Clinical Study Protocol

KCP-330-012

A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

Study Name: STORM (Selinexor Treatment of Refractory Myeloma)

Drug Development Phase:	Phase 2b
Investigational Product:	Selinexor (KPT-330)
Indication:	Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab
EudraCT Number:	2016-003094-18
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Protocol Date and Version:	24 December 2014, Version 1.0 05 February 2015, Version 2.0 25 September 2015, Version 3.0 11 August 2016, Version 4.0- ROW (Rest of World) 06 February 2017, Version 4.1 US (Country-specific) 28 April 2017, Version 5.0 13 December 2017, Version 6.0

CONDUCT

In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 13 December 2017 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved by:

PPD

PPD , PPD

PPD

Karyopharm Therapeutics Inc.

13 December 2017

Date

PPD

PPD

PPD , PPD

Karyopharm Therapeutics Inc.

13 December 2017

Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. KCP-330-012 dated 13 December 2017 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices, ICH E6, and applicable FDA regulatory requirements:

Name of Principal Investigator:

Principal Investigator's Signature: _____

Principal Investigator's Name: _____

Institution: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Developmental Phase: Phase 2b

Title of Study:

A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

Protocol Number: KCP-330-012: STORM (Selinexor Treatment of Refractory Myeloma)

Indication: Multiple myeloma previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (penta-refractory MM)

Objectives:

Primary:

Evaluate the efficacy (overall response rate [ORR]) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (herein referred to as penta-refractory MM).

ORR will include patients who experience partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on International Myeloma Working Group (IMWG) response criteria (*Kumar 2016*) for patients with penta-refractory MM in Part 2 (Expansion).

Secondary:

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM (i.e., previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mab), (b) Part 1 patients with penta-refractory MM, and (c) Part 2 (expansion) patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR = Duration from first observation of at least PR to time of disease progression, or deaths due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression)

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- Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to next treatment (TTNT)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the PK properties of selinexor in this patient population (Part 1 only)

CCI [redacted]

Background and Study Rationale

Background

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of a variety of agents, nearly all patients will

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eventually relapse with their disease becoming drug-resistant. With over 12,600 deaths from MM anticipated in 2016 in the US alone, there is an unmet medical need for therapies in patients with relapsed and/or refractory (RR) MM that has progressed on available treatments.

Selinexor is an orally bioavailable, selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Selinexor and other SINE compounds have demonstrated anti-MM activity in preclinical studies. In the Phase-1 study, selinexor alone (all doses) showed an ORR of 5%, and with low-dose dexamethasone (Sd; all doses) the ORR was 32%. Therefore, the Sd regimen was carried forward into this ongoing Phase 2 study.

Rationale for Expansion (protocol version 4.0)

For Part 1 of this study, 78 patients with measurable RR MM have been evaluated (79 patients were enrolled, but 1 patient did not have measurable MM at baseline): 48 patients with quad-refractory MM (IMIDs and PIs) and 30 patients with penta-refractory MM (quad + anti-CD38 refractory). Patients were initially dosed with 6 doses of Sd per cycle, and this was increased to 8 doses of Sd per cycle. The ORR adjudicated by a four-physician Independent Review Committee (IRC) across all patients was 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with "penta" and "quad" MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing. The median duration of response (DOR) was ~5 months, with 9 patients continuing on study. There was a trend towards higher ORR in the 8-dose per cycle Sd regimen, with little difference in tolerability. Furthermore, there was a trend to increased time on study in patients with baseline hemoglobin (Hb) $\geq$ 8.5 gm/dL. Therefore, based on the current unmet medical need for patients with RR MM and these preliminary clinical results, this study is now being expanded to evaluate the efficacy and safety of twice-weekly Sd in patients with penta-refractory MM.

Methodology:

This is a Phase 2b, single-arm, open-label, multicenter study of Sd, dosed twice weekly each week in four-week cycles, in patients with penta-refractory MM (Parts 1 and 2) or quad-refractory MM (Part 1 only).

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Response results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received at least one dose of study drug, presented overall and by study part, and separately for Part 1 penta-refractory and quad-refractory patient populations.

Patients will receive treatment until progressive disease (PD), death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

Inclusion/Exclusion Criteria:

Inclusion:

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

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥ 18 years at the time of signing informed consent.
3. Measurable MM based on IMWG guidelines as defined by at least one of the following:
   a. Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
   b. Urinary M-protein excretion ≥ 200 mg/24 hours
   c. FLC ≥ 100 mg/L, provided that the FLC ratio is abnormal.
   d. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry is acceptable.
4. Patients must have previously received ≥ 3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
5. MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and daratumumab. Refractory is defined as ≤ 25% response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
6. Multiple myeloma that is refractory to the patient's most recent anti-MM regimen. (Documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor.)
7. Any clinically significant non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that patients experienced from treatments in previous clinical studies must have resolved to Grade ≤ 2 by Cycle 1 Day 1.
8. Adequate hepatic function within 21 days prior to Cycle 1 Day 1: total bilirubin < 2x upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3x ULN), AST < 2.5x ULN and ALT < 2.5x ULN.
9. Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of ≥ 20 mL/min, calculated using the formula of Cockroft and Gault.
10. Female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception) and have a negative serum pregnancy test at Screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose of study treatment.
11. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
12. Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1 (See Exclusion Criterion #20 for transfusion washout periods for RBCs and platelets):
    a. Total WBC count > 1,000/mm^3
    b. ANC ≥ 1000/mm^3

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c. Platelet count ≥ 75,000/mm^3 (patients in whom < 50% of bone marrow nucleated cells are plasma cells) or ≥ 50,000/mm^3 (patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells. [Platelet transfusions < 1 week prior to Cycle 1 Day 1 are prohibited (see below).]

