approved for administration on a once weekly schedule with dose of 20 mg/m2 on D1 of cycle one followed by 70 mg/m2 on days 1, 8 and 15 of 28 days schedule in combination with dexamethasone. When used in combination with agents that may have increased risk for overlapping toxicities 56 mg/m2 is being utilized as weekly dosing in ongoing clinical trials. A dose of 56 mg/m2 will be used in planned combination with selinexor and dexamethasone.

3.3.3 Benefit/Risk Assessment

In clinical studies evaluating selinexor, broad antitumor activity has been observed with continual selinexor treatment. A summary of the clinical studies and the antitumor responses observed in each study is provided in the Selinexor IB.

In ongoing clinical studies, the most common AEs reported as at least possibly related to selinexor in CSTs have been low-grade nausea, fatigue, anorexia, thrombocytopenia, and vomiting. Most of these AEs can be managed effectively with dose modification and/or supportive care initiated prior to first dose. In addition, 8 tumor lysis syndrome (TLS) cases have been reported (as of March 2019). No fatal outcomes due to TLS have been reported in any studies with selinexor, or in the ongoing expanded access program. Although the incidence of TLS is low (~0.3%), the causal relationship between selinexor treatment and TLS cannot be completely excluded. Early recognition of signs and symptoms in patients at risk for TLS, including identification of abnormal clinical and laboratory values, is key and Investigators must ensure that patients being treated with selinexor maintain adequate caloric and fluid intake. Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are most relevant. See Section 7.13.2 for supportive care and Table 6 for selinexor dose modification guidance More detailed information about the known and expected benefits and risks of selinexor is provided in the Selinexor IB.

Selinexor in combination with partner agents including pomalidomide, carfilzomib, daratumumab along with dexamethasone are being evaluated in the ongoing phase 1b/2 STOMP trial. Primary objective for the dose escalation phase of this study includes identification of RP2D for each combination with weekly dosing, these results were incorporated into this studies design to minimize potential toxicities. Pomalidomide, carfilzomib and daratumumab have some potential for overlapping toxicities with selinexor which will be monitored closely with plan for management per protocol specifications.

4 STUDY OBJECTIVES

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the overall response rate achieved with physician's choice selinexor-based combination therapy	ORR by IMWG criteria (based on Kumar et al 2016) [appendix 5]
Secondary	
• To evaluate the minimal residual disease negative response rate achieved with physician's choice selinexor-based combination therapy	MRD negative response rate assessed via NGS or multiparametric flow cytometry with sensitivity of 10^{-5}
• To evaluate the duration of disease control and survival for patients treated with physician's choice selinexor-based combination therapy	PFS, DOR, OS, TTNT
• To evaluate safety and tolerability of selinexor in combination with partner backbone agents	Occurrence, nature and severity of Adverse Events
Exploratory	
• Feasibility of My-DST testing to inform treatment choice	Rate of assay failure; Rate of identification of preferred partner therapy or combination
• Evaluation of My-DST related predictors of response	ORR in patients with concordance or discordance between My-DST results and physicians selected regimen

5 STUDY DESIGN

This study will be a single institution, open-label phase II study to evaluate the overall response rate achieved with physician's choice selinexor and dexamethasone based three-drug combination therapy in RRMM. Patients with relapsed/refractory multiple myeloma will be eligible for enrollment.

During screening, bone marrow aspirate will be collected and in addition to standard of care testing will be evaluated using the My-DST platform. The following agents will be evaluated for sample sensitivity: pomalidomide, carfilzomib and daratumumab. Agents will be tested individually, in combination with selinexor and in combination with selinexor and dexamethasone. My-DST performance characteristics and results will be used for exploratory analyses but will not be available to providers at time of, or incorporated into treatment decision making. Providers will choose to assign patients to one of the following treatment regimens based on clinical judgement/expertise: SPd (arm 1), SDd (arm 2) or SKd (arm 3), dosing is described for combinations in figure 1 and schedules in table 2. Providers will identify their planned treatment arm for each patient using their best clinical judgement. Treatment will be continued until progression of disease on unacceptable toxicity.

6 STUDY POPULATION

6.1 Study Population

The study will enroll patients with relapsed or refractory MM.

6.2 Inclusion Criteria

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

1. Age ≥ 18 years
2. Willing and able to provide written informed consent in accordance with federal, local, and institutional guidelines. The patient must provide informed consent prior to the first screening procedure.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
4. Histologically confirmed diagnosis, measurable disease and evidence of disease progression of MM after 1 or more prior lines of therapy with either of:
   a) Documented evidence of PD after achieving at least SD for ≥ 1 cycle during a previous MM regimen (i.e., relapsed MM)
   b) ≤ 25% response (i.e, patient never achieved ≥ MR) or PD during or within 60 days from end of the most recent MM regimen (i.e., refractory MM)
5. Patients must have measurable disease as defined by at least one of the following:
   a) Serum M-protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
   c) Urinary M-protein excretion at least 200 mg/24 hours
   d) Serum FLC ≥ 10 mg/dL, provided that FLC ratio is abnormal
   e) If no measurable disease by serum or urine, then the presence of a plasmacytoma of ≥ 2cm in one dimension prior to start of study can be used to follow response via radiologic imaging

6. Adequate hepatic function:
   f) Total bilirubin <1.5 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of <3 × ULN), and
   g) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2.5 × ULN.
7. Adequate renal function as determined by serum creatinine of ≤ 2 mg/dL OR estimated creatinine clearance of ≥ 20 mL/min, calculated using the Cockcroft and Gault formula (140 – Age) • Mass (kg)/ (72 • creatinine mg/dL); multiply by 0.85 if female (Cockcroft 1976).
8. Adequate hematopoietic function within 28 days prior to C1D1: absolute neutrophil count ≥1000/mm^3, hemoglobin ≥8 g/dL and platelet count ≥100,000/mm^3 (patients for whom <50% of bone marrow nucleated cells are plasma cells) or ≥50,000/mm^3 (patients for whom ≥50% of bone marrow nucleated cells are plasma cells).
   a) Patients may receive hematopoietic growth factor support, including erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and platelet stimulators (eg, eltrombopag, romiplostim, or interleukin-11) at any time
   b) Patients may receive RBC and/or platelet transfusions as clinically indicated per institutional guidelines during the study.
9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening. Female patients of childbearing potential and fertile male patients who are sexually active with a female of childbearing potential must use highly effective methods of contraception throughout the study and for 3 months following the last dose of protocol required therapies. Highly effective methods of contraception are listed in Section 9.3.1.

6.3 Exclusion Criteria

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

1. Has received selinexor or another XPO1 inhibitor in a previous line of therapy
2. Has any concurrent medical condition or disease (eg, uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.) that is likely to interfere with study procedures.
3. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to Cycle 1 Day 1 (C1D1). Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable.
4. Known intolerance, hypersensitivity, or contraindication to glucocorticoids.
5. Pregnant or breastfeeding females.
6. Major surgery within 4 weeks prior to C1D1.
7. Active, unstable cardiovascular function, as indicated by the presence of:
   a) Symptomatic ischemia, or
   b) Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on anti-arrhythmics are excluded; patients with first degree atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or
   c) Congestive heart failure of New York Heart Association Class ≥3 or known left ventricular ejection fraction <40%, or
   d) Myocardial infarction within 3 months prior to C1D1.
8. Subjects with active hepatitis B virus (Hep B) are allowed if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/ml prior to first dose of trial treatment.

Subjects with untreated hepatitis C virus (HCV) are allowed. Subjects with Human Immunodeficiency Virus (HIV) who have CD4+ T-cell counts ≥ 350 cells/µL and no history of AIDS-defining opportunistic infections in the last year are allowed.

9. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment, including prior gastric bypass or bowel resection procedures.
10. Inability or unwillingness to take supportive medications such as anti-nausea and anti-anorexia agents as recommended by the NCCN CPGO for antiemesis and anorexia/cachexia (palliative care).
11. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent.
12. Contraindication to any of the required concomitant drugs or supportive treatments.
13. Patients unwilling or unable to comply with the protocol, including providing 24-hour urine samples for urine protein electrophoresis at the required time points.

7 STUDY TREATMENTS AND TREATMENT ASSIGNMENT

7.1 Treatments Administered

7.1.1 Study Treatments

The following study treatment(s) will be used in this study:

Selinexor: Provided in either of two formulations (both coated, immediate-release tablets for oral administration): (a) 20 mg tablets in wallet-sized blister packs. Each blister pack has 12 tablets(see IST Pharmacy Manual for more information). Patients will be given a supply of selinexor for nonclinic dosing days.

Selinexor will be provided as tablets for oral administration in blister packs (see IST Pharmacy Manual for more information). Selinexor tablets will contain 20 mg of the active pharmaceutical ingredient (API).

Study treatments must be dispensed only by a pharmacist or appropriately qualified staff. Study treatments are to be dispensed only to patients enrolled in this study.

Pomalidomide: Patients in the SPd Arm will receive a 21-day supply of pomalidomide 4 mg oral capsules for each 28-day treatment cycle.

Daratumumab: Patients in the SDd Arm will receive daratumumab subcutaneous injections, (QW for Cycles 1 and 2; every 2 weeks for Cycles 3-6; and every 4 weeks for Cycles > 6) as indicated in the Darzalex™ (daratumumab) package insert. Daratumumab will be administered by trained staff in the clinic only.

Carfilzomib: Patients in the SKd Arm will receive carfilzomib IV infusions (QW on Days 1, 8, and 15 of each 28-day cycle). Carfilzomib will be administered by trained staff in the clinic only.

7.2 Study Treatment Labeling and Storage

7.2.1 Labeling

All labels will include conditions for storage, lot number, and other information required by the Food and Drug Administration (FDA), International Council for Harmonisation (ICH), and/or Annex 13, and all local regulations for investigational medications.

7.2.2 Storage

Refer to the IST Pharmacy Manual for selinexor storage.

Pomalidomide, carfilzomib and daratumumab should be stored as described in the prescribing information.

7.3 Study Treatment Dosing and Administration

7.3.1 Dispensing Directions

Dispensing instructions for selinexor will be provided in the IST Pharmacy Manual.

For doses of oral selinexor to be taken on nonclinic days, patients will be provided with an adequate supply of selinexor for self-administration at home until at least their next scheduled study visit. Patients will be provided with a take home diary to complete on home dosing days; the patient diary will be reviewed at each clinic visit.

7.3.2 Dosing Information

7.3.2.1 Selinexor

Refer to the IST Pharmacy Manual for details of selinexor formulation, preparation, and administration.

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water at approximately the same time each day. It can be taken with or without food. Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

For doses of selinexor that are to be taken on nonclinic days, the patient will be provided with selinexor by the site pharmacy and selinexor may be self-administered by the patient on an outpatient basis.

7.3.2.2 Pomalidomide, Carfilzomib and Daratumumab

For details of pomalidomide, carfilzomib and daratumumab formulation, preparation, and administration, please refer to the full prescribing information for each respective agent

Carfilzomib and daratumumab will only be administered by qualified site personnel during clinic visits in accordance with the prescribing information for carfilzomib and daratumumab respectively (in the appropriate local language).

7.3.3 Dose Sequence and Timing for Combination Treatments

Each study treatment dose can be given at the same time or in any order.

7.4 Method of Assigning Patients to Treatment Groups

Patients will be assigned to treatment arms 1, 2 or 3 by investigator's choice following completion of screening assessments including MyDST testing.

7.5 Blinding

Not applicable, this is an open-label study.

7.6 Dose Schedules for Evaluation

The following dose schedule(s) will be evaluated:

See Section 7.8 for dose modifications.

7.6.1 Selinexor/Pomalidomide/Dexamethasone Arm (1)

The dose schedule for the selinexor/pomalidomide/dexamethasone Arm (4-week [28-day] cycle) is provided in Table 2 Schedule of Study Activities and Assessments – ARM 2(SDd)

	Screening[a]	**Cycle 1**					**Cycle 2**		**Cycles ≥3**		**End-of-Treatment (EoT) Visit**	**Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)**
Activity/Assessment	**Day -28 to Day 1**	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
		-1 day[s]	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Daratumumab (SQ/IV)		X		X	X	X	X	X	X	X (day 15. Stop this dose at cycle 7+)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording				*Continuous (until 30 days after last dose of protocol required therapies)*								
SAE reporting[q]		*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*										
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

u Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

v After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

w Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

x ICF must be signed before any study-specific procedures are performed.

y BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

z Patients must rest for at least 5 minutes prior to the ECG recording.

aa Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

bb Details for clinical laboratory tests are provided in Table .

cc For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

dd Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

ee Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

ff Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

gg If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

hh Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis
b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

ii After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

jj Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

kk SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

ll Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

mm Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

nn These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

Table 3 Schedule of Study Activities and Assessments – ARM 3 (SKd)

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Carfilzomib (SQ/IV)		X		X	X		X	X	X	X		

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
								(day 8, 15)		(day 8, 15)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]	*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*											
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

u Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

v After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

w Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

x ICF must be signed before any study-specific procedures are performed.

y BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

z Patients must rest for at least 5 minutes prior to the ECG recording.

aa Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

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cc For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

dd Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

ee Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

ff Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

gg If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

hh Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
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b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

ii After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

jj Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

kk SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

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mm Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

nn These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

.

- selinexor will be given as a 60 mg dose on Days 1, 8, 15 of each 28-day cycle.
- pomalidomide will be given at a dose of 4 mg on Days 1-21 of each 28-day cycle.
- dexamethasone will be given at a dose of 40 mg on days 1, 8, 15 of each 28-day cycle.