13. Hemoglobin level ≥ 8.5 g/dL. In certain cases, patients with stable baseline hemoglobin level > 8.0 may be included following approval by the Medical Monitor. [Red blood cell transfusions < 2 weeks prior to Cycle 1 Day 1 are prohibited (see below).]
14. Confirmation of patient eligibility for specific key criteria for study participation with the Medical Monitor.

Exclusion Criteria:

1. Active smoldering MM.
2. Active plasma cell leukemia.
3. Documented systemic amyloid light chain amyloidosis.
4. Active central nervous system (CNS) MM.
5. Pregnancy or breastfeeding.
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.
7. Active graft vs. host disease (after allogeneic stem cell transplantation) at Cycle 1 Day 1
8. Life expectancy of < 4 months.
9. Major surgery within four weeks prior to Cycle 1 Day 1.
10. Active, unstable cardiovascular function:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
    c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3, or
    d. Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1.
11. Active, uncontrolled hypertension.
12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
15. Prior malignancy that required treatment, or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to enrollment. Cancer treated with curative intent > 5 years previously and without evidence of recurrence will be allowed.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.

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17. Grade ≥ 3 peripheral neuropathy, and Grade ≥ 2 painful neuropathy, within 21 days prior to Cycle 1 Day 1.
18. Serious, active psychiatric or medical conditions which, in the opinion of the Investigator, could interfere with treatment.
19. Participation in an investigational anti-cancer study within 21 days prior to Cycle 1 Day 1.
20. Receipt of transfusions as follows:
    a. Platelet infusion within 1 week prior to Cycle 1 Day 1.
    b. RBC transfusion within 2 weeks prior to Cycle 1 Day 1.
21. Receipt of the following blood growth factors within 2 weeks prior to Cycle 1 Day 1: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), or megakaryocyte growth factor.
22. Known intolerance to or contraindication for glucocorticoid therapy at Cycle 1 Day 1.
23. Prior exposure to a SINE compound, including selinexor.
24. Unable or unwilling to comply with protocol requirements, including providing a 24-hour urine samples at the required study time points.

Documentation Requirements

For enrollment consideration, patients may be eligible if they have *documented evidence* of previous treatment for MM that substantiates disease status as follows:

- Refractory to a glucocorticoid
- Refractory to lenalidomide and/or pomalidomide (only 1 required) *and* evidence of prior treatment* with *both* lenalidomide and pomalidomide
- Refractory to bortezomib and/or carfilzomib (only 1 required) *and* evidence of prior treatment* with *both* bortezomib and carfilzomib
- Refractory to daratumumab

* Prior treatment is defined as either refractory, treatment with ≥ 2 cycles, or documented severe intolerance.

Documented evidence will include at least one of the following:

1. Medical records that support start and stop dates (month/year) of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
2. Myeloma marker values (SPEP, UPEP, Immunoglobulin, FLC) at the time of prior treatment start, stop and time of progression (accompanied by #1).
3. Formal, signed physician letter by Investigator (on hospital/clinic letterhead), to be included in the patient's medical and research record, indicating start/stop dates of prior treatment (both dose and schedule), best response on treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
4. Formal, signed physician letter from referring physician (on hospital/clinic letterhead), to be included in the patient's medical and research record, that includes prior treatment history indicating start/stop dates of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).

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Test Product, Dose and Mode of Administration:

Selinexor will be given at an oral fixed milligram (mg) dose of 80 mg twice weekly each week for four-week cycles (total of 8 selinexor doses per cycle).

Dexamethasone 20 mg will be given with each dose of selinexor. If a patient develops partial intolerance to glucocorticoids (as determined by the Investigator) during the study, a minimum dose of dexamethasone 10 mg is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis.

In select cases (e.g., for patients showing SD, MR or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg (i.e., to 100 mg twice weekly) after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations after completing a minimum of 2 cycles of study therapy. However, in no case may the dose for a given patient exceed 70 mg/m^2.

Concomitant Medications:

To minimize nausea, unless contraindicated, all patients should receive 5-hydroxytryptamine (5-HT3) antagonists (e.g., ondansetron 8 mg or equivalent) starting on Day 1 before the first dose of selinexor and continued 2-3 times daily, as needed. Alternative anti-emetic agents should be used if the patient does not tolerate 5-HT3 antagonists. Additional anti-nausea and anti-anorexia agents may be given as needed (per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for Antiemesis and NCCN Clinical Practice Guidelines® for Palliative Care). Patients will also receive therapy as needed to mitigate selinexor side effects, as part of best supportive care.

Blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia are also permitted.

Patients may continue their baseline medication(s). Medications to treat concomitant diseases such as diabetes, hypertension, etc., are allowed. Patients will also receive concomitant medications that are medically necessary as standard care to treat symptoms, AEs and intercurrent illnesses. Patients may receive red blood cell or platelet transfusions, or blood growth factors, if clinically indicated, per institutional guidelines.

Concurrent therapy with any other approved or investigational anti-cancer therapy is not allowed. Other investigational agents should not be used during the study.

Study Numbers:

Approximately 210 patients will be enrolled overall, including 79 patients (with quad-refractory MM and penta-refractory MM) in Part 1 and ~130 patients (with penta-refractory MM only) in Part 2 (to achieve the target population size of N = 122 for the primary efficacy analysis).

Study Duration:

The enrollment period for this study is expected to be approximately 24 months. There is no maximum treatment duration for the study or pre-defined number of treatment cycles

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per patient. The study will end when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).

Criteria for Evaluation:

Safety:

Safety and tolerability will be evaluated by adverse event (AE) reports, physical examinations, and laboratory safety evaluations. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 will be used for grading of AEs. For all AEs, Investigators will provide their assessment of causality with study treatment as either related or not related.