7.6.2 Selinexor/Daratumumab/Dexamethasone Arm (2)

The dose schedule for the selinexor/daratumumab/dexamethasone Arm (4-week [28-day] cycle) is provided in Table 2 Schedule of Study Activities and Assessments – ARM 2(SDd)

	Screening[a]	**Cycle 1**					**Cycle 2**		**Cycles ≥3**		**End-of-Treatment (EoT) Visit**	**Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)**
	Day -28 to Day 1	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
Activity/Assessment		**-1 day[s]**	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												

	Screening[a]	**Cycle 1**					**Cycle 2**		**Cycles ≥3**		**End-of-Treatment (EoT) Visit**	**Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)**
	Day -28 to Day 1	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
Activity/Assessment		**-1 day[s]**	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Daratumumab (SQ/IV)		X		X	X	X	X	X	X	X (day 15. Stop this dose at cycle 7+)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording				*Continuous (until 30 days after last dose of protocol required therapies)*								
SAE reporting[q]		*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*										
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

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ccc After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

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ggg Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

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	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
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		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Carfilzomib (SQ/IV)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]	*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*											

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

oo Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

pp After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

qq Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

rr ICF must be signed before any study-specific procedures are performed.

ss BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

tt Patients must rest for at least 5 minutes prior to the ECG recording.

uu Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

vv Details for clinical laboratory tests are provided in Table .

ww For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

xx Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

yy Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

zz Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

aaa If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

bbb Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis
b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

ccc After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

ddd Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

eee SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

fff Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

ggg Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

hhh These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

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- selinexor will be given as a 80 mg dose on Days 1, 8, 15 of each 28-day cycle.
- daratumumab will be given at a dose of 1,800mg/30,000 units (may be substituted with IV Dara, if directed by Investigator) on Days 1, 8, 15, 22 in cycle 1 and 2, Days 1, 15 in cycles 3-6 and Day 1 of cycles greater than 6 of 28-day cycles.
- dexamethasone will be given at a dose of 40 mg on days 1, 8, 15, 22 of each 28-day cycle.

7.6.3 Selinexor/Carfilzomib/Dexamethasone Arm (3)

The dose schedule for the selinexor/carfilzomib/dexamethasone Arm (4-week [28-day] cycle) is provided in Table 2 Schedule of Study Activities and Assessments – ARM 2(SDd)

	Screening[a]	**Cycle 1**					**Cycle 2**		**Cycles ≥3**		**End-of-Treatment (EoT) Visit**	**Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)**
	Day -28 to Day 1	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
Activity/Assessment		**-1 day[s]**	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X	X	X		

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
								(day 8, 15)		(day 8, 15)		
Daratumumab (SQ/IV)		X		X	X	X	X	X	X	X (day 15. Stop this dose at cycle 7+)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]		*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*										
Concomitant medication recording		*Continuous*										
Nutritional consultation		*Perform if clinically indicated*										
Contact subject			X[c]									
Collection of information regarding												X

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
antineoplastic therapy used after EoT												
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

iii Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

jjj After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

kkk Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

lll ICF must be signed before any study-specific procedures are performed.

mmm BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

nnn Patients must rest for at least 5 minutes prior to the ECG recording.

ooo Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

ppp Details for clinical laboratory tests are provided in Table .

qqq For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

rrr Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

sss Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

ttt Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

uuu If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

vvv Bone marrow samples

a. Aspirates at Screening for:

i. My-DST Assessment
ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
iii. Baseline MRD analysis

b. At time of response, an aspirate and core biopsy are needed to:
i. Core biopsy to confirm CR and sCR, (per IMWG)
ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

www After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

xxx Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

yyy SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

zzz Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

aaaa Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

bbbbThese procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

Table 3 Schedule of Study Activities and Assessments – ARM 3 (SKd)

	Screening[a]	**Cycle 1**					**Cycle 2**		**Cycles ≥3**		**End-of-Treatment (EoT) Visit**	**Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)**
	Day -28 to Day 1	**Day 1**	**Day 3** Phone Call[c]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8, 15, 22**	**Day 1**	**Day 8, 15, 22**	≤14 Days Post-Last Dose	
Activity/Assessment		**-1 day[s]**	**+ 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 14 days**
ICF[d]	X											
Inclusion/exclusion criteria	X											
Patient History												
Demographics	X											

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
Medical history	X											
Clinical Assessments												
Height	X											
Weight	X	X					X		X		X	
Body Surface Area (BSA)[e]	X											
Vital signs[g]	X	X		X	X		X		X		X	
ECOG	X						X		X		X	
Physical Exam	X	X					X		X		X	
Symptom-directed PE				*Perform if clinically indicated)*								
12-lead ECG[f]	X	*Perform if clinically indicated)*									X	
Echocardiogram or MUGA[t]	*Perform if clinically indicated)*											
Laboratory Assessments												
Urinalysis[h]	X										X	
CBC with differential[h]	X	X		X	X		X		X		X	
Complete serum chemistry[h]	X	X		X	X		X		X		X	
LDH, CRP, TSH, PT/INR, PTT	X										X	
Pregnancy test (if applicable)[i]	X						X		X (even cycles only)		X	
Dose Administration												
Selinexor (PO)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Carfilzomib (SQ/IV)		X		X	X		X	X (day 8, 15)	X	X (day 8, 15)		
Dexamethasone (PO/IV)		X		X	X	X	X	X	X	X		
Multiple Myeloma Disease Assessments												
SPEP and serum protein immunofixation[k,o]	X	X					X		X		X	

Activity/Assessment	Screening[a]	Cycle 1					Cycle 2		Cycles ≥3		End-of-Treatment (EoT) Visit	Durability of Response (Every 3 months) and Survival Follow-up[b] (Yearly)
	Day -28 to Day 1	Day 1	Day 3 Phone Call[c]	Day 8	Day 15	Day 22	Day 1	Day 8, 15, 22	Day 1	Day 8, 15, 22	≤14 Days Post-Last Dose	
		-1 day[s]	+ 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		± 14 days
UPEP (24-hr urine) and urine protein immunofixation[k,o,t]	X						X		X		X	
Quantitative Immunoglubilin levels (IgG, IgA, IgM)[k,o]	X	X					X		X		X	
Serum FLC[k,o]	X	X					X		X		X	
β_2-microglobulin	X										X	
Skeletal survey[l,o]	X										X	
Plasmacytoma assessment[m,o]	X	X					X		X		X	
Bone marrow aspirate[n,t]	X						X		X			
Bone marrow core biopsy[t]	X											
HR-QoL[q]	X						X		X		X	
Adverse events recording		*Continuous (until 30 days after last dose of protocol required therapies)*										
SAE reporting[q]	*Continuous (Only SAEs related to study procedures during screening. Report until 30 days after last dose of protocol required therapies)*											
Concomitant medication recording	*Continuous*											
Nutritional consultation	*Perform if clinically indicated*											
Contact subject			X[c]									
Collection of information regarding antineoplastic therapy used after EoT												X
Survival Follow Up												X

AE: adverse event; BSA: body surface area; CBC: complete blood count; C1D1: Cycle 1 Day 1; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; hCG: human chorionic gonadotropin; ICF: informed consent form; HR-QoL: health-related quality of life; <MUGA: multiple gated acquisition> PDn: pharmacodynamics; PE: physical examination; PK: pharmacokinetics; SAE: serious adverse event;<TSH: thyroid-stimulating hormone>.

iii Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

jjj After End of Treatment, if feasible and clinically indicated, MM evaluations should be performed every 3 months for patients who have not progressed to assess durability of response. If MM evaluations cannot be performed, at a minimum, contact will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and

overall medical condition of the patient and collect information on any antineoplastic therapies used after End of Treatment (see Section 8.5.3). These procedures should only be performed for subjects who have not had disease progression. Otherwise, after end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for two years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

kkk Contact with patient to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. The contact with the patient should take place on Day 3 following the Cycle 1 Day 1 selinexor dosing.

lll ICF must be signed before any study-specific procedures are performed.

mmm BSA should be calculated during Screening and as needed during the study to make sure that no patient receives a dose of selinexor >70 mg/m^2.

nnn Patients must rest for at least 5 minutes prior to the ECG recording.

ooo Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study. Vital signs do not need to be repeated if they are performed as part of the physical examination. Vital signs should be assessed predose on the scheduled visit day, if possible.

ppp Details for clinical laboratory tests are provided in Table .

qqq For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycle 2 and even numbered cycles ≥3 while on treatment (a negative pregnancy test must be documented prior to administration of study drug) and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

rrr Generally, with some exceptions, the storage, processing and analysis of samples for correlative studies in KPT ISTs are the responsibility of the study Sponsor-Investigator.

sss Response criteria include SPEP, UPEP (24-hr urine), serum and urine protein immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1

ttt Skeletal survey to be performed using X-rays per institutional guidelines. If clinically appropriate, MRI, CT, or PET/CT may be used instead. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.

uuu If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on Day 1 of each cycle and at the EoT visit.

vvv Bone marrow samples

a. Aspirates at Screening for:
   i. My-DST Assessment
   ii. FISH analysis to confirm diagnosis and classify MM sub-type (per IMWG),
   iii. Baseline MRD analysis
b. At time of response, an aspirate and core biopsy are needed to:
   i. Core biopsy to confirm CR and sCR, (per IMWG)
   ii. Aspirate for MRD analysis for patients who achieve CR or sCR, MRD will be assessed by either Adaptive Biotech's Clonoseq NGS platform (preferred) or Mayo Flow Cytometry, both validated at a detection capacity of 10^{-5}

www After End of Treatment, if possible, for patients whose disease is not progressing, SPEP with serum protein immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and bone marrow aspirate and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) will be performed every 3 months for 1 year to assess DOR. See Section 6.14.5. If these assessments cannot be performed, (and for patients who had PD and are therefore not followed for response), contact will be made to the patient (or the patient's family) annually for 2 years to inquire about the patient's survival, MM status, general health, and information on any antineoplastic therapies utilized since End of Treatment.

xxx Patient should complete all of the HR-QoL instruments (ie, EORTC QLQ-C30 and QLQ-MY20) on these visits before any study-related procedures (including discussions with medical personnel and other study-related evaluations).

yyy SAEs must be reported to KPT within 24 hours of first awareness. See required form in Appendix 1. Line listings of all AEs must be submitted to KPT twice per year. See required template in Appendix 2 For information about cross-reported SUSARs from KPT's CSTs, see memo in Appendix 3.

zzz Patients will be given nutritional consultation, if clinically indicated, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This may be completed between within the screening period for the study and prior to administration of study treatment on C1D1. The nutritional consultation can be done by a study investigator or nurse and can be done on a phone call.

aaaa Evaluations may be performed on day-1 of cycle 1 if required due to infusion related logistics.

bbbb These procedures should be performed per Investigator discretion, as appropriate for response assessment. UPEP, BM aspirate and BMBX will be performed at baseline, then as applicable based on baseline results for response assessment through the trial.

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- selinexor will be given as a 80 mg dose on Days 1, 8, 15 of each 28-day cycle.
- carfilzomib will be given at a dose of 20 mg/m^2 on Day 1 of cycle 1 then 56 mg/m^2 on Days 8, 15 of cycle 1 and Days 1, 8, 15 of each subsequent 28-day cycle.
- dexamethasone will be given at a dose of 40 mg on days 1, 8, 15, 22 of each 28-day cycle.

7.7 Missed or Vomited Doses

7.7.1 Missed Doses of Selinexor

Missed doses should be managed as follows:

- **If a dose was missed**, the schedule of that week should be altered to accommodate two doses in that week with at least 36 hours between 2 consecutive doses.
- **If a dose must be skipped** (eg, due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

If a patient missed a full 1- or 2-week period of dosing for non-study treatment-related events (eg, a required medical procedure or an unanticipated personal emergency), the days missed will be replaced. For example, if the patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then the patient will start the next dosing on Cycle 2 Day 7 following the break. Similarly, if a patient misses Cycle 3 Day 1 to Cycle 3 Day 15, then the patient will start the next dosing on Cycle 3 Day 1.

7.7.2 Vomited Doses of Selinexor

If a dose of selinexor is vomited within 1 hour of ingestion, and all intact tablets are seen, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

7.8 Dose Modifications

All dose modifications will be captured in the site's record, as applicable.

7.8.1 Selinexor Dose Reduction Guidelines

Dose reductions and/or schedule modifications are allowed in order to optimize the antitumor activity and tolerability of selinexor. For some AEs, dose interruption and/or reduction is recommended. See Table 2 for pre-specified dose modifications for AEs related to study treatment and see Table 3 for dose reduction and interruption recommendations.

While drug-related major organ toxicities are not prominent, thrombocytopenia and a number of constitutional side effects can limit dosing with selinexor. Therefore, patients should also be treated with supportive care to reduce toxicities (see Section 7.10.2). In addition, it should be noted that the constitutional side effects often attenuate over the first 4 to 6 weeks of dosing.

The CTCAE v 5.0 is used for grading the severity of AEs; the therapy modifications described in Table 3 are applied according to this severity grading. Toxicity will be documented as described in Section 9.1.3. If more than 1 type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay, as well as the reason, must be documented (Table 2 and Table 3).

Table 2 summarizes the starting doses (Dose Level 1) and preferred dose modifications (ie, Dose Levels -1 through -3) for AEs listed in Table 3Table 3. General supportive care guidelines are provided in Section 7.10.1 and Section 7.10.2.

Table 2 Pre-specified Dose Modifications for AEs Related to Study Treatment

Selinexor Dose Level[a]	Selinexor Dose Schedule
Dose level 0 (starting dose)	80 mg (4 tablets) weekly (Day 1)
Dose level -1[b]	60 mg weekly (Day 1)
Dose level -2[c]	40 mg weekly (Day 1)
Dose level -3[d]	20 mg weekly (Day 1)

[a]For some AEs, dose interruption rather than reduction is recommended. See Table 3 for specific recommendations.
[b]This is dose level 0 for Arm 1
[c]This is dose level -1 for Arm 1
[d]This is dose level -2 for Arm 1

Table 3 Suggested Supportive Care and Dose Adjustment Guidelines for AEs Related to Selinexor

Adverse Event	Occurrence	Action
Hematologic Adverse Events		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce selinexor by 1 dose level (see Table 2)

Adverse Event	Occurrence	Action
Platelet count 25,000 to less than 75,000/mcL *with* concurrent bleeding	Any	• Interrupt selinexor • Restart selinexor at 1 dose level lower after bleeding has resolved (see Table 2) • Administer platelet transfusions per clinical guidelines
Platelet count than 25,000/mcL	Any	• Interrupt selinexor • Monitor until platelet count returns to at least 50,000/mcL • Restart selinexor at 1 dose level lower (see Table 2)
Neutropenia		
ANC 0.5 to 1.0 × 10^9/L without fever	Any	• Reduce selinexor by 1 dose level (see Table 2)
ANC <0.5 × 10^9/L OR febrile neutropenia	Any	• Interrupt selinexor • Monitor until ANC returns to ≥1.0 × 10^9/L • Restart selinexor at 1 dose level lower (see Table 2)
Anemia		
Hb <8.0 g/dL	Any	• Reduce selinexor by 1 dose level (see Table 2) • Administer blood transfusions and/or other treatments per clinical guidelines
Life-threatening consequences	Any	• Interrupt selinexor • Monitor until Hb returns to ≥8.0 g/dL • Restart selinexor at 1 dose level lower (see Table 2) • Administer blood transfusions and/or other treatments per clinical guidelines
Nonhematologic Adverse Events		
Hyponatremia		
Sodium ≤130 mmol/L	Any	• Interrupt selinexor, evaluate, and provide appropriate supportive care • Monitor until sodium returns to >130 mmol/L • Restart selinexor at 1 dose level lower (see Table 2)
Fatigue		
Grade 2 lasting >7 days OR Grade 3	Any	• Interrupt selinexor • Monitor until fatigue resolves to Grade 1 or baseline • Restart selinexor at 1 dose level lower (see Table 2)
Nausea and Vomiting		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss,	Any	• Maintain selinexor and initiate additional anti-nausea medications

Adverse Event	Occurrence	Action
dehydration or malnutrition) OR Grade 1 or 2 vomiting (5 or fewer episodes per day)		
Grade 3 nausea (inadequate oral caloric or fluid intake) OR Grade ≥3 vomiting (6 or more episodes per day)	Any	• Interrupt selinexor • Monitor until nausea or vomiting has resolved to ≤Grade 2 or baseline. • Initiate additional anti-nausea medications • Restart selinexor at 1 dose level lower (see Table 2)
Diarrhea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	First	• Maintain selinexor and institute supportive care
	Second and subsequent	• Reduce selinexor by 1 dose level (see Table 2) • Institute supportive care
Grade ≥3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt selinexor and institute supportive care • Monitor until diarrhea resolves to Grade ≤2 • Restart selinexor at 1 dose level lower (see Table 2)
Weight Loss and Anorexia		
Weight loss of 10% to <20% OR anorexia associated with significant weight loss or malnutrition	Any	• Interrupt selinexor and institute supportive care • Monitor until weight returns to >90% of baseline weight • Restart selinexor at 1 dose level lower (see Table 2)
Other Nonhematologic Adverse Events		
Grade 3 or 4	Any	• Interrupt selinexor • Monitor until resolved to ≤Grade 2 • Restart selinexor at 1 dose level lower (see Table 2)

ANC = absolute neutrophil count; Hb = hemoglobin.

7.8.1.1 **Selinexor Dose Adjustment in the Setting of Infection**

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

7.8.1.2 Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be interrupted or reduced in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (eg, urate) abnormalities that are reversible with standard interventions
- Isolated values of Grade ≥3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed.

7.8.2 Dose Modifications for Overlapping Toxicities

Thrombocytopenia and neutropenia are potential overlapping toxicities for selinexor with the non-selinexor drug (e.g., bortezomib). If a patient has drug-induced thrombocytopenia or neutropenia while receiving the combinations under investigation in this study, the Investigator should attempt to determine which drug may be responsible and treat appropriately, including dose modifications, as necessary. If the cause cannot be attributed to a single drug, suggested management strategies for possibly drug-induced thrombocytopenia and neutropenia Grade 3/4 events are provided below.

7.8.2.1 Thrombocytopenia

1. Grade 2 - Consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]) and platelet transfusions, per institutional guidelines. Monitor platelet counts weekly. (See Table 6, under Thrombocytopenia.)
2. Grades ≥ 3 - Interrupt/adjust selinexor dose as described in Table 6, under Thrombocytopenia.
3. Grades ≥ 3 - Interrupt/adjust the dose for the non-selinexor drug as described in that product's approved labeling.

7.8.2.2 Neutropenia

1. Grade 3 without fever – Maintain selinexor dose and consider supportive care as described in Table 6, under Neutropenia.
2. Grade 4 without fever – Reduce selinexor dose by one level. See additional supportive care in Table 6, under Neutropenia.
3. Grades 3/4 with fever – Interrupt selinexor dosing until fever resolves and patient is clinically stable. When patient is clinically stable, restart selinexor one dose level lower. See additional supportive care in Table 6, under Neutropenia.
4. Grades 3/4 – If interrupting selinexor does not resolve the neutropenia, consider interrupting/adjusting the dose of the non-selinexor drug as

described in that product's approved labeling.

The manufacturers of the non-selinexor drugs have provided dose adjustment guidelines for managing Grade 3-4 thrombocytopenia that occur during treatment with their products in their respective product monograph/labeling.

These guidelines, together with the recommended dose adjustments for selinexor provided in Table 6, should be consulted by the Investigator to manage thrombocytopenia associated with study treatments, as needed.

7.8.3 Carfilzomib Dose Modifications

Carfilzomib Dose Reduction	
Dose Level 0 (Starting Dose)	Carfilzomib IV 56 mg/m^2 on days 1,8,15 of a 28-day cycle
Dose Level -1	Carfilzomib IV 45 mg/m^2 on days 1,8,15 of a 28-day cycle
Dose Level -2	Carfilzomib IV 36 mg/m^2 on days 1,8,15 of a 28-day cycle

Specific dose adjustment/modification/delay considerations:

Cardiac Toxicity Grade 3 or 4, new onset or worsening of: • congestive heart failure; • decreased left ventricular function; • or myocardial ischemia	• Withhold until resolved or returned to baseline. • After resolution, restart with 1 dose level reduction • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Hypertension	• Withhold until resolved or returned to baseline. • After resolution, restart with 1 dose level reduction • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Complications • Grade 3 or 4	• Withhold until resolved or returned to baseline. • After resolution, restart with 1 dose level reduction • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Renal Toxicity • Serum creatinine greater than or equal to 2 × baseline, or • Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) • If attributable to Kyprolis, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reductiona • If not attributable to Kyprolis, dosing may be resumed at the discretion of the physician • For patients on hemodialysis receiving Kyprolis, the dose is to be administered after the hemodialysis procedure
Hepatic Impairment Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of: (1) total bilirubin (> 33%	25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.

direct) > 1x ULN to < 3x ULN OR (2) an elevation of AST and/or ALT with normal bilirubin	
Grade 3 elevation in ALT and/or AST (> 5x ULN)	Hold carfilzomib until resolution to baseline. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatotoxicity is excluded.
Grade 3 elevation in total bilirubin	Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly. Upon resolution of total bilirubin to normal, resume carfilzomib dosing with a 25% dose reduction if drug-induced hepatotoxicity is excluded.
Drug-induced hepatotoxicity (attributable to carfilzomib)	**Discontinue carfilzomib**
Posterior Reversible Encephalopathy Syndrome (PRES)	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.
Thrombotic Microangiopathy (TMA)	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted.

7.8.4 Pomalidomide Dose Modifications

Pomalidomide Dose Reduction	
Dose Level 0 (Starting Dose)	Pomalidomide 4 mg oral on days 1-21 of a 28-day cycle
Dose Level -1	Pomalidomide 3 mg oral on days 1-21 of a 28-day cycle
Dose Level -2	Pomalidomide 2 mg oral on days 1-21 of a 28-day cycle

7.9 Duration of Treatment and Follow-up

There is no maximum treatment duration. Patients will continue to receive treatment during the study until disease progression (however patients may stay on treatment if they have clinical benefit per the Investigator), death, toxicity (i.e., AEs that cannot be managed with medical care), or withdrawal from the study. After completion of treatment patients will be monitored for survival and subsequent therapies annually for 2 years.

7.10 Supportive Care, Contraception Requirements, Concomitant Medications, and Restrictions

7.10.1 Required Anti-emetic Support

In order to minimize nausea, unless contraindicated, all patients should receive serotonin receptor subtype (5-HT3) antagonists (ondansetron 8 mg or equivalent), starting Q8 hours before each

dosing and continue 2 -3 times daily for a few days after dosing. In addition to the required prophylactic therapy with 5-HT3 antagonists (Section 7.10.1) a second antimetic support for all patients receiving selinexor will include planned neurokinin 1 antagonist (eg aprepitant, fosaprepitant or rolapitant) or olanzapine 5mg at bedtime.

Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists or olanzapine. If an NK1 receptor antagonist is needed, rolapitant is preferred given that the other agents in this class (aprepritant, fosaprepritant, netupitant) may result in drug-drug interactions via inhibition of CYP3A4 which could increase selinexor exposures.

Patients may receive other supportive care, including hydration prophylaxis, antibiotics, as appropriate.

7.10.2 Recommended Supportive Care for All Patients

Supportive measures for optimal medical care should be provided to all patients during participation in this study. Additional supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (CPGO) (NCCN CPGO) should be used as clinically indicated at the discretion of the Investigator.

Supportive care guidelines for managing AEs are provided in Table 3.

7.10.3 Contraception Requirements

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

Female patients of childbearing potential and fertile male patients must agree to use highly effective contraception listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

Highly effective methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Please see Section 9.3.1 for additional safety information related to pregnancy.

7.10.4 Concomitant Medication and Treatment

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

7.10.5 Permitted Concomitant Medication

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

7.10.6 Prohibited Medications

Concurrent therapy with palliative radiation is allowable per Investigator direction and discretion. Investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor-Investigator. Refer to the full prescribing information for pomalidomide, carfilzomib or daratumumab depending on treatment arm for the most current information on prohibited concurrent medications.

7.10.7 Restrictions for Study Treatment

7.10.7.1 Restrictions for Selinexor

Medications: There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen use must not exceed a total daily dose of 1 g.

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

7.10.7.2 Restrictions for pomalidomide, daratumumab and carfilzomib

Refer to the full prescribing information for pomalidomide, daratumumab or carfilzomib based on appropriate corresponding treatment arm for the most current information for restrictions.

8 STUDY ASSESSMENTS

Refer to Schedule of Assessments and Study Schematics

Table 1 for the timing of all assessments.

Procedures that are performed as part of standard of care should not be repeated if they are within the Screening window and are done prior to signing the ICF.

8.1 Informed Consent

Assessments may not be performed until the patient provides written informed consent (see Section 13.6).

8.2 Demographic and Baseline Characteristics Assessments

8.2.1 Demographics

Patient demographics (including date of birth, sex, race, ethnicity, and age at the time of consent) will be collected.

8.2.2 Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline symptoms as well as a detailed history of prior procedures for the patient's myeloma and other prior cancer therapies (ie, chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, PD during or after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will be collected.

Data from standard-of-care procedures will be part of the patient's medical history and may be used for study purposes.

8.3 Efficacy Assessments

8.3.1 Multiple Myeloma Disease Assessments

Patient response will be assessed by the procedures summarized in Table 7 and graded according to IMWG (Appendix 5)

Table 7 Multiple Myeloma Disease-Specific Assessments

Patients will have their disease assessed by the following procedures per modified IMWG (see Appendix 5). Assessments on dosing days should be performed pre-dose. Time points are provided in Table 1.

Procedure	Notes
SPEP with M-spike quantification, and serum protein immunofixation	Per IMWG
UPEP (24-hour urine for total protein) with M-spike quantification and urine protein immunofixation	Per IMWG *(Only applicable if directed by MM disease)*
Serum FLC	Per MWG
Quantitative immunoglobulin (Ig) levels	If SPEP is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry or turbidometry are acceptable. For IgA myeloma, by quantitative IgA.
β_2-microglobulin	For MM staging, not for assessing response
Skeletal survey	A skeletal survey (using X-rays and/or other clinically appropriate imaging [MRI, whole body CT, or PET/CT]) will be performed during Screening and as clinically indicated, per Investigator's discretion, during the study. If X-rays are used, they should include a lateral radiograph of skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri. If lytic bone lesions or plasmacytomas are observed at Screening, their location and measurement should be recorded in the CRF. They should be re-assessed during the study, as clinically appropriate (per Investigator's discretion) using the same imaging modality that was used at Screening.
Plasmacytoma	If plasmacytomas ≥2cm in at least one dimension are detected at baseline by physical examination or imaging (MRI, ultrasound, whole body CT, or PET/CT), they should be serially measured and recorded for response determination. Plasmacytomas that are measurable by physical exam must be assessed during the physical exam on Day 1 of each cycle. Plasmacytomas that are seen by imaging during Screening should be re-assessed during the study as clinically appropriate (per Investigator discretion) using the same imaging modality that was used at Screening.
Bone marrow aspirate/core biopsy	The bone marrow aspirate obtained at Screening will be used for (a) My-DST assessment (b) fluorescence in situ hybridization (FISH) analysis to confirm diagnosis and classify MM sub-type, and A bone marrow aspirate and/or core biopsy is/are required when there is negative immunofixation of serum and urine, and disappearance of any soft tissue plasmacytomas.

Response will be assessed per modified IMWG response criteria for MM as the following (see appendix 5):

- Stringent complete response (sCR)
- Complete response (CR)
- Very good partial response (VGPR)
- Partial response (PR)
- Minimal response (MR)
- Stable disease (SD)
- Progressive disease (PD)

8.4 Safety Assessments

8.4.1 Adverse Events

Information regarding AEs and SAEs will be collected. See Section 9.

8.4.2 Concomitant Medications

Concomitant medications will be documented for each patient at each scheduled visit after consent. A detailed history of medications will be documented. At each study visit, patients will be asked whether they have taken any medication other than the study treatment (from screening through the end of treatment). All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, should be recorded.

Necessary supportive care such as appetite stimulants, anti-emetics, and anti-diarrheals, etc., is allowed (see Section 7.10.1, Section 7.10.2, and Table 3).

8.4.2.1 Medications Administered During Hospitalizations

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach may be utilized for the CRF.

8.4.3 Clinical Safety Assessments

8.4.3.1 Weight, Height, and BSA

Height (without shoes) in centimeters and weight (indoor clothing without shoes) in kilograms will be recorded. BSA will be calculated by the Dubois (Dubois 1916) or Mosteller (Mosteller 1987) method to determine the volume of carfilzomib to be administered and to ensure that an individual patient's selinexor dose does not exceed 70 mg/m^2 or 120 mg per dose for any adult patient or 55 mg/m^2 for any pediatric patient.

8.4.3.2 Physical Examination, Vital Signs, and ECOG Performance Status

Complete physical examinations should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations.

Symptom-directed physical examinations should include body systems as appropriate. These examinations will be performed according to the standards at each institution.

Information about the physical examinations must be present in the source documentation at the study site. Clinically relevant findings made after the start of study dosing, which meet the definition of an AE, must be recorded.

Vital signs include systolic and diastolic blood pressure, pulse measurements, and body temperature. Vital signs should be assessed predose on the scheduled visit day, if possible. Blood pressure and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes and assessed on the same arm throughout the study.

The ECOG performance status assessments (Oken 1982) will be performed during the study to assess how the disease affects the daily living abilities of the patients (<Appendix 4>).