Efficacy:

Response will be assessed per IMWG for MM (*Kumar 2016*) as:

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

Efficacy endpoints include the following:

- ORR and DOR
- CBR and duration of clinical benefit
- DCR and duration of disease control
- PFS
- OS
- TTP
- QoL using the FACT-MM

Pharmacokinetics[CCI redacted]

- Pharmacokinetic (PK) properties of selinexor in patients enrolled in Part 1 (only)
- [CCI redacted]
- Minimal residual disease (MRD) in patients who achieve sCR

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Criteria for Treatment Discontinuation:

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

- Disease progression
- Unacceptable AE(s) or failure to tolerate the study treatment
- Patient decides to discontinue study therapy and withdraws consent
- Any medically appropriate reason or significant protocol violation, per the Investigator.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the study. The reason for discontinuation should be clearly documented. If clinical or biological progression, study data must be available. If the patient withdraws consent or is removed by the study Investigator, the reason for withdrawal should be documented.

Statistical Methods:

CCI

[redacted]

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Efficacy Evaluation:

The primary statistical analysis of efficacy will be performed on ORR (proportion of patients who achieve sCR, CR, VGPR, or PR) using the modified intent-to-treat (mITT) population, defined as Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to participate in the study), and received at least 1 dose of study treatment (partial or complete). The primary analysis will be performed on the Part 2 patients with penta-refractory MM only.

A per-protocol (PP) population will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance ≥ 70%,
- Have at least 1 adequate post-baseline response assessment unless died or withdrew from study before that.
- No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.

The PP population will be used for supportive inferences concerning efficacy.

Secondary CCI [redacted] endpoints will be assessed using the mITT population and the PP population. Time-to-event endpoints (including DOR) will be assessed using Kaplan-Meier methods.

Quality of life (QoL) will be assessed using the Functional Assessment of Cancer Therapy with MM-specific subscale (FACT-MM). The trial outcomes index (TOI) will be the primary measurement of interest, comprised of the physical and functional subscales plus the MM-specific subscale.

Safety Evaluation:

Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part.

Table 1: Schedule of Assessments and Study Activities

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3[14]	Day 8	Day 15	Day 1	Day 15	Day 1	≤ 14 Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days		+ 7 days	± 14 days
Informed consent[1]	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history[2]	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA)[3]	X										
Physical examination, full including vital signs[4]	X								X		
Physical examination, symptom-directed, including vital signs[4]		X		X	X	X	X	X			
ECOG[5]	X					X		X	X		
Echocardiogram or MUGA[6]	X										
12-lead ECG	X								X		
Ophthalmic exam[7]	X								X		
Clinical Labs											
Urinalysis[5]	X								X		
CBC with differential[5]	X				X	X	X	X	X		
TSH[5]	X								X		
Complete serum chemistry[5]	X					X		X	X		
Limited serum chemistry				X	X		X				
Coagulation tests[5]	X								X		

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3[14]	Day 8	Day 15	Day 1	Day 15	Day 1	≤ 14 Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days		+ 7 days	± 14 days
Serum hCG pregnancy test[8]	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation[9]	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation[9]	X	X				X		X	X		X
Quantitative Ig levels[9]	X	X				X		X	X		X
Serum FLC[9]	X	X			X	X	X	X	X		X
β_2-microglobulin	X								X		
Skeletal survey[10]	X					(X)		(X)	X		(X)
Plasmacytoma assessment[11]	X					(X)		(X)	X		(X)
CCI											
CCI											
FACT-MM questionnaire	X					X		X	X		
Study drug dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events[16]	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		
Nutritional consultation	X										
Telephone contact[14]			X							X	X
Antineoplastic therapy after EoT									X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the C1D1 visit.
Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

[1] Prior to the first study-specific measure.

[2] Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 (±15 days) will be provided.

[3] Body Surface Area (BSA) will be calculated by *Dubois 1916* or *Mosteller 1987* method during Screening and prior to any dose escalation. No patient may receive a dose of selinexor > 70 mg/m^2.

[4] Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs to include vital signs (blood pressure, pulse and body temperature).

[5] The following procedures may be performed at Screening or pre-dose on C1D1 and as shown in the Schedule during the study: ECOG performance assessment, echocardiogram or MUGA scan, 12-lead ECG, ophthalmic exam, urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests, and nutritional consultation.

[6] Echocardiogram or MUGA scan at Screening and as clinically indicated during the study.

[7] A full ophthalmic examination will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; fundoscopy and slit lamp to document lens clarity.

[8] 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 Cycles ≥ 2 and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

[9] Response criteria include SPEP, UPEP (24-hr urine), serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and must be taken either on Day -1 or pre-dose on C1D1. The assessments must be repeated at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local lab, assessments will be confirmed by a central lab using portions of the samples collected. See the *Study Manual* for additional information. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 (±15 days) will be provided as part of Medical History.

[10] Skeletal survey to be performed using x-rays per institutional guidelines. 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 clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be read by the local laboratory.

[11] If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.