8.4.4 Electrocardiography

A standard 12-lead ECG will be performed. Patients must rest for at least 5 minutes prior to the ECG recording. The date and time the ECG was performed and the following parameters will be recorded: heart rate, PR interval, QT interval, QRS interval, and QT corrected using Fridericia's formula (Fridericia 1920). The Investigator will interpret the ECG using 1 of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant.

8.4.5 Laboratory Safety Assessments

8.4.5.1 Clinical Laboratory Tests

Table 8 presents the clinical laboratory tests that will be performed during the study.

Table 8: Clinical Laboratory Tests

Complete Blood Count with Differential				
Hemoglobin	Hematocrit	Lymphocytes		
WBC count	RBC			
Neutrophils	Platelets			
Complete Serum Chemistry				
Sodium*	Potassium*	Chloride*	Bicarbonate*	Urea or BUN*, [b]
Creatinine*	Glucose*	Calcium	Phosphate	Magnesium
ALT*	AST*			
Pregnancy Test (if applicable)		Beta 2 Microglobulin		
Coagulation				
PT	PTT	INR		
Urinalysis				
Multiple Myeloma Assessment[+]				
SPEP, Protein, total for SPEP/ Serum Protein Immunofixation	24 hr UPEP/Urine Protein Immunofixation	Quantative Immunoglobulins (IgA, IgG, IgM)	Serum Free light chains	
ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen;; LDH: lactate dehydrogenase; RBC: red blood cell; WBC: white blood cell, CRP; C-reactive protein				

*=Limited serum chemistry; [+] = as applicable to MM disease, reference IE

a. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.
b. Urea (mg/dL) = Blood urea nitrogen (mg/dL) × 2.14.
c. Microscopy will only be performed if clinically indicated.

All laboratory safety assessments will be performed and analyzed at each site by a certified local laboratory. The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline.

Any laboratory value that remains abnormal at the End of Treatment (EoT) Visit and that is considered clinically meaningful will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline. Toxicity will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5

A copy of the laboratory certification and normal ranges for each parameter measured must be provided to the Sponsor.

8.4.5.2 Pregnancy Testing

For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Test sensitivity for hCG must be ≥ 25 mIU/mL. A serum hCG pregnancy test is also required for these patients at the EoT Visit.

Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of cycles 1, 2 and subsequent even numbered cycles while on treatment. A negative pregnancy test must be documented prior to administration of study drug.

Pregnancy testing may also be performed as clinically indicated during the study.

8.5 Other Assessments

8.5.1 Nutritional Consultation

Patients will be given nutritional consultation, if clinically indicated and per investigator discretion, to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This consultation may be given by a study investigator or nurse and can be done by phone.

8.5.2 Subject Contact

A telephone call, email or in-person visit will be performed at the following time points:

- Selinexor-containing regimens only: On C1D3, 2 days following the first dose of selinexor on C1D1. The purpose of this telephone call is to evaluate supportive care medications, concomitant medications, and AEs, and to adjust supportive care as appropriate. The contact with the patient should take place on C1D3, 2 days following the first dose of selinexor on C1D1.
- At the Safety Follow-up. The purpose of this telephone call, email or in-person visit with the patient is to assess the overall medical condition of the patient and status of their MM, follow up on any AEs that were not resolved at the EoT Visit, and collect information regarding any antineoplastic therapies used after Endo fo Treatment.

8.5.3 Durability of Response and Survival Follow-up Visit(s)

After discontinuation of selinexor based combination (End of Treatment), if feasible and clinically indicated, the following assessments should be performed at Durability of Response and Survival Follow-up Visits for patients who have not progressed to assess durability of response:

- SPEP and serum protein immunofixation
- Urine protein electrophoresis (UPEP; 24-hour urine) and urine protein immunofixation (if applicable per MM Disease protocol, consult Investigator)
- Serum FLC
- Quantitative Ig levels
- Bone marrow aspirate, as clinically indicated, to assess progression
  - Re-assessment of plasmacytomas by physical examination (if detected by physical examination at Screening)
  - Skeletal survey (imaging) for bone lesions, including tumor measurements as clinically indicated to document response, at frequency determined by the Investigator

If these assessments cannot be performed, at a minimum, a telephone call, email or in-person visit will be made to the patient (or the patient's family) to assess the survival status, status of the patient's MM, and overall medical condition of the patient and collect information on any antineoplastic therapies used after discontinuation of study treatment.

For subjects who have had progressive disease, none of the above assessments are required.

9 SAFETY DEFINITIONS, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Life-threatening adverse event or life-threatening suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth

defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (See Section 10.2.3 for additional information about SAE reporting.)

- *Suspected adverse reaction*: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
- *Unexpected adverse event or unexpected suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not but are not specifically mentioned as occurring with the particular drug under investigation.

9.1.2 Recording of Adverse Events

Adverse Events will be reported and recorded in the eCRF from the time of the first dose of study drug through 30 days after the last dose of protocol required therapies or until the start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. SAEs during screening will only be reported if related to study procedure.

AE monitoring should be continued for at least 30 days following the last dose of protocol required therapies (ie, through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator).

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

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

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

9.1.2.1 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (ie, are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded as an AE. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening Visit) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be recorded as an AE. A Grade 3 or 4 event (considered to be severe per the current version of NCI CTCAE) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 9.1.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such.

9.1.3 Adverse Event Severity

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, ‘severe’ headache). This is not the same as a “serious” AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If there is not a specific NCI CTCAE grading scale for an AE, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- Grade 1 (mild) events are usually transient and do not interfere with the patient’s daily activities.
- Grade 2 (moderate) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Grade 3 (severe) events interrupt the patient’s usual daily activities.
- Grade 4 events are those that are considered to be life-threatening.

9.1.4 Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to each study treatment, as defined below.

- Not related: These events will lack a strong temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible.

Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.

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

9.2 Serious Adverse Events

See Section 9.1.1 for the definition of an SAE. Please note that SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment). Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (ie, an overnight stay to facilitate 24-hour urine collection) are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as in inpatient to the hospital (eg, undesirable effects of any administered treatment) and must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period (see Section 9.2.2). Sudden or unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

9.2.1 Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment, SAEs during screening will only be reported if related to study procedure. All SAEs must be reported on Karyopharm's SAE Report Form in addition to being recorded in the sponsor's database. The original SAE Report Form must be retained in the Investigator's site file.

All applicable sections of the SAE Report Form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the SAE Report Form in English.

9.2.2 Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the Karyopharm study drug, occurring after the patient has signed informed consent until at least 30 days after the patient has stopped the Karyopharm study drug must be reported to the HCTU Quality Team and Karyopharm Pharmacovigilance Department within *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the HCTU Quality Team and Karyopharm Pharmacovigilance Department (Appendix 1).Appendix1

The investigator will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Karyopharm within 24 hours of site awareness.
- Other SAEs, regardless of relationship, will be submitted to the Karyopharm within 72 hours of site awareness.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com and HCTU.quality@ucdenver.edu

Fax: +1-617-334-7617 (USA)
+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to HCTU Quality Team and Karyopharm if the Investigator suspects that the SAE has causal relationship to the Karyopharm study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed and an assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome of the event.

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

The study sponsor (sponsor-investigator) will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Karyopharm may report applicable SAEs to other applicable regulatory authorities and Investigators utilizing selinexor, as may be required.

9.2.3 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected (per the Reference Safety Informantion section of the current version of the IB for selinexor or the product label for daratumumab, carfilzomib and pomalidomide) and judged by the Sponsor-Investigator or Karyopharm to be related to the Karyopharm study drug administered. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" (FDA 2012) or as per national regulatory requirements in participating countries.

Selinexor SUSARs originating from Karyopharm's CSTs **in specific countries** do not need to be cross-reported to the Competent Authorities. Please see memo in Appendix 3, for more information (list of countries).

In addition, Karyopharm will communicate all cases of cerebellar toxicity, Grade 3 or higher, to regulatory authorities, central ethics committees (eg, IRBs), and Investigators, in the format of an expedited Safety Report, within 7 days of awareness of the event.

9.2.4 Adverse Event Reporting

The Investigator will report all AEs (including all non-serious AEs) to Karyopharm Pharmacovigilance twice per year in the form of line-listings in an excel spreadsheet.

Karyopharm, the drug supplier, will supply the cut-off dates of each requested line listing. The line listings will contain the following information: study ID, unique subject ID, adverse event term, serious event (yes or no), onset date (complete or partial), end date (complete or partial), action taken with selinexor, causality to selinexor, event ongoing (yes or no), outcome of AE, severity CTCAE Grade (1-5), subject dosed with selinexor (yes or no), date of first dose of selinexor, MedDRA preferred term, system organ class (optional)

See the excel spreadsheet template in Appendix 2.

9.3 Procedures for Handling Special Situations

9.3.1 Pregnancy and Breastfeeding

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

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (ie, results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 3 months after the end of treatment.

A list of highly effective methods of contraception is provided in Section 7.10.3.

A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, on Day 1 of Cycles ≥2 while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor investigator of this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm Pharmacovigilance.

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

All pregnancies occurring within 3 months after the patient's last dose of protocol required therapies must be reported to Karyopharm, regardless of whether the patient received the

Karyopharm study drug or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 9.2.2).

A pregnancy in a female partner of a male patient must be reported to Karyopharm Pharmacovigilance within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with a selinexor-containing regimen.

10 DISCONTINUATION CRITERIA

10.1 Early Study Termination, Study Treatment Discontinuation, and Patient Withdrawal Criteria

10.2 Early Termination of the Study

The study may be terminated at the discretion of the Sponsor or drug supplier for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients.

The Sponsor, in conjunction with appropriate regulatory authorities and the drug supplier, would then decide if the study should be modified or terminated.

An efficacy-based stopping rule will be in place for this study. Efficacy will be assessed using the proportion of patients who achieve at least a partial response, as defined by IMWG criteria. The complementary failure rate—the rate of patients who do not achieve at least a partial response—will be assessed throughout the study. If at any time in the study the upper bound of the 90% confidence interval for the failure rate exceeds 50%, then the study will be stopped for efficacy.

A safety-stopping rule will also be implemented. In order to monitor toxicity events in this trial, we will assess the number of SAEs or non-hematologic grade 4 or higher toxicity events after 6 patients have been given the treatment regimen. Assuming 25% as an acceptable rate of toxicity events and assuming 40% as an unacceptable rate of toxicity events for this trial, we determine the following stopping rule (equivalent to determining Pocock boundaries with the same significance level used at both looks and an overall alpha level of 0.05): stop the trial if more than 3 toxicity events are observed in the first 6 patients. Assuming no more than 3 toxicity events are observed in the first 6 patients, we treat an additional 6 patients (for a total n = 12) and declare acceptable toxicity levels in the trial if no more than 4 total toxicity events are observed in the first 12 patients.

Table 1 summarizes the probability of observing a specified number of toxicity events in the first 12-patient cohort being studied as well as the 90% confidence interval of the true proportion of

toxicity events. These probabilities do not assume any underlying toxicity rate of the treatment regimen.

Table 1.

Observed Number of drug-related SAEs or grade 4 non-heme toxicities (N=12)	Percent of Toxicity Events	90% CI for the Percent of Toxicity Events
0	0.0%	(0.0%-22.1%)
1	8.3%	(0.4%-33.9%)
2	16.7%	(3%-43.8%)
3	25.0%	(7.2%-52.7%)
4	33.3%	(12.3%-60.9%)
5	41.7%	(18.1%-68.5%)
6	50.0%	(24.5%-75.5%)
7	58.3%	(31.5%-81.9%)

If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team.

10.3 Discontinuation of Study Treatment and/or Withdrawal of Patients from the Study

The Investigator may remove a patient from study treatment for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care (this must be linked in the study database to the AE or toxicity event to support discontinuation).
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

The Investigator must remove a patient from study treatment for any of the following reasons:

- Disease progression
- Patient elects to discontinue study treatment
- Pregnancy

Patients may discontinue study treatment for any reason. Patients who choose to discontinue study treatment should be encouraged to continue in the study so that follow-up information on PD and survival status may be obtained.

Patients may elect to withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study.

The reason for the patient's discontinuation of study treatment must be clearly documented in the study database and include supporting data (ie, discontinuation for PD must be accompanied

by data points in the database to support PD; additionally, if the reason for discontinuation is physician decision, ample justification must be provided and linked to PD values, AEs, etc.).

Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

All patients will be followed until disease progression, they withdraw consent, are withdrawn from the study by the Investigator, have died, or have been lost to follow up.

11 STUDY VISITS

11.1 Description of Study Days

11.1.1 Screening

Screening will include the study procedures described below and will be performed within 28 days prior to the start of therapy (ie, Day -28 to Day 1), as summarized in Schedule of Assessments and Study Schematics

Table 1. The Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF. Data from SOC procedures will be part of the patient's medical history and may be used for study purposes.

Screening may be divided into two (or more) clinic visits at the discretion of the Investigator. The procedures to be performed during screening are listed below assuming such a division, however the decision is up to the Investigator, as long as all procedures are performed and Treatment assignment occurs prior to the first day of study administration.