[redacted]

[14] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of selinexor on C1D1).
[15] After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) should be performed every 3 months for 1 year to assess durability of response. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for one year to inquire about the patient's survival, MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.
[16] Serious adverse events that occur after signing patient signs the ICF (including prior to first dose on C1D1) and adverse events that occur after first dose on C1D1.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT3	5-hydroxytryptamine
ACS	acute cerebellar syndrome
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplantation
AST	aspartate transaminase (SGOT)
AUC_{last}	area under the curve, first-last measurement
$AUC_{(0-\infty)}$	area under the curve, time zero to last
AV	arterioventricular
bid	twice daily
BMSC	bone marrow stroma cells
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
°C	degrees Centigrade
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation
anti-CD38 mAb	monoclonal antibodies against CD38 antigen expressed by leukocytes
CD-ROM	compact disc, read-only-memory
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cm	centimeter
C_{max}	maximum serum concentration
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete response
CRA	clinical research associate

Abbreviation	Definition
CRF	case report form
CRM1	chromosomal region maintenance protein 1
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
cyclo	cyclophosphamide
DCR	disease control rate
Dex	dexamethasone
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOR	duration of response
Dox	doxorubicin
DSMC	Data Safety Monitoring Committee
DT	dexamethasone + thalidomide
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
F%	oral bioavailability
°F	degrees Fahrenheit
FACT-G	Functional Assessment of Cancer Therapy (general version)
FACT-MM	Functional Assessment of Cancer Therapy - Multiple Myeloma
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FISH	fluorescent in situ hybridization
FLC	free light chain (kappa/lamba ratio)
FLT3	fms-like tyrosine kinase
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor

Abbreviation	Definition
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
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC/MS-MS	high performance liquid chromatography/tandem mass spectrometry
hr	hour
IC_{50}	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNα	interferon alpha
IFNγ	interferon gamma
IgA	immunoglobulin A
IgVH	immunoglobulin heavy chain variable region
IL-1α	interleukin 1 alpha
IL-6	interleukin 6
IL-8	interleukin 8
IL-10	interleukin 10
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalization ratio
IRC	Independent Review Committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
LAFB	left anterior fascicular block
LDH	lactate dehydrogenase
LMW	low molecular weight

Abbreviation	Definition
LOCSIII	Lens Opacities Classification System
m^2	square meters
MAb	monoclonal antibody
MCP1	monocyte chemo-attractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
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	minimal response
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition
5'NT	5'-nucleotidase
NAC	N-acetylcysteine
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NES	nuclear export sequences
NHL	non-Hodgkin’s lymphoma
NK1R	neurokinin 1 receptor
NPC	nuclear pore complex
NPM1	nucleophosmin
NYHA	New York Heart Association
OPG	osteoprotegerin
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDn	pharmacodynamic
PE	physical examination

Abbreviation	Definition
PFS	progression free survival
PI	proteasome inhibitor (within drug treatment context)
PI	principal investigator (within clinical context)
PK	pharmacokinetic
po	by mouth
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
prn	as needed
PT	prothrombin time
qAM	every morning
qd	once daily
qhs	at bedtime
qid	four times daily
QoL	quality of life
qRT-PCR	quantitative real time polymerase chain reaction
RBBB	right bundle branch block
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPPA	reverse phase protein array
RR	resistant/refractory
RT	Richter's transformation
SAE	serious adverse event
SAM	S-adenosylmethionine
sCR	stringent complete response
Sd	selinexor 80 mg plus dexamethasone 20 mg ("low-dose" dexamethasone)
SD	stable disease
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SINE	selective inhibitor of nuclear export
SOC	standard of care (within treatment context)
SOC	system organ class (within adverse event context)
SOP	standard operating procedure
SPEP	serum protein electrophoresis

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
tid	three times daily
TK	toxicokinetic
T_{max}	time to maximum serum concentration
TNFα	tumor necrosis factor alpha
TOI	trial outcomes index
TSH	thyroid stimulating hormone
TSP	tumor suppressor protein
TTP	time to progression
TUNEL	terminal deoxyribonucleotidyl transferase-dUTP nick end labeling
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VEGFα	vascular endothelial growth factor alpha
VGPR	very good partial response
WBC	white blood cell
XPO1	exportin 1

1. OVERVIEW

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. Despite the increased effectiveness of first-line agents, the majority of patients will eventually relapse and become resistant to all classes of available anti-MM therapies. With over 30,000 new cases and approximately 12,600 deaths from MM anticipated in 2016 in the USA alone (*ACS 2016*), there remains a need for novel therapies for the treatment of refractory MM that can improve the overall survival rate.

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates Exportin 1 (XPO1), thereby forcing the nuclear retention of key tumor suppressor proteins (TSPs). XPO1 protein levels are significantly elevated in MM, leading to the nuclear exclusion of TSPs, the glucocorticoid receptor (GR), and enhanced translation of certain oncogene mRNAs (*Tai 2014)*. Transient retention of TSPs in the nucleus at high levels via XPO1 blockade activates their cell cycle checkpoint and genome surveying actions. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released. XPO1 also exports the GR, leading to attenuation of its transcriptional activity. In the presence of glucocorticoids, XPO1 blockade leads to nuclear accumulation and activation of the GR. In addition, XPO1 inhibition leads to the nuclear entrapment of cap-binding protein (eIF4E)-dependent oncogene mRNAs, thus preventing their translation into proteins in the cytoplasm. In this way, SINEs lead to reduction in key oncoproteins such as c-Myc, Cyclin D, hDM2 and others. The reactivation of multiple TSP pathways as well as glucocorticoid signaling, along with reduced translation of key oncoproteins through inhibition of a non-redundant, single protein, i.e., XPO1, represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

Single-agent Phase 1 studies with oral selinexor have been conducted in advanced hematological malignancies including MM, acute myeloid leukemia (AML), non-Hodgkin's leukemia (NHL) and chronic lymphocytic leukemia (CLL) (KCP-330-001), in solid tumors (KCP-330-002), and in soft tissue and bone sarcomas (KCP-330-003). Broad antitumor activity has been observed in all of these studies. In addition, Phase 2 studies are ongoing in MM, AML, DLBCL, Richter's transformation, glioblastoma, gynecological malignancies, and dedifferentiated liposarcoma (DDLS). More than 2,000 patients with objectively progressing tumors at study entry have received selinexor as of 31 March 2017.

The most frequently reported side effects of selinexor seen in clinical studies to date are anorexia, fatigue, nausea, vomiting, and thrombocytopenia. These adverse events (AEs) may be mitigated or eliminated with standard supportive care. In addition, their prevalence and intensity typically decline after 4-8 weeks of treatment. Selinexor treatment is not associated with significant major organ toxicity. Moreover, clinically-relevant cumulative toxicities have not been observed during long term treatment, with more than 28 patients receiving single-agent selinexor for over 1 year and 6 patients for over 2 years. Please see the current *Selinexor Investigator's Brochure (IB)* for more information.

Selinexor has shown single-agent, durable, anti-cancer activity in patients with multiple RR hematologic and solid tumor malignancies, including MM, at doses of ≥ 6 mg/m^2 body surface area (BSA) in initial Phase 1 dose-escalation studies. In addition, results from a small number of patients suggests that selinexor in combination with dexamethasone 20 mg has increased efficacy in RR MM patients relative to selinexor alone (*Chen 2014, Data on file*).

In the current study, patients will receive low-dose dexamethasone (20 mg) to both improve the tolerability of selinexor and provide additional efficacy benefit as selinexor has been shown to activate glucocorticoid signaling through its receptor. Dexamethasone has been shown in previous studies to be an effective prophylactic treatment for the common AEs of selinexor described above. While untreated MM is exquisitely sensitive to glucocorticoids, this benefit wanes over time with treatment, which usually includes glucocorticoids in combination therapy. Patients with MM which has relapsed after multiple treatments are unlikely to respond to glucocorticoid treatment alone, but dexamethasone should provide symptomatic relief of selinexor-associated toxicity. In addition, dexamethasone may provide synergistic efficacy in combination with selinexor, which can reactivate glucocorticoid receptor (GCR) signaling. The current study will evaluate selinexor combined with dexamethasone for the treatment of MM in patients whose disease is refractory to previous treatment with a glucocorticoid, proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and the anti-CD38 monoclonal antibody (anti-CD38 mAb) daratumumab.

2. MULTIPLE MYELOMA

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, or M protein in the serum or urine, bone disease, kidney disease, and immunodeficiency. It is more common in elderly patients (median age at diagnosis is 65-70 years; only 2% of patients are younger than 40 years) (*Raab 2009*).

MM is the second most common hematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. With current therapy, median survival is 5.2 years after diagnosis (*Kumar 2014*).

Although the cause of MM is unknown, a number of mutated genes have been found with significant frequency in patients with MM. These include mutations in NRAS, KRAS, TP53 and BRAF, which are well known oncogenic drivers for other cancers (*Lohr 2014*) and mutations in many genes associated with NFκB activation (*Keats 2007*). Also, certain risk factors make patients more susceptible to the disease. MM is more common in individuals over the age of 65, in males, and in those with family members affected by MM. Fifty percent (50%) of patients with MM harbor mutations in the immunoglobulin heavy-chain locus on chromosome 14q32, partial or complete loss of chromosome 13, and partial loss of chromosome 17 (*Raab 2009*; *Kyle 2004*).

The diagnosis of MM is based on the key characteristics of the disease, occupation of the bone marrow cavity, the presence of space occupying bone lesions, and the production of paraprotein (*Raab 2009*; *IMWG 2003)*. The staging of MM is based on β_2-microglobulin level, which is directly correlated to renal function, tumor mass, and albumin level (*Greipp 2005*). The stages are summarized in Appendix 2.

The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy (i.e., alkylating agents) and autologous stem cell transplantation, the introduction of immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors, bortezomib and carfilzomib. However, despite the increased effectiveness of these agents, most patients develop highly resistant MM and succumb to the disease. With over 12,500 deaths from MM expected in the USA in 2016 (*ACS 2016*), there remains a high unmet medical need to develop anti-MM agents with novel mechanisms.

3. NUCLEAR EXPORT

3.1. Inhibition of XPO1 in Human Cancer

Many important tumor suppressing proteins (TSPs) have been identified in cancer pathogenesis, including but not limited to TP53, FOXO3a, IκB, BRCA1, APC, PP2A, and Rb (*Turner 2012; Senapedis 2014; Tan 2014; Yang 2014*). TSPs mediate tumor suppression pathways via various functions including recognition of cellular damage, arrest of the cell cycle until repairs can be made, and induction of apoptosis in cells that are beyond repair (*Brown 2011*). Similarly, glucocorticoid binding to, and nuclear localization of, the GCR is required for its signaling.

The tumor suppression and anti-cancer activity of these TSPs and the GCR requires their presence in the nucleus. Conversely, export to the cytoplasm by nuclear export shuttle protein XPO1 can inactivate their abilities to regulate cellular processes (*Xu 2010*) and cancer cells exploit these functions to successfully evade normal DNA-damage controls as well as anti-neoplastic therapy. XPO1 is the only known nuclear export protein for the vast majority of TSPs and the GCR. Of note, XPO1 has been identified as a selective survival gene in MM by unbiased high-throughput short interfering ribonucleic acid (siRNA) screening (*Tiedemann 2012*) and is commonly overexpressed in MM (*Tai 2014*).

XPO1 blockade causes transient nuclear retention of TSPs, the GCR, and other growth modulators, re-establishing their tumor suppressing and growth regulating effects on cancer cells and potentially reversing mechanisms leading to chemotherapy resistance (which holds possible future implications for combination therapies) (*Lain 1999*).

Certain growth-promoting (including oncogene) messenger RNAs (mRNAs) require specialized nuclear export via a “cap-binding complex” in order to exit the nucleus into the cytoplasm where they are translated into proteins (*Culjkovic 2013; Koehler 2007*). Several key MM genes including c-Myc, Cyclin D1, hDM2 and others utilize this complex via binding to the protein eIF4E in order to exit the nucleus and undergo efficient translation into protein. The cap-binding complex protein eIF4E is exported out of the nucleus into the cytoplasm exclusively by XPO1. As these proteins tend to have very short half-lives, constant translation is required to maintain their cellular levels. Inhibition of XPO1-mediated nuclear export leads to reduced translation of these growth-promoting proteins, and subsequently significant drops in their levels.