DAY -28 TO DAY -1

- Sign written informed consent (note age on day consent signed)
- Demographics (date of birth, age, gender, race, and ethnicity)
- Height
- Weight
- Vital signs (BP, pulse, and temperature)
- ECOG
- Complete physical exam
- 12 lead ECG
- ECHO or MUGA
- Laboratory Assessment (CBC w/diff, chemistries, coagulation tests, urinalysis, LDH, CRP, TSH, PT/INR, PTT, pregnancy test)
- Multiple Myeloma Assessment (SPEP/SIFE, 24-hour UPEP/UIFE, quantitative immunoglobulins (IgG, IgA, IgM), serum free light chains, skeletal survey, bone marrow aspirate and core biopsy). Bone marrow aspirate and core biopsy and imaging (skeletal survey, CT, MRI, PET) may be done from day -45 to Day -1.
- QOL questionnaire

- Physician indicates choice of therapy without My-DST guidance.
- My-DST assessment and cohort assignment as per discretion of treating physician

11.1.2 Cycle 1

11.1.2.1 Study Procedures (Days 1-28)

The procedures will be followed for all cohorts:

- Weight (Days 1, 8, and 15)
- Medical history review at baseline prior to first selinexor dosing (Day 1)
- Vital signs (BP, pulse, and temperature Days 1, 8, and 15)
- Symptom directed (limited) PE
- Laboratory assessments (CBC with Differential and complete serum chemistry Days 1, 8 and 15)
- Multiple myeloma assessments, as applicable to MM disease, *reference IE* (SPEP/SIFE, 24-hour UPEP/UIFE, quantitative immunoglobulins, serum free light chains Day 1)

11.1.2.2 Study Treatment Dosing

Arm 1 SPd

- Selinexor 60 mg oral Days 1, 8, 15
- Pomalidomide 4 mg oral on Days 1-21
- Dexamethasone 40 mg IV or oral on Days 1, 8, 15, 22
- 28 Day treatment cycle

Arm 2 SDd

- Selinexor 80 mg oral Days 1, 8, 15
- Daratumumab 1,800mg/30,000 units subcutaneous injection Days 1, 8, 15, 22 (may be substituted with IV Dara, if directed by Investigator)
- Dexamethasone 40mg IV or oral Days 1, 8, 15, 22
- 28 Day treatment cycle

Arm 3 SKd

- Selinexor 80 mg oral Days 1, 8, 15
- Carfilzomib 20 mg/m2 IV infusion Day 1, 56mg/m2 Days 8, 15
- Dexamethasone 40 mg IV or oral Days 1, 8, 15, 22
- 28 Day treatment cycle

11.1.2.3 Cycle 1 Day 3 (+1 day) Contact

Telephone, email or in-person visit contact

11.1.3 Cycles ≥2

The procedures will be followed for all cohorts:

11.1.3.1 Study Procedures

- Weight (Day 1 of each cycle)
- Vital signs (BP, pulse, and temperature)
- Symptom-directed (limited) PE
- Laboratory assessments (CBC with Differential and complete serum chemistry Day 1 of each cycle
- Multiple myeloma assessments, as applicable to MM disease, *reference IE* (SPEP/SIFE, 24-hour UPEP/UIFE, quantitative immunoglobulins, serum free light chains Day 1 of each cycle)
- QOL Questionnaire

11.1.3.2 Study Treatment Dosing

The treatments to be provided are summarized below, by cohort. Procedures will be performed pre-dose when they occur on clinic visit days.

Arm 1 SPd
- Selinexor 60 mg oral Days 1, 8, 15
- Pomalidomide 4 mg oral on Days 1-21
- Dexamethasone 40 mg IV or oral on Days 1, 8, 15, 22
- 28 Day treatment cycle

Arm 2 SDd
- Selinexor 80 mg oral Days 1, 8, 15
- Daratumumab 1,800mg/30,000 units subcutaneous injection Days 1, 8, 15, 22 of cycle 2; Days 1, 15 of cycles 3-6; Day 1 of cycles 7+ (may be substituted with IV Dara, if directed by Investigator)
- Dexamethasone 40 mg IV or oral Days 1, 8, 15, 22
- 28 Day treatment cycle

Arm 3 SKd
- Selinexor 80 mg oral Days 1, 8, 15
- Carfilzomib 56 mg/m2 IV infusion Days 1, 8, 15
- Dexamethasone 40 mg IV or oral Days 1, 8, 15, 22
- 28 Day treatment cycle

11.1.4 End-of-Treatment Visit (≥30 Days after Last Dose)

Study procedures will be performed at 30 days (+ 7 days) after the last dose of protocol required therapies for all patients, including early termination patients, as summarized below.

- Weight
- Vital signs (BP, pulse, and temperature)
- ECOG
- Complete physical exam
- 12 lead ECG
- TTE or MUGA
- Laboratory Assessment (CBC w/diff, complete serum chemistry, coagulation tests (PT/INR and PTT), urinalysis, CRP, LDH, TSH)
- Multiple Myeloma Assessment, as applicable to MM disease, *reference IE* (SPEP/SIFE, 24-hour UPEP/UIFE, quantitative immunoglobulins, serum free light chains, skeletal survey)
- QOL Questionnaire

11.1.5 Survival Follow-Up

After end of treatment visit, a telephone call, email or visit will be made to the patient (or the patient's family) annually, for 2 years, to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since last contact.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

PhD biostatistician and member of the Center for Innovative Design and Analysis at the University of Colorado-Anschutz has responsibility for statistical analysis for this study. Analyses will be conducted using SAS version 9.4. All individuals enrolled in the study will be included in analysis. In the event that an individual is lost to follow-up and does not have data for the endpoint of interest, that individual cannot be included to determine response rate. However, sensitivity analysis will be conducted for individuals lost to follow-up to determine how this might affect results. Sample size calculations assume a power of 80% and Type I error rate of 10%. Analysis Type I error rates for time to event endpoints will be set at 5%.

Efficacy endpoints include proportions (overall response rate, MRD negative response rate, occurrence rate for adverse events, rate of assay failure) and time to event outcomes (progression free survival, duration of response, overall survival, and time to next treatment). For endpoints that are proportions, the study proportion will be calculated using the Intent to Treat Population. Accompanying one-sided 90% confidence intervals surrounding the proportion will be reported. For time to event endpoints, survival curves and median survival times with corresponding two-sided 95% confidence intervals will be computed using Kaplan Meier methods.

12.2 Determination of Sample Size

The primary endpoint of this study will be the overall response rate achieved with physician's choice selinexor based combination therapy. With this treatment approach, we anticipate the response rate will increase to 75%. The null hypothesis is that the true response rate is 51%. Using a one-sided type I error rate of 10%, then given a sample size of 18, there is 80% power to detect a difference with an effect size of 24% when performing a difference in proportion test with normal approximation.

12.3 Analysis Populations

Analysis of the primary endpoint of response rate (partial response rate or better) will be performed on the Intent-to-treat (ITT) population, which will include all subjects who have been enrolled for the study. For individuals lost to follow-up, sensitivity analyses will be performed to see how missing data for response rate affects analysis results. Sample sizes for each treatment arm individually will be too small to formally test hypotheses for each treatment arm, and response rates for these arms will be descriptive in nature.

Secondary endpoints will be descriptive in nature, and no formal statistical analyses will be conducted on them.

12.3.1 Safety Population

There is no safety population—only summary response rates for a standard of care population.

12.4 Demographics and Baseline Characteristics

Demographic and baseline characteristic data will be collected including myeloma specific data, prior treatment exposures, lab and bone marrow biopsy/aspirate results. No formal tests of hypotheses will be made for baseline and demographic data. Qualitative variables will be summarized by frequency tables. Quantitative measures will be summarized by mean and standard deviation values.

12.5 Efficacy Analysis

Efficacy will be assessed using the proportion of patients who achieve at least a partial response, as defined by IMWG criteria. The complementary failure rate—the rate of patients who do not achieve at least a partial response—will be assessed throughout the study. If at any time in the study the upper bound of the one-sided 90% confidence interval for the failure rate exceeds 51%, then the study will be stopped for efficacy.

The table below shows the number of failures to respond to treatment, the corresponding response failure rate in the study population, and the one-sided 90% confidence interval for the failure rate. If the proposed study finds more than 5 patients fail to respond, then a 51% failure rate could no longer be ruled out with 90% confidence.

Number of Patients Who Fail to Respond	Failure Rate	One-sided 90% Confidence Interval for Failure Rate

0	0%	0% - 12.0%
1	5.6%	0% - 20.0%
2	11.1%	0% - 26.9%
3	16.7%	0% - 33.4%
4	22.2%	0% - 39.6%
5	27.8%	0% - 45.5%
6	33.3%	0% - 51.2%

12.6 Safety Analysis

Adverse events including regimen toxicities will be summarized using tables and descriptive statistics as described below.

12.6.1 Adverse Events

Adverse Events (AEs) will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered to be treatment emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of protocol required therapies through 30 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates. In all tabulations, a patient may contribute only once to the count for a given AE preferred term.

The number and percentage of patients with TEAEs will be summarized, as well as the number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same TEAE, the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations.

Serious AEs (SAEs) will also be tabulated.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment emergent and post-treatment) will be listed in patient data listings.

Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

12.6.2 Laboratory Data

The actual value and change from baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, by arm, and for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (ie, those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

12.6.3 Vital Signs and Physical Examinations

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data will be recorded. All examination findings will be presented in a data listing.

13 ADMINISTRATIVE MATTERS

13.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP). Applicable local regulations, including European Directive 2001/20/EC and United States Code of Federal Regulations Title 21, and the ethical principles outlined in the Declaration of Helsinki will be followed.

13.2 Ethics Committees

The protocol, the proposed ICF, and any other relevant records must be reviewed and approved by a properly constituted ethics committee (eg, IRB) before study start.

13.3 Regulatory Authority Approval

Before implementing this study, the protocol must be approved by relevant, competent regulatory authorities.

13.4 Protocol Adherence

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the instructions and procedures found in this protocol and to give access to all relevant data and records to the drug supplier, Quality Assurance representatives, designated agents of the Sponsor-Investigator, ethics committees, and regulatory authorities as required. Investigators attest they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report (CSR). A significant protocol deviation is defined as any change to the execution of the protocol, that affects the scientific integrity or design of the study, or the rights, safety or welfare of study patients.

13.5 Amendments to the Protocol

Any significant change or addition to the protocol by the Sponsor-Investigator can only be made in a written protocol amendment that must be provided by the Sponsor-Investigator, reviewed/approved by the drug supplier, and approved by Health Authorities where required, and the ethics committee (eg, IRB). Only amendments that are required for clarification or patient safety, by the Sponsor-Investigator, may be implemented prior to ethics committee (eg, IRB) approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor-Investigator should be notified of this action and the ethics committee (eg, IRB) at the study site should be informed according to local regulations but not later than 10 working days.

13.6 Informed Consent

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

Informed consent must be obtained before conducting any study-specific procedures. Procedures that are part of the clinical routine evaluations during the initial diagnostic work-up of the patient may be performed before the ICF is signed and dated (ie, procedures that are not specific to the conduct of the study).

Informed consent must also be obtained for patients before conducting any study-specific procedures for treatment.

The process of obtaining informed consent should be documented in the patient source documents. A copy of the ICF must be given to the patient or to the person signing the form on behalf of the patient. The Investigator or designee must record the date when the study ICF was signed in the medical records of the patient. The name and role of the witness, if required, should also be documented.

The Sponsor-Investigator will provide to the drug supplier, in a separate document, a proposed ICF that is appropriate for this study and complies with the ICH GCP guideline and regulatory requirements.

13.7 Patient Confidentiality and Disclosure

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

13.8 Collection, Auditing Study Documentation, and Data Storage

13.8.1 Study Documentations, Record Keeping and Retention of Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of ICH E6 GCP, and according to the regulatory and institutional requirements.

Source data include all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The study database is the primary data collection instrument for the study. The Investigator is responsible for the accuracy, completeness, and timeliness of the data reported in the database and all other required reports. Data reported in the database, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the source documents must be recorded. Any missing data must be explained. If electronic records are used, an audit trail will be maintained by the system, in compliance with 21 CFR Part 11.

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

Essential documents (written and electronic) should be retained for a period of not less than 15 years from the completion of the clinical study unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations, and/or guidelines.

13.8.2 Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- Has the authority to suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

13.8.3 Clinical Monitoring, Audit Procedures

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, , legible, attributable, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico technical departments involved in a clinical trial.

Monitoring for this study will be performed by a qualified research monitor in accordance with the clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 13.8.1.

To facilitate source data verification, the investigators and institutions must provide the study monitor(s) direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

13.9 Termination of the Study

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

14 REFERENCE LIST

Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

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.

FDA Guidance, December 2012. Guidance for industry and investigators: safety reporting requirements for INDs and BA/BE studies.
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf

Fridericia L. Die Systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. [The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease.]. Acta Medica Scandinavica. 1920;53:469-86.

Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317:1098.

National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Available on line at
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655

Berenson, J. R., Cartmell, A., Bessudo, A., Lyons, R. M., Harb, W., Tzachanis, D., . . . Berdeja, J. G. (2016). CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood, 127*(26), 3360-3368. doi:10.1182/blood-2015-11-683854

de Weers, M., Tai, Y. T., van der Veer, M. S., Bakker, J. M., Vink, T., Jacobs, D. C., . . . Parren, P. W. (2011). Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol, 186*(3), 1840-1848. doi:10.4049/jimmunol.1003032

Dimopoulos, M. A., Moreau, P., Palumbo, A., Joshua, D., Pour, L., Hajek, R., . . . Investigators, E. (2016). Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol, 17*(1), 27-38. doi:10.1016/S1470-2045(15)00464-7

Dimopoulos, M. A., Oriol, A., Nahi, H., San-Miguel, J., Bahlis, N. J., Usmani, S. Z., . . . Investigators, P. (2016). Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med, 375*(14), 1319-1331. doi:10.1056/NEJMoa1607751

Fonseca, R., Bergsagel, P. L., Drach, J., Shaughnessy, J., Gutierrez, N., Stewart, A. K., . . . International Myeloma Working, G. (2009). International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia, 23*(12), 2210-2221. doi:10.1038/leu.2009.174

Hideshima, T., Chauhan, D., Shima, Y., Raje, N., Davies, F. E., Tai, Y. T., . . . Anderson, K. C. (2000). Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood, 96*(9), 2943-2950.

Kronke, J., Hurst, S. N., & Ebert, B. L. (2014). Lenalidomide induces degradation of IKZF1 and IKZF3. *Oncoimmunology, 3*(7), e941742. doi:10.4161/21624011.2014.941742

Kuhn, D. J., Chen, Q., Voorhees, P. M., Strader, J. S., Shenk, K. D., Sun, C. M., . . . Orlowski, R. Z. (2007). Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood, 110*(9), 3281-3290. doi:10.1182/blood-2007-01-065888

Kumar, S. K., Callander, N. S., Alsina, M., Atanackovic, D., Biermann, J. S., Chandler, J. C., . . . Kumar, R. (2017). Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw, 15*(2), 230-269.