In normal cells, XPO1 inhibition transiently arrests the cell cycle without cytotoxicity followed by recovery after the inhibitor is removed (*Lain 1999*; *van der Watt 2009*; *Gray*

2007). Several attempts to develop this class of anti-cancer drug have failed due to off-target effects of the drugs which led to significant weight loss, diarrhea, and marked fatigue and asthenia in the early clinical trials (*Mutka 2009*; *Newlands 1996*; *Roberts 1986*).

It is now well recognized that forced nuclear retention of TSPs can counteract a multitude of oncogenic, growth stimulatory (and inflammatory) pathways that perpetuate the neoplastic phenotype. Similarly, nuclear retention of the GR in the presence of glucocorticoids could restore its activity. Finally, inhibition of eIF4E/XPO1-mediated mRNA export of oncoproteins lead to reductions in their levels. Because restoration of TSP ± GR activity and reduction in oncogenic signals are relevant to essentially any cancer, XPO1 inhibition is expected to have activity against MM and many other malignancies (Table 2).

Table 2: Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway Affected	Effect of XPO1 Inhibition	Reference
XPO1 overexpression	XPO1 reduction	Walker 2013
Glucocorticoid Receptor (GR) Inactivation (nuclear export)	Nuclear GR retention (in presence of glucocorticoids) and reactivation	Chen 2014
p53 mutation	p73 activation, p21 activation	Ranganathan 2012
hDM2 (MDM2) activation	Nuclear p53 retention and activation, hDM2 protein reduction	Kojima 2013
c-Myc amplification	MYC protein reduction	Schmidt 2013
Cyclin D1 overexpression	Cyclin D1 reduction	Gao 2014
NPM1 mutation	Restoration of nuclear NPM1	Falini 2007
CEBPA down-regulation	Nuclear retention and activation	Ranganathan 2012
CDKN2A reduction	p53/p73 stabilization	Azmi 2013
Rb reduction	Rb hypophosphorylation, p14/p16 elevation	Fragomeni 2013
FLT3 activation	FLT3 reduction	Ranganathan 2012
c-KIT activation	c-KIT reduction	Ranganathan 2012
NF-κB activation	IκB nuclear retention and activation	Lapalombella 2012
PIK3 or AKT activation	FOXO1, -3, -4 activation	Lapalombella 2012
Survivin – cytoplasmic	Survivin nuclear retention	Altura 2003
Bcr-Abl activation	PP2A activation	Walker 2013

4. SELINEXOR (KPT-330)

4.1. Introduction

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 responsible for the unidirectional export of ~220 different cargo proteins from the nucleus to the cytoplasm (*Xu et al., 2010*). The anti-neoplastic activity of SINE compounds is mediated

through at least three distinct pathways involving tumor suppressor proteins (TSPs), oncoproteins, and the glucocorticoid receptor. First, SINE compounds induce nuclear localization and functional activation of multiple TSPs, leading to rapid apoptosis of multiple myeloma (MM) (*Tai et al., 2014*) and other malignant cells. By forcing the nuclear localization and activation of TSPs, all cell types exposed to SINE compounds undergo G1 ± G2 cell cycle arrest, followed by a 'genomic fidelity' review. Cells with genomic damage (ie, malignant cells) are induced to undergo apoptosis both in vitro and in vivo. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the XPO1 block is relieved. A second anti-neoplastic effect of SINE compounds is mediated through the mRNA cap-binding protein eIF4E, which is also an XPO1 cargo. Amongst other functions, eIF4E is responsible for the efficient nuclear export and delivery of several growth-promoting (oncoprotein) mRNAs to cytoplasmic ribosomal for translation. By forcing the nuclear retention of the eIF43 bound to XPO1, SINE compounds reduce the cytoplasmic ribosomal synthesis of oncoprotein mRNAs including c-Myc, hDM2, Cyclin D1 and Bcl-XL. Finally, SINE compounds also lead to restoration of anti-myeloma glucocorticoid receptor (GR) signaling in the presence of glucocorticoids; selinexor and other SINE compounds do not appear to exacerbate the hyperglycemic effects of glucocorticoids. Thus, by inhibiting the key nuclear/cytoplasmic control protein XPO1, SINE compounds exhibit broad and deep anti-cancer activities.

4.2. Preclinical Data

In this section, a brief summary of preclinical data is provided. Additional information is presented in the current *Selinexor/KPT-330 Investigator's Brochure*.

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture, including multidrug-resistant cancers. Moreover, selinexor demonstrated cytotoxicity in MM and CLL cells in the absence or presence of bone marrow stroma cells (BMSC).

Pharmacokinetic (PK) studies were conducted in mice, rats and monkeys. Selinexor showed dose proportional exposure with no accumulation. Please see the current *Selinexor/KPT-330 Investigator's Brochure* for more information.

Several studies were conducted to evaluate the effect of SINE compounds on MM *in vivo*. In MM1.S xenograft tumors, treatment with the SINE compound KPT-276 showed a marked decreased in tumor volume (40%) whereas tumor volume increased by 36% with placebo (*Schmidt 2013*). KPT-276 was also active in the Vk*MYC mouse model of MM, which has a positive predictive value of 67% for the activity of single-agent compounds in clinical trials (*Schmidt 2013; Chesi 2012*).

4.2.1. Selinexor plus Dexamethasone Combination Studies

In vitro studies showed selinexor and dexamethasone in combination were found to have a synergistic effect on reducing MM1.S human MM cell viability relative to either drug alone (*Chen 2014*). Increased GR nuclear localization and concomitantly activated GCR-mediated transcription in the presence of glucocorticoids were at least partly responsible for the synergistic cytotoxicity of this combination. (*Gao 2014*).

Enhanced activity of the selinexor plus dexamethasone combination was also observed in two xenograft models of human MM. The addition of dexamethasone to selinexor enhanced activity (86%) relative to selinexor alone.

In summary, the combination of selinexor and dexamethasone is synergistic *in vitro* and *in vivo* in MM cell cytotoxicity assays through increased nuclear localization of GCR and amplified GCR transcriptional activity. Taken together, these studies demonstrate that SINE compounds are active anti-MM compounds that cause decreased cell viability, increased apoptosis, and cell cycle arrest *in vitro* and potent inhibition of MM tumor growth *in vivo*, and that the addition of dexamethasone can augment these effects.

4.3. Clinical Experience

As part of a Phase 1 clinical study of selinexor in patients with advanced hematological malignancies (KCP-330-001), 68 patients with MM that was relapsed and/or refractory to all available classes of approved therapies and was progressing on study entry received selinexor on a twice-weekly dose schedule. Preliminary results, as of 13 December 2016, are summarized below.

4.3.1. Preliminary Results for Patients with MM, Study KCP-330-001, as of 13 December 2016

4.3.1.1. Preliminary Efficacy Results for Patients with MM, Study KCP-330-001

Selinexor plus Dexamethasone

As of 13 December 2016, the best responses among the 22 evaluable patients who received selinexor plus dexamethasone (Sd) were: 1 CR (5%), 5 PRs (23%), 3 MRs (14%), 8 SDs (36%), and 5 PDs (23%). The ORR was 27% and the CBR was 41%. Several patients remained on study for >9 months and one patient remained on study for >1 year.

Single-agent Selinexor

Selinexor showed modest efficacy as a single-agent with 4% of patients achieving an objective response (≥PR in 2 of 46 patients) and 26% showing clinical benefit (≥ MR in 12 of 46 patients). Overall, these preliminary Phase 1 results suggest that selinexor ± dexamethasone has clear anti-MM activity in heavily pretreated patients.

4.3.1.2. Preliminary Safety Results for Patients with MM, Study KCP-330-001

Adverse events in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Preliminary Results for Patients with MM, Study KCP-330-012, as of 01 December 2016

Preliminary efficacy and safety results from the first 79 patients were presented at the 2016 American Society of Hematology annual meeting and are summarized below (Vogl et al., 2016).

4.3.1.3. Preliminary Efficacy (Response) Results for Patients with MM, Study KCP-330-012

Response rates in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and refractory to one proteasome inhibitor (PI), one immunomodulatory drug (Imid) and glucocorticoids ("quad" refractory) and in patients with MM refractory to the "quad" agents as well as to an anti-CD38 Ab ("penta" refactory) were adjudicated by an Independent Review Committee (IRC) and are presented in Table 3. for the first portion of the study overall, for 8 vs. 6 doses per 28-day cycle and "penta" vs. "quad" MM (Vogl et al., 2016). One patient did not have measurable myeloma at baseline and is not included in the efficacy analyses. The ORR across all patients is 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with "penta" and "quad" MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing. The additional 122 patients with "penta" MM to be added will receive 8 doses / cycle based on these analyses.

Table 3: Response by Doses per Cycle and Prior Therapy Status as of 01 Dec 2016

Category	N[a]	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)	NE (%)
Overall	78	16 (21%)	26 (33%)	4 (5%)	12 (15%)	10 (13%)	27 (35%)	9 (12%)	16 (21%)
8 doses/cycle	27	6 (22%)	11 (41%)	1 (4%)	5 (19%)	5 (19%)	6 (22%)	5 (19%)	5 (19%)
6 doses/cycle	51	10 (20%)	15 (29%)	3 (6%)	7 (14%)	5 (10%)	21 (41%)	4 (8%)	11 (22%)
Penta[b]	30	6 (20%)	12 (40%)	2 (7%)	4 (13%)	6 (20%)	6 (20%)	5 (17%)	7 (23%)
Quad[c]	48	10 (21%)	14 (29%)	2 (4%)	8 (17%)	4 (8%)	21 (44%)	4 (8%)	9 (19%)

CBR=Clinical Benefit Rate (sCR+PR+MR), MR=Minor Response, NE=Non-Evaluable, ORR=Overall Response Rate (sCR+PR), PD=Progressive Disease, PR=Partial Response, SD=Stable Disease, VGPR=Very Good Partial Response

[a] one patient not included, did not have measurable myeloma at baseline

[b] the majority of these patients (19 of 30) received 8 doses per cycle

[c] the majority of these patients (40 of 48) received 6 doses per cycle

4.3.1.4. Preliminary Safety Results for Patients with MM, Study KCP-330-012

Common treatment-related adverse events (TRAEs) based on a preliminary analysis of safety and tolerability (N=92; safety data cut off 31 March 2017):

- Hematological: thrombocytopenia (overall: 64%, Grades 3/4: 51%), neutropenia (overall: 26%, Grades≥ 3 19%), and anemia (overall: 39%, Grade 3/4: 22%). There was one case of febrile neutropenia (1%) and one case of clinically significant bleeding related to thrombocytopenia (1%).

- Non-hematological: nausea (overall: 68%, Grade 3: 8%), fatigue (overall: 64%, Grade 3: 14%) anorexia (overall: 51%, Grade 3: 2%), vomiting (overall 41%, Grade 3: 2%), hyponatremia (overall 33%, Grade 3: 18%), diarrhea (overall 40%, Grade 3: 4%), and weight loss (overall: 33%, Grade 3: 1%).

These results are generally consistent with the overall TEAE results reported for all selinexor studies in patients with hematological malignancies (see the *Selinexor/KPT-330 IB*).