Kumar, S. K., Dimopoulos, M. A., Kastritis, E., Terpos, E., Nahi, H., Goldschmidt, H., . . . Durie, B. G. M. (2017). Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia, 31*(11), 2443-2448. doi:10.1038/leu.2017.138

Laubach, J., Garderet, L., Mahindra, A., Gahrton, G., Caers, J., Sezer, O., . . . Richardson, P. G. (2016). Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia, 30*(5), 1005-1017. doi:10.1038/leu.2015.356

Lokhorst, H. M., Plesner, T., Laubach, J. P., Nahi, H., Gimsing, P., Hansson, M., . . . Richardson, P. G. (2015). Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med, 373*(13), 1207-1219. doi:10.1056/NEJMoa1506348

Lonial, S., Weiss, B. M., Usmani, S. Z., Singhal, S., Chari, A., Bahlis, N. J., . . . Voorhees, P. M. (2016). Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet, 387*(10027), 1551-1560. doi:10.1016/S0140-6736(15)01120-4

Lu, G., Middleton, R. E., Sun, H., Naniong, M., Ott, C. J., Mitsiades, C. S., . . . Kaelin, W. G., Jr. (2014). The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science, 343*(6168), 305-309. doi:10.1126/science.1244917

Mark, T. M., Forsberg, P. A., Rossi, A. C., Pearse, R. N., Pekle, K. A., Perry, A., . . . Niesvizky, R. (2019). Phase 2 study of clarithromycin, pomalidomide, and dexamethasone in relapsed or refractory multiple myeloma. *Blood Adv, 3*(4), 603-611. doi:10.1182/bloodadvances.2018028027

O'Connor, O. A., Stewart, A. K., Vallone, M., Molineaux, C. J., Kunkel, L. A., Gerecitano, J. F., & Orlowski, R. Z. (2009). A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. *Clin Cancer Res, 15*(22), 7085-7091. doi:10.1158/1078-0432.CCR-09-0822

Overdijk, M. B., Jansen, J. H., Nederend, M., Lammerts van Bueren, J. J., Groen, R. W., Parren, P. W., . . . Boross, P. (2016). The Therapeutic CD38 Monoclonal Antibody Daratumumab Induces Programmed Cell Death via Fcgamma Receptor-Mediated Cross-Linking. *J Immunol, 197*(3), 807-813. doi:10.4049/jimmunol.1501351

Overdijk, M. B., Verploegen, S., Bogels, M., van Egmond, M., Lammerts van Bueren, J. J., Mutis, T., . . . Parren, P. W. (2015). Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs, 7*(2), 311-321. doi:10.1080/19420862.2015.1007813

Palumbo, A., Chanan-Khan, A., Weisel, K., Nooka, A. K., Masszi, T., Beksac, M., . . . Investigators, C. (2016). Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med, 375*(8), 754-766. doi:10.1056/NEJMoa1606038

Palumbo, A., Rajkumar, S. V., Dimopoulos, M. A., Richardson, P. G., San Miguel, J., Barlogie, B., . . . International Myeloma Working, G. (2008). Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia, 22*(2), 414-423. doi:10.1038/sj.leu.2405062

Papadopoulos, K. P., Siegel, D. S., Vesole, D. H., Lee, P., Rosen, S. T., Zojwalla, N., . . . Badros, A. (2015). Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. *J Clin Oncol, 33*(7), 732-739. doi:10.1200/JCO.2013.52.3522

Parlati, F., Lee, S. J., Aujay, M., Suzuki, E., Levitsky, K., Lorens, J. B., . . . Bennett, M. K. (2009). Carfilzomib can induce tumor cell death through selective inhibition of the chymotrypsin-like activity of the proteasome. *Blood, 114*(16), 3439-3447. doi:10.1182/blood-2009-05-223677

Richardson, P. G., Schlossman, R. L., Weller, E., Hideshima, T., Mitsiades, C., Davies, F., . . . Anderson, K. C. (2002). Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood, 100*(9), 3063-3067. doi:10.1182/blood-2002-03-0996

San Miguel, J., Weisel, K., Moreau, P., Lacy, M., Song, K., Delforge, M., . . . Dimopoulos, M. (2013). Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol, 14*(11), 1055-1066. doi:10.1016/S1470-2045(13)70380-2

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA Cancer J Clin, 69*(1), 7-34. doi:10.3322/caac.21551

Sonneveld, P., Avet-Loiseau, H., Lonial, S., Usmani, S., Siegel, D., Anderson, K. C., . . . Orlowski, R. (2016). Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood, 127*(24), 2955-2962. doi:10.1182/blood-2016-01-631200

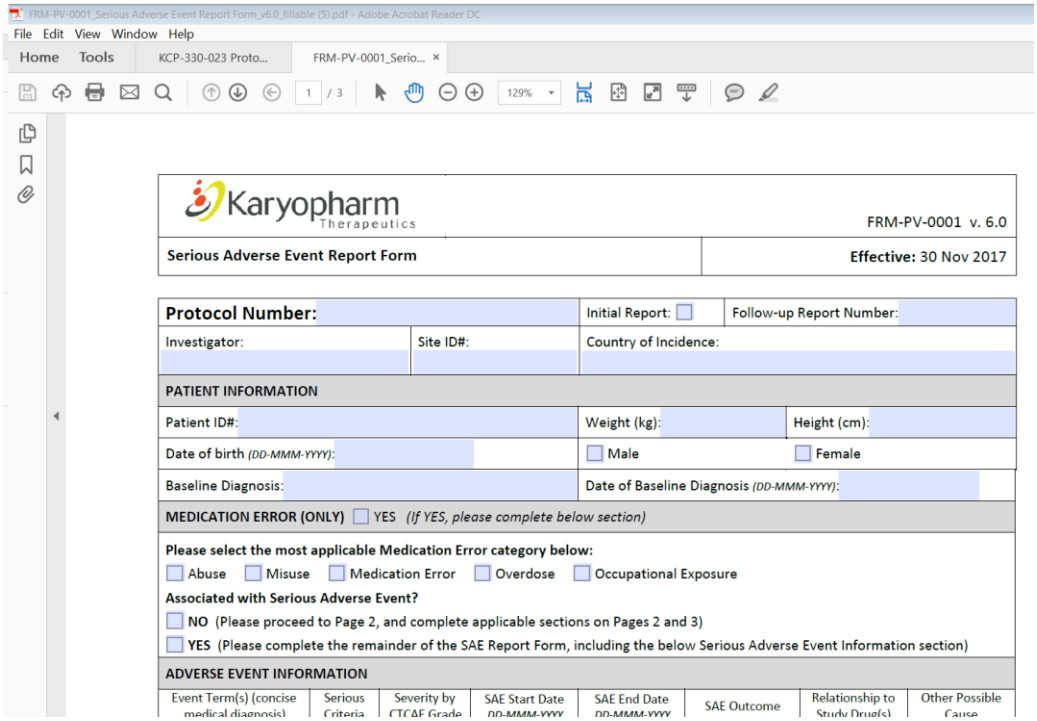
van Bueren, J. L., Jakobs, D., Kaldenhoven, N., Roza, M., Hiddingh, S., Meesters, J., . . . Parren, P. W. H. I. (2014). Direct in Vitro Comparison of Daratumumab with Surrogate Analogs of CD38 Antibodies MOR03087, SAR650984 and Ab79. *Blood, 124*(21).

Vij, R., Wang, M., Kaufman, J. L., Lonial, S., Jakubowiak, A. J., Stewart, A. K., . . . Siegel, D. S. (2012). An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. *Blood, 119*(24), 5661-5670. doi:10.1182/blood-2012-03-414359

Walker, Z. J., VanWyngarden, M. J., Stevens, B. M., Abbott, D., Hammes, A., Langouet-Astrie, C., . . . Sherbenou, D. W. (2020). Measurement of ex vivo resistance to proteasome inhibitors, IMiDs, and daratumumab during multiple myeloma progression. *Blood Adv, 4*(8), 1628-1639. doi:10.1182/bloodadvances.2019000122

Appendix 1 Serious Adverse Event Report Form

<Karyopharm will provide the most recently approved version of this form to the Sponsor-Investigator, as needed.>



FRM-PV-0001_Serious Adverse Event Report Form_v6.0_fillable (5).pdf - Adobe Acrobat Reader DC

File Edit View Window Help

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Karyopharm Therapeutics

FRM-PV-0001 v. 6.0

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

Protocol Number:		Initial Report: ☐	Follow-up Report Number:
Investigator:	Site ID#:	Country of Incidence:	
PATIENT INFORMATION			
Patient ID#:		Weight (kg):	Height (cm):
Date of birth *(DD-MMM-YYYY)*:		☐ Male	☐ Female
Baseline Diagnosis:		Date of Baseline Diagnosis *(DD-MMM-YYYY)*:	

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

Please select the most applicable Medication Error category below:

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

Associated with Serious Adverse Event?

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

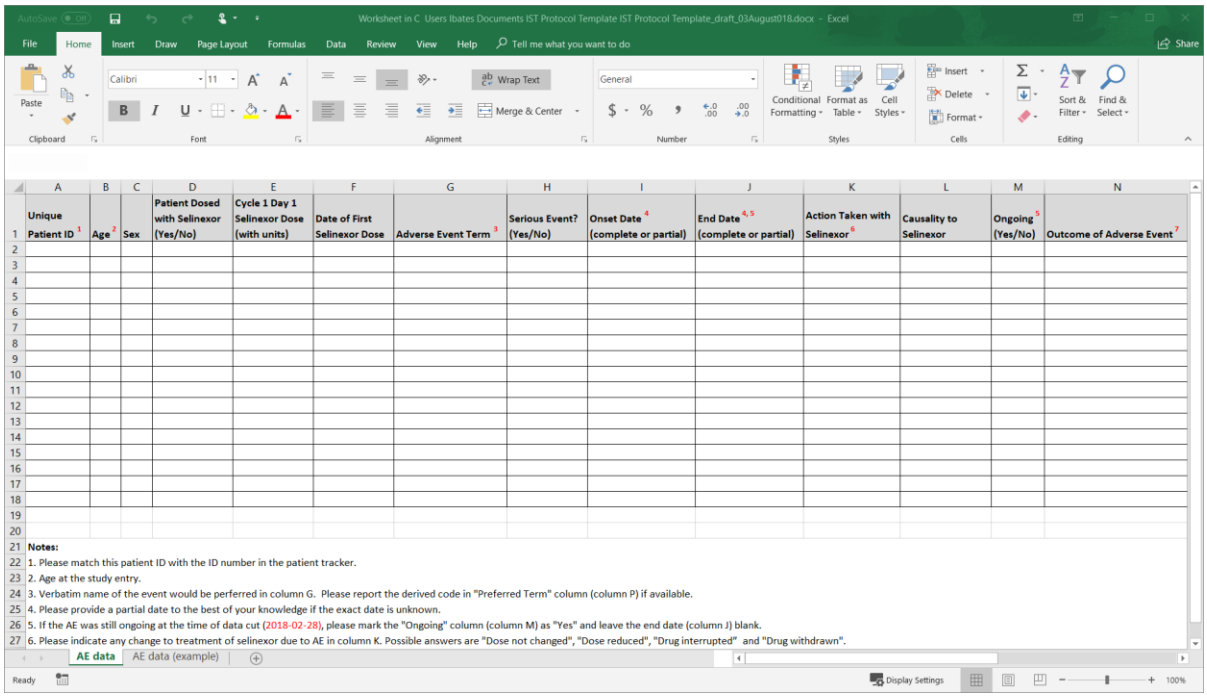
☐ **YES** (Please complete the remainder of the SAE Report Form, including the below Serious Adverse Event Information section)

ADVERSE EVENT INFORMATION

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

Appendix 2 Template for Line Listing of Adverse Events

<Karyopharm will provide the most recently approved version of this form to the Sponsor-Investigator, as needed.>



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Unique Patient ID [1]	Age [2]	Sex	Patient Dosed with Selinexor (Yes/No)	Cycle 1 Day 1 Selinexor Dose (with units)	Date of First Selinexor Dose	Adverse Event Term [3]	Serious Event? (Yes/No)	Onset Date [4] (complete or partial)	End Date [4,5] (complete or partial)	Action Taken with Selinexor [6]	Causality to Selinexor	Ongoing [5] (Yes/No)	Outcome of Adverse Event [7]
2														
3														
4														
5														
6														
7														
8														
9														
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11														
12														
13														
14														
15														
16														
17														
18														
19														
20														
21	**Notes:**													
22	1. Please match this patient ID with the ID number in the patient tracker.													
23	2. Age at the study entry.													
24	3. Verbatim name of the event would be perferred in column G. Please report the derived code in "Preferred Term" column (column P) if available.													
25	4. Please provide a partial date to the best of your knowledge if the exact date is unknown.													
26	5. If the AE was still ongoing at the time of data cut (2018-02-28), please mark the "Ongoing" column (column M) as "Yes" and leave the end date (column J) blank.													
27	6. Please indicate any change to treatment of selinexor due to AE in column K. Possible answers are "Dose not changed", "Dose reduced", "Drug interrupted" and "Drug withdrawn".													

Appendix 3 Memo Regarding Cross-reported SUSARs from KPT CSTs

Date: 25 October 2017

Karyopharm Therapeutics, Inc.
85 Wells Ave., 2nd floor Newton, MA 02459
Phone: 617-658-0600

Fax: 617-244-9420

To: Investigator Sponsored Trials that Utilize Selinexor

RE: Reporting of Selinexor SUSARs Originating from Company Sponsored Trials

From: Karyopharm Pharmacovigilance

Dear Sponsor - Investigator:

This memo is to clarify that Karyopharm reports all selinexor SUSARs originating from Company Sponsored Trials to all Competent Authorities involved in the review and approval of these Company Sponsored Trials. Your IST may be reviewed and approved by the same Competent Authority as a Karyopharm Company Sponsored Trial.

Selinexor SUSARs originating from Company Sponsored Trials therefore do not need to be cross reported to the Competent Authorities of the Countries listed below. Please continue to cross report to your IRB/IEC and other applicable authorities as required by Good Clinical Practice and all national and local regulatory requirements.

United States
Canada
Austria
Belgium
Bulgaria
Czech Republic
Denmark
France
Germany
Greece
Hungary
Israel
Italy
Netherlands
Poland
Russia
Serbia
Spain
United Kingdom
Ukraine

Appendix 4 Eastern Cooperative Oncology Group Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655)

Appendix 5 INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA, MYELOMA

International Myeloma Working Group Response Criteria, Myeloma (Kumar et al 2016)

Response Subcategory	Response Criteria
Stringent complete response (sCR)	Complete response as defi ned below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofi xation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response (PR)	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease 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 unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required.
Minimal response (MR)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confi rmed response value in one or more of the following

	criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the diff erence between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Source: *Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; 17: e328–46

Principal Investigator: Peter Forsberg, MD
COMIRB No: 20-2202
Version Date: v4, 22NOV2022

Study Title: Personalized Selinexor-based therapy for Relapsed/Refractory Multiple Myeloma

Key Information

Please read all the information below and ask questions about anything you don't understand before deciding if you want to take part.

You are being asked to be in a research study. Participation in Research is voluntary.

Purpose of the Study: We are doing this study to learn more about how selinexor (the study drug) treats multiple myeloma when taken with dexamethasone and one of three standard of care treatments: pomalidomide, daratumumab, or carfilzomib. The study drug has not been FDA approved, and is therefore considered investigational.

Procedures: If you agree to participate, the following will happen:

- You will have a screening visit to make sure you are eligible to be in the study. This will include a bone marrow aspirate biopsy and a PET/CT scan.
- If you are eligible and agree to participate, you will receive the study drug and dexamethasone in addition to standard treatment.
- You will visit the clinic on days 1, 8, 15, and 22 of each study cycle; each cycle lasts for 28 days.
- You may have a bone marrow aspirate or core biopsy during cycles 2 and 3 or at disease assessment.
- Treatment will continue until your disease progresses or the study doctor determines that the study drug is no longer good for you.
- After you stop taking the study drugs, you will be contacted by the study team every 3 months to learn about any disease relapse and survival status.

Risks: Participation in research involves risks, including the following:

- Risks associated with Selinexor may include: gastrointestinal problems; muscle pain or spasms; respiratory problems; sleep problems; weight loss; loss of energy; change in appetite or thirst; cognitive and neurological problems; skin or hair problems; peripheral edema; numbness and tingling; eye disorders; dry mouth or stomatitis; tachycardia; nosebleed; changes in levels of electrolytes, creatinine, pancreatic enzymes, liver enzymes, blood pressure, blood sodium, blood sugar, blood platelets, lymphocytes, red and white blood cells, aspartate aminotransferase, or blood alkaline; peripheral neuropathy; sepsis; tumor lysis syndrome; infections; cardiac failure, multiple organ dysfunction syndrome; encephalopathy; injury to kidney; pulmonary embolism; or hypoxia

- Risks associated with Dexamethasone may include: increased blood glucose or blood pressure; weight gain; skin or hair problems; edema; heartbeat irregularities; hormone imbalance; stomach ulcer; pancreatitis; muscle weakness; osteoporosis; headache; depression or emotional instability; impaired vision

- Risks associated with bone marrow biopsy: A bone marrow biopsy may result in bleeding, infection, local nerve damage, pain from the needle sticks, and pain from aspirating the bone marrow with a syringe.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: There may be other ways of treating your type of cancer, and you may be able to receive other treatments without participating in this study. Please discuss other treatment options with your doctor.

Detailed Consent

Why is this study being done?

This study plans to learn more about how the study drug, Selinexor, in combination with other standard of care drugs might work to treat multiple myeloma. The combination standard of care drugs include Pomalidomide, Dexamethasone, Daratumumab, Carfilzomib.

You are being asked to take part in this study because you have been diagnosed with multiple myeloma, a cancer of the plasma cells (a type of immune cell that produces antibodies) which has returned after your most recent treatment regimen (relapsed) or has not responded to your most recent treatment regimen (refractory). The purpose of this research study is to see if Selinexor (also known as KPT-330) and the drug combinations have any effect against your cancer. This study drug combinations with Selinexor are considered investigational, which means the combination has not been approved by the U.S. Food and Drug Administration (FDA), Health Canada, the European Medicines Agency (EMA) or any other national competent authority. The proposed Selinexor combinations of therapy (SPd, SKd and SDd) regimens are investigational and not approved therapy for RRMM. Other approved regimens with known benefits are available for your condition.

Cancer is the uncontrolled growth of human cells. The growth of normal human cells is controlled by multiple mechanisms. Cancer cells can escape one or more of these control mechanisms leading to uncontrollable growth. One specific way cancer cells continue to grow is by getting rid of certain proteins called “tumor suppressor proteins” that would normally cause cancer cells to die.

Selinexor works by trapping “tumor suppressing proteins” within the cell and thus causing the cancer cells to die or stop growing.

Selinexor has previously been tested in humans to define a safe dose to be administered. It is not known at this time if it will treat your cancer. Selinexor is currently being tested in other clinical trials in patients with advanced cancers. This study will examine its effects on your cancer and on your body including any side effects that you may experience.

Your participation in this study is voluntary. You may decide to not take part or to withdraw from the study at any time without losing any benefit of your current care.

Other people in this study

Up to 18 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are 3 parts to the study:

1. Screening
2. Treatment
3. Follow Up

The next section of this form lists what will be expected of you if you join this study.

Study Procedures

While you are taking part in this study, some of the tests and procedures are the same type that would be performed as part of your regular cancer care even if you did not join the study. Some of the tests and procedures are required only for the study and are considered research procedures. Research procedures cannot be conducted before this consent form is signed.

The screening tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

<u>Screening Phase (within 28 days before treatment)</u>

- Informed consent
- Review of medical history
- Review of medications
- Physical exam, including weight and vital signs
- Disease status
- Blood draw for routine tests
- Pregnancy test, for women of child-bearing age (blood or urine)
- Counseling on the risks of pregnancy while in this study
- Bone marrow aspiration and biopsy
- Electrocardiogram (EKG)
- PET/CT scan

After screening is completed and the study doctor agrees that you can continue with the study, you will begin the study treatment.

Study Treatment Phase

You are expected to to have the following visits and procedures during this study:

- You will visit the clinic on the following days
    - Cycle 1 – days 1, 8, and 15
    - Cycle 2 - days 1 and 15
    - Cycle 3+ - day 1
    - End of Treatment
- Weight (Day 1 of each 28-day cycle and end of treatment)
- Vital signs (blood pressure, pulse, and temperature)
- Symptom directed Physical Examinations
- Laboratory assessments, including bloodwork
- Multiple myeloma assessments
- Quality Of Life Questionnaire
- Study drug: Selinexor and Dexamethasone in combination with your clinically-assigned standard of care medication. For each cycle, all subjects will receive Selinexor (for 3 weeks) and Dexamethasone (for one month) weekly. Additionally:
    - Arm 1: Subjects will receive Pomalidomide daily (for 3 weeks).
    - Arm 2: Subjects will receive Daratumumab weekly during cycles 1 and 2, every two weeks during cycles 3-6, and only once during any subsequent cycles.
    - Arm 3: Subjects will receive Carfilzomib weekly (for 3 weeks).

Study Follow Up

When you have completed the treatment part of the study, you will begin study follow up.

The follow-up part of the study includes contact from the study team to discuss and record any relapse of your cancer, any new anti-cancer therapy and survival status. The study team will follow up with you via health portal, email, or phone every 3 months for a minimum of two years.

What are the possible discomforts or risks?

Discomforts you may experience while in this study are indicated below. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. Some risks described in this consent document, if severe, may cause death.

Side Effects of Selinexor

Very common side effects (≥10%):

In 100 people with hematologic malignancies receiving Selinexor more than 10 people may have:

- nausea
- low platelets in the blood (thrombocytopenia), which may increase the risk of bleeding
- fatigue

- decreased appetite
- decrease in red blood cells (anemia) causing fatigue
- diarrhea
- vomiting
- weight loss
- decrease in neutrophils (a type of white blood cell that helps fight infections)
- constipation
- low blood sodium which may increase the risk of seizures
- cough
- shortness of breath
- fever
- loss of energy; weakness
- dizziness
- peripheral edema – swelling in extremities due to accumulation of fluid, usually in legs
- decrease in white blood cells (leukopenia), which may increase the risk of infection
- blurred vision
- low potassium which may cause weakness, muscle cramps and spasms
- peripheral neuropathy – weakness, numbness, and pain from nerve damage, usually in the hands and feet
- change in taste (dysgeusia)
- difficulty falling asleep
- upper respiratory tract infection
- abdominal pain
- back pain
- dehydration
- pneumonia

Common serious side effects (≥1 - <10%):
In 100 people receiving selinexor about 1 to 10 people may have:

- febrile neutropenia
- sepsis (including septic shock) potentially life-threatening complication of an infection headache
- high blood sugar which may cause fatigue, increased thirst/hunger, frequent urination, weight loss, numbness and tingling in hands/feet
- acute kidney injury
- fainting
- confusion
- cognitive disorder
- respiratory failure
- rash
- cataract (new or worsened)
- syncope
- night sweats
- dry mouth
- stomatitis – a condition that causes painful swelling and sores inside the mouth
- dyspepsia – indigestion
- chills

- hypotension – low blood pressure
- hypertension
- tachycardia – fast heart rate
- nosebleed
- contusion (bruise due to body injuries such as fall)
- electrolyte disturbances including:
  - low phosphate which may cause muscle weakness and fatigue
  - low magnesium which may cause muscle twitches and cramps
  - low calcium which may cause numbness and tingling in hands/feet/face, muscle stiffness and cramps
  - high potassium which may cause muscle weakness, palpitations or irregular heartbeats and chest pain
- low albumin (which may cause swelling especially of the hands/feet, weakness or exhaustion)
- decrease in lymphocytes – a specific type of white blood cell that are part of your immune system
- increase of creatinine in the blood due to a reduction in kidney function, often related to dehydration
- elevated liver enzymes including alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
- elevated pancreatic enzymes including high amylase and high lipase
- muscle weakness
- pain in joints and muscles
- malaise (a general feeling of being ill or bodily weakness)
- muscle spasms
- hair loss
- itching
- depression

Uncommon serious side effects (>0.1 - 1%):
In 1,000 people receiving selinexor about 1 to 10 people may have:

- cardiac disorders
- urinary tract infection
- gait disturbance
- loss of blood flow to part of the brain
- pulmonary blood clot stuck in an artery in the lungs, blocking the flow of blood (pulmonary embolism)
- bleeding between the brain tissue and skull or within the brain
- buildup of fluid between the layers of tissue that line the lungs and chest cavity (pleural effusion)
- accumulation of fluid in the peritoneal cavity, causing abdominal swelling
- pancreatitis

Dexamethasone: increased blood glucose, increased blood pressure, weight gain, skin thinning, edema, heartbeat irregularities, hair loss, hormone imbalance, stomach ulcer, pancreatitis, muscle weakness, osteoporosis, headache, depression or emotional instability, impaired vision, worsening cataracts.

Possible Risks Associated with Daratumumab

Not all of the possible side effects and risks related to daratumumab are known. Daratumumab can cause side effects, although not everybody gets them.

Very common side effects with daratumumab (may affect more than 1 in 10 patients):

- fever
- feeling very tired
- flu
- diarrhea
- headache
- nerve damage that may cause tingling, numbness, or pain
- high blood pressure
- muscle spasms
- swollen hands, ankles and feet
- lung infection (pneumonia)
- infections of the airways - such as nose, sinuses or throat
- low number of white blood cells which help fight infections (neutropenia, lymphopenia)
- low number of a type of blood cell called platelets, which help to clot blood (thrombocytopenia)
- low number of red blood cells which carry oxygen in the blood (anemia)
- Eye pain

Common (may affect up to 1 in 10 patients):

- Irregular heartbeat (atrial fibrillation)
- buildup of fluid in the lungs making you short of breath

Uncommon (may affect 1 in 1,000 patients):

- inflamed liver (hepatitis)

Infusion-related reactions - A side effect to daratumumab that occurs during or shortly after an infusion is completed (when the medicine is given into a vein) is called an infusion-related reaction.

Tell your doctor right away if you get any of the following signs of an infusion-related reaction during or in the 3 days after the infusion. You may need other medicines, or the infusion may need to be slowed down or stopped. When these reactions go away, or get better, the infusion can be started again.

Very common (may affect more than 1 in 10 patients):

- chills
- sore throat, cough
- feeling sick (nausea)

- vomiting
- itchy, runny or blocked nose
- cough
- feeling short of breath or other breathing problems
- blurred vision

Other common symptoms (affects up to 1 in 10):

- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing

If you get any of the infusion-related reactions above, tell your doctor right away. These reactions are most likely to happen with the first infusion. If you have had an infusion-related reaction once it is less likely to happen again. Your doctor may decide not to use daratumumab if you have a strong infusion reaction.

Before each infusion of daratumumab you will be given medicines, which help to lower the chance of infusion-related reactions. These may include:

- anti-histamines (for an allergic reaction)
- corticosteroids (for inflammation)
- acetaminophen (for fever)

If you have breathing problems such as chronic obstructive pulmonary disease (COPD) or asthma, you will be given medicines to inhale which help your breathing problems:

- bronchodilators to help the airways in your lungs to stay open
- corticosteroids to lower swelling and irritation in your lungs

Decreased blood cell counts - Daratumumab can decrease white blood cell counts which help fight infections and platelets which help to clot blood. Tell your doctor if you develop fever or if you have signs of bruising or bleeding.

Blood transfusions - If you need a blood transfusion, you will have a blood test first to match your blood type. Daratumumab can affect the results of this blood test. Tell the person doing the test that you are using daratumumab. Your study doctor will provide you with additional information about the risks and side effects, including rare side effects, of daratumumab.

Possible Risks Associated with Pomalidomide

Pomalidomide has been studied in healthy volunteers and in subjects with cancer of the blood and other organs of the body as well as in subjects with other diseases. As with any other experimental treatment there may be side effects or risks that are unknown or cannot be predicted at this time, but you will be carefully monitored for any problems and you are encouraged to report anything that is bothering you to your study doctor or nurse.

The following is a list of important side effects reported with pomalidomide. In some cases, side effects can be serious, long-lasting, may never go away, or can cause death. The study doctor may give you medicines to help lessen the side effects. Some side effects go away soon after you stop the study drug. This is not a complete list of all side effects but your study doctor will answer any questions you might have and can provide you with more information.

Very common (greater than 10% chance this may happen): Infections including: Infection of the lungs (influenza, pneumonia, respiratory tract infection), inflammation of airways of lungs caused by infection (bronchitis), infection of the bladder or kidneys (urinary tract infection), dizziness, nausea and vomiting, changes in sensations including decreased sense of touch, burning sensation, tingling (peripheral neuropathy), abnormal shaking (tremor), abnormal levels of blood electrolytes, including: low blood level of sodium (hyponatremia), high blood level of calcium (hypercalcemia), low blood level of calcium (hypocalcemia), low blood level of potassium (hypokalemia), rash, confusion (confusional state), unable to sleep (insomnia), decreased kidney function (renal failure), itching (pruritus), decrease in platelets, the cells that help your blood to clot (thrombocytopenia), Gastrointestinal disorders, including: changes in bowel movement (constipation, diarrhea), cough, decrease in red blood cells carrying oxygen to your body (anemia), loss of appetite (decreased appetite), high levels of sugar in the blood (hyperglycemia), fever (pyrexia), Abnormal levels of blood cells, including: decrease in white blood cells (leukopenia, neutropenia lymphopenia) which help fight infection, muscle cramp (muscle spasms), bone pain, back pain, decreased strength in the muscles (muscular weakness), shortness of breath (dyspnoea), swelling including arms and legs (edema peripheral), and tiredness (fatigue).