4.3.1.5. Summary

Based on the promising preliminary efficacy results described above and on the considered feedback from MM experts that the population of patients with penta-refractory MM represents a current and growing high unmet medical need where there are no approved agents and there is no established standard of care, Karyopharm is expanding the number of patients with penta-refractory MM enrolled in this single-arm study to a total of ~160 patients with penta-refractory MM to receive Sd twice weekly for every week of each four-week cycle (8 doses/cycle).

4.4. Potential Risks

Selinexor is currently in clinical development and has not been approved by the FDA for commercial use. Over 2,000 patients have received selinexor (as of 31 March 2017), however the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring.

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

In ongoing clinical studies with selinexor, the most common AEs possibly related to selinexor are anorexia, fatigue, nausea, vomiting, diarrhea, and thrombocytopenia. Virtually all of these side effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. Overall, the most frequently observed laboratory abnormalities include thrombocytopenia, hyponatremia, and a decrease in red blood cells. The majority of these have been mild to moderate. Please refer to the current *Selinexor/KPT-330 Investigator's Brochure* for more information.

Acute cerebellar syndrome (ACS) was reported at high doses in one adult (85 mg/m^2) and two pediatric (70 mg/m^2) patients in two phase 1 studies. The maximum doses in adults (70 mg/m^2) and children (55 mg/m^2) have been established largely based on these events. An adult patient, heavily pre-treated for recurrent pancreatic cancer, developed ACS following 3 doses of selinexor at 85 mg/m2 twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Selinexor was discontinued and the patient's symptoms resolved to near baseline by ~6 weeks. A five-year old with refractory AML developed ACS following 4 doses of selinexor (70 mg/m^2) followed by 5 days of fludarabine and cytarabine (without intrathrecal therapy). The patient was empirically treated with intravenous immunoglobulin for 5 days, improved significantly over the next 3 weeks, and

had resolution of symptoms after 6 weeks. A repeat MRI 10 days after the initial image showed near complete resolution of diffusion abnormalities. A 19-month-old male (70 mg/m^2) with relapsed AML developed ACS after receiving 4 doses of selinexor. Because the clinical and imaging findings were consistent with cerebellar toxicity, protocol therapy was discontinued and his ataxia showed improvement over the course of two weeks.

No other patients have reported such symptoms to date. All cases of cerebellar toxicity of Grade 3 or higher must be captured as an SAE and reported in an expedited Safety Report within 7 days of awareness of the event.

4.4.1. Reproductive Risks

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies; most resolved or partially resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. Please see the Selinexor (KPT-330) Investigator's Brochure for additional information. As it is unknown if selinexor produces any reproductive toxicity in humans, all patients must agree to use effective contraception (see Section 11.4.7) during the study and for 3 months after the end of treatment.

5. RATIONALE FOR THE STUDY

Multiple myeloma is the second most common hematological malignancy. With conventional treatment methods, median survival is 5.2 years after diagnosis (*Kumar 2014*). Multiple myeloma is highly treatable but is not considered to be curable with currently available therapies. Common treatments include glucocorticoids, chemotherapy, proteasome inhibitors, immunomodulatory drugs, stem cell transplants, and radiation therapy.

Selinexor has demonstrated anti-MM activity in pre-clinical studies *in vitro* and *in vivo*. A summary of clinical results for 81 patients with MM seen in Study KCP-330-001, as of 01 August 2016, is provided in Section 4.3.

The original design of this protocol (KCP-330-012) was based on the primary treatment options for RR MM (i.e., IMiDs and PIs) that were in common use at the time that the protocol was developed, in order to evaluate whether selinexor would provide a useful, new therapeutic option to patients whose disease was RR to these treatments (i.e., patients with quad-refractory MM). In that design, a subset of patients with penta-refractory MM was also included as an CCI [redacted], as treatment with anti-CD38 mAbs was not yet common. With the recent approval of daratumumab and ongoing development of isatuximab, the clinical use of anti-CD38 mAbs to treat RR MM has become more common, suggesting that selinexor would be best considered as a therapeutic option in patients with penta-refractory MM.

5.1. Rationale for Selinexor Dose Schedule

More than 2,000 patients with advanced cancers have received selinexor in Phase 1 and Phase 2 studies as of 31 March 2017. In study KCP-330-001, patients who received selinexor

45 mg/m^2 (~80 mg) plus dexamethasone 20 mg, both dosed twice weekly, experienced durable response without clinically relevant cumulative toxicities. (See Section 4.3.)

Patients in the present study will receive selinexor 80 mg (45 mg/m^2 BSA) plus dexamethasone 20 mg, both dosed twice weekly, for each week of four-week cycles.

Dexamethasone 20 mg will be given with each dose of selinexor. For patients with partial intolerance to glucocorticoids (as determined by the Investigator) a minimum dose of dexamethasone 10 mg with each dose of selinexor is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis.

In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg to 100 mg, based on efficacy and safety considerations, after a minimum of two cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the BSA for the patient should be calculated. Patients with BSA < 1.4 m^2 may not have their dose increased, as this would result in a dose > 70 mg/m^2 selinexor.

6. STUDY OBJECTIVES

6.1. Primary Objectives

Evaluate the efficacy (overall response rate [ORR]) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab; and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (herein referred to as “penta-refractory” MM).

ORR will include patients who experience partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on International Myeloma Working Group (IMWG) response criteria (*Kumar 2016*) for patients with penta-refractory MM in Part 2 (expansion phase).

6.2. Secondary Objectives

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM, (b) Part 1 patients with penta-refractory MM, and (c) Part 2 (expansion) patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR = Duration from first observation of at least PR to time of disease progression, or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression)

- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression.
- Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to next treatment (TTNT)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the PK properties of selinexor in this patient