Common (between a 1-10% chance that this may happen): Severe life-threatening infection may include possible low blood pressure, kidney failure, and/or heart failure **(**neutropenic sepsis, sepsis, septic shock), serious infection resulting in diarrhea and inflammation of the lower intestine (clostridium difficle colitis), rapid, irregular heart beat (atrial fibrillation), lightheadedness, loss of balance (vertigo), condition in which the lens of the eye becomes cloudy (cataract), feeling of fullness and tightness in the abdomen (abdominal distention), pain in the abdomen (abdominal pain), dry mouth; mouth sores (stomatitis), build-up of fluid in the body causing swelling (edema), non-cardiac chest pain, sore throat (nasopharyngitis), Abnormal levels of blood electrolytes, including: high blood level of potassium (hyperkalemia), low blood level of magnesium (hypomagnesemia), low blood level of phosphate (hypophosphatemia), walking/balance problems (fall), abnormal liver lab test (alanine aminotransferase increased), weight decreased, less alert (depressed level of consciousness), abnormal taste (dysgeusia), temporary loss of consciousness (syncope), depression, blood clots in legs or lungs (pulmonary embolism, deep vein thrombosis), high blood pressure (hypertension), low blood pressure (hypotension), difficulty in passing urine (urinary retention), decrease in red blood cells, white blood cells, and platelets (pancytopenia), low number of white blood cells with fever (febrile neutropenia) and pelvic pain.

Uncommon (between 0.1- 1% chance that this may happen): Elevated blood levels of bilirubin (hyperbilirubinemia).

Other Important Side Effects
Events that do not meet the criteria for inclusion above but are also considered important enough for you to be made aware:

- New Cancer: second primary malignancies (SPMs) are new cancers that are diagnosed in subjects following a prior diagnosis of a first cancer.
- Pneumonitis, Interstitial Lung Disease: Inflammation of your lungs.
- Tumor lysis syndrome: rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage.
- Hepatoxicity: liver injury and/or abnormal liver tests, this may cause jaundice (yellow skin).
- Severe allergic conditions including:
  - Swelling under skin (Angioedema)

  - Severe skin reactions involving lining of the nose, mouth, stomach and intestines or rash leading to the separation of the top layer of skin [Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), respectively]
  - A skin reaction [such as rash or skin peeling (exfoliative dermatitis)], elevated level of eosinophils (eosinophilia), fever, and/or swollen glands (lymphadenopathy) with other organ complications such as inflammation of the liver (hepatitis), inflammation of the kidney nephrons (nephritis), inflammation of the lungs (pneumonitis), inflammation of the heart (myocarditis), and/or inflammation of the sac surround the heart (pericarditis) [Drug reaction with eosinophilia and systemic symptoms (DRESS)]
- Cardiac failure: heart problems which can cause shortness of breath and/or ankle swelling.
- Hepatitis B virus reactivation: a reactivation of the hepatitis B virus in patients who have previously been infected with hepatitis B. The reactivation can lead to serious liver injury.
- Herpes zoster: also called shingles, causes a rash with blisters on the body and is very painful.
- Gastrointestinal hemorrhage: bleeding that starts in the lining of the stomach or intestines which may cause dark, bloody stool, large amounts of blood passed from the rectum or in streaks on feces, and vomiting of blood.
- Basal cell carcinoma: A type of skin cancer that can have many different appearances: a red patch or irritated area; a small, pink pearly bump; a white or yellow scar-like area; a smooth growth with a dent in the center; or an open sore that bleeds or oozes and most commonly found on the face, neck, hands, or other parts of the body that are frequently exposed to the sun.
- Squamous cell carcinoma of the skin: is an uncontrolled growth of abnormal skin cells arising mostly the on the skin's upper layers (the epidermis). The growth often looks like scaly red patches, open sores, elevated growths with a central depression, or warts; they may crust or bleed. They can become disfiguring and sometimes deadly if allowed to grow.

Additional Important Precautions
Other than the subject, females who are able to become pregnant and males who are able to father a child, should not touch or handle the pomalidomide capsules or the powder they contain.

We do not know if pomalidomide has any effect on your being able to have a child in the future, please speak with your doctor about family planning options for the future.

Please let your Study Doctor know all of your present and past diseases and allergies and any medication you may be taking including over-the-counter medications, vitamins, herbal, homeopathic or holistic medications or treatments. This is important because a possible interaction with some medications, vitamins, and remedies may cause serious side effects, and/or may still be unknown.

Possible Risks Associated with Carfilzomib
Not all of the possible side effects and risks related to carfilzomib are known. Carfilzomib can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor straight away if you get or notice any of the following symptoms:

- Chest pains, shortness of breath, or if there is swelling of your feet, which may be symptoms of heart problems
- Difficulty breathing, including shortness of breath at rest or with activity or a cough (dyspnoea),
- rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung toxicity
- Very high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure
- A side effect called tumour lysis syndrome, which can be caused by the rapid breakdown of tumour cells and may cause irregular heartbeat, kidney failure or abnormal blood test results
- Fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain can occur as a reaction to the infusion
- Unusual bruising or bleeding, such as a cut, that takes longer than usual to stop bleeding; or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools; or bleeding in the brain leading to sudden numbness or paralysis on one side of the face, legs or arms, sudden severe headache or trouble seeing or difficulty speaking or swallowing
- Leg or arm pain or swelling (which could be a symptom of blood clots in the deep veins of the leg or arm), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be symptoms of liver problems including liver failure
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhoea, and acute kidney failure, which may be signs of a blood condition known as thrombotic microangiopathy
- Headaches, confusion, seizures (fits), visual loss, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as posterior reversible encephalopathy syndrome (PRES).

Other possible side effects

Very common side effects (may affect more than 1 in 10 patients): serious lung infection (pneumonia), respiratory tract infection (infection of the airways), low platelets, which may cause easy bruising or bleeding (thrombocytopenia), low white blood cell count, which may decrease your ability to fight infection and may be associated with fever, low red blood cell count (anaemia) which may cause tiredness and fatigue, changes to blood tests (decreased blood levels of potassium, increased blood levels of sugar and/or creatinine), decreased appetite, difficulty sleeping (insomnia), headache, numbness, tingling, or decreased sensation in hands and/or feet, dizziness, high blood pressure (hypertension), shortness of breath, cough, diarrhoea, nausea, constipation, vomiting, stomach pain, back pain, joint pain, pain in limbs, hands or feet, muscle spasms, fever, chills, swelling of the hands, feet or ankles, feeling weak, tiredness (fatigue).

Common side effects (may affect up to 1 in 10 patients): infusion reaction, heart failure and heart problems including rapid, strong or irregular heartbeat, heart attack, kidney problems, including kidney failure, blood clots in the veins (deep vein thrombosis), feeling too hot, blood clot in the lungs, fluid in the lungs, wheezing, serious infection including infection in the blood (sepsis), lung infection, liver problems including an increase in liver enzymes in the blood, flu-like symptoms (influenza), reactivation of the chicken pox virus (shingles) that can cause a skin rash and pain (herpes zoster), urinary tract infection (infection of structures that carry urine), cough which could include chest tightness or pain, nasal congestion (bronchitis), sore throat, inflammation of the nose and throat, runny nose, nasal congestion or sneezing, viral infection, infection of the stomach and intestine (gastroenteritis), bleeding in the stomach and bowels, changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin or c-reactive protein), dehydration, anxiety, feeling confused, blurred vision, cataract, low blood pressure (hypotension), nose bleed, change in voice or hoarseness, indigestion, toothache, rash, bone pain, muscle pain, chest pain, muscle weakness, aching muscles, itchy skin, redness of the skin, increased sweating, pain, pain, swelling, irritation or discomfort where you received the injection into your vein, ringing in the ears (tinnitus), a general feeling of illness or discomfort

Uncommon side effects (may affect up to 1 in 100 patients): bleeding in the lungs, inflammation of the colon caused by a bacteria called Clostridium difficile, allergic reaction to carfilzomib, multi-organ failure, reduced blood flow to the heart, bleeding in the brain, stroke, difficulty breathing, rapid breathing and/or fingertips and lips looking slightly blue (acute respiratory distress syndrome), swelling of the lining of the heart (pericarditis), symptoms include pain behind the breast bone, sometimes spreading across to the neck and shoulders, sometimes with a fever, fluid build-up in the lining of the heart (pericardial effusion), symptoms include chest pain or pressure and shortness of breath, a blockage in the flow of bile from the liver (cholestasis), which can cause itchy skin, yellow skin, very dark urine and very pale stools, perforation of the digestive system, a central nervous system infection known as progressive multifocal leukoencephalopathy (PML), hepatitis B virus (HBV) reactivation.

Other possible risks

Risks Associated with Pregnancy

While participating in this research study, you should not become pregnant, nurse a baby, or father a baby. Both men and women who are able to have children must use a highly effective means of birth control approved by your study doctor. You must continue the use of birth control at least 28 days before starting study drugs, during the entire time of your study participation and to at least 6 months after the last dose of study drugs.

If you are a female who has stopped having menstrual periods for at least 1 year (menopause), please discuss with your study doctor the need for birth control. If you become pregnant, you must stop taking selinexor at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.

If you are a male, you are responsible for informing your partner(s) that the effects of selinexor on an unborn fetus or embryo in humans are unknown. You and your partner(s) are responsible for using acceptable birth control as described above. Discuss with your partner acceptable forms of contraception. If your partner becomes pregnant while you are on study, you must notify your doctor immediately. You and your partner may be asked questions about the outcome of the pregnancy and the baby. Written informed consent for release of medical information from your partner will be obtained prior to collecting any information about the pregnancy and baby.

Risk of Loss of Confidentiality
There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

Risks Associated with Study Procedures

Risks of Having Blood Taken
In this study we will need to get about between 3-10 teaspoons of blood from you in a visit. We will get blood by putting a needle into one of your veins and letting the blood flow into a tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risks of Having an IV Inserted In Your Vein
In this study, we may insert a needle, connected to a plastic tube, into a vein. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for up to 12-24 hours.

Risks of Bone Marrow Aspirate / Biopsy
The risks of this procedure are small and include bleeding, infection, local nerve damage, pain from the needle sticks, and pain from aspirating the bone marrow with a syringe. This study may require that two biopsy cores are collected. The additional risk of the second biopsy core is minimal, though you may experience additional discomfort when the second biopsy core is obtained. Care will be taken to avoid these complications.

Risks of an ECG
You may have itching or bruising of the skin where the machine patches are placed for the ECG.

Risks of an Echocardiogram (ECHO)
ECHO is a noninvasive scan of the heart using sound waves. This test will be used to see how well your heart pumps blood. This test has no known risks or side effects.

Risks of Computed Tomography (CT) Scan
As part of this study we may perform a CT scan of your brain, chest, and abdomen. Additional areas of your body may be scanned if your doctor decides it is necessary to assess your disease. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to your body (give you) is about the same as you would get from living in your environment for 6 years.

This is an estimate. The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. There is no evidence of such risks for diagnostic procedures.

The risk of this procedure is not equal for everyone. The risk is much higher for unborn babies if the mother has this procedure. The risk is also much higher for young children and teenagers. The risk is much lower for people over the age of 30.

Risks of Positron Emission Tomography (PET) Scan
There is a chance that you may experience discomfort, pain, or swelling at the site where the radiotracer is injected. There may be a risk of having an allergic reaction to the radiotracer FDG chemical. However, this reaction has been rarely observed. The amount of radiation to your body is small and the radiation from the radiotracer will be gone from your body in a few hours.

Risks of Magnetic Resonance Imaging (MRI)
In this study we may take Magnetic Resonance Images (MRI's) of your brain, chest, and abdomen. Additional areas of your body may be scanned if your doctor decides it is necessary to assess your disease. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

If you are pregnant, be sure to tell the person giving you the MRI.

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus, which are currently unclear

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the effect Selinexor has on those diagnosed with multiple myeloma.

This study is not designed to treat any illness or to improve your health. If you agree to take part in this study, there may or may not be direct medical benefit to you. While it is possible that you may benefit, we do not know if you will and there is no guarantee of this. We hope the information learned from this study will benefit other individuals with Multiple Myeloma in the future.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with an approved therapy.
- You may choose to participate in a different study with another experimental drug.
- You may choose to receive comfort/ palliative care.
- You may choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Karyopharm Therapeutics Inc. is providing funding support for this study. Karyopharm Therapeutics Inc. manufactures the study drug, Selinexor, and will provide this drug for the study. This research is being conducted by Dr. Peter Forsberg. The research study will only pay for procedures not considered standard of care.

Karyopharm Therapeutics is providing funding support for this research study. Please feel free to ask any questions you may have about this matter.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, Karyopharm, will pay for the cost of the study drug, Selinexor. The funding for this study will also pay for any tests or procedures that are not considered standard of care.

The other drugs are considered standard treatment for your type of cancer. These drugs will be obtained through your insurance, and you will be responsible for any applicable copays required by your insurance policy. These drugs include Pomalidomide, Dexamethasone, Daratumumab, Carfilzomib.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as blood draws. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study, if these expenses

are related to standard of care procedures. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Forsberg immediately. His phone number is 720-848-9307.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Peter Forsberg, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Forsberg at 720-848-9307. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Forsberg with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver | Anschutz Medical Campus (the University) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver | Anschutz Medical Campus
- University of Colorado Health

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Peter Forsberg, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Members of your care team that have access to your electronic medical records.
- Karyopharm Therapeutics Inc., manufacturer of Selinexor who is also providing funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that may be seen, collected, used or disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.

- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Tissue samples and the data with the samples.
- Billing or financial information.

Your care team, including family doctor, may be made aware of your participation in the study through your electronic medical records.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

The data we collect will be used for this study but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary, and I do not have to sign this form if I do not want to be part of this research study.

Subject Signature: _____ Date: _____

Subject Print Name:_____

Consent form explained by: _____ Date: _____

Print Name: _____

---------- ***Use Only if Applicable*** ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Interpreter or Witness Signature:_____ Date:_____

Interpreter or Witness Print Name: _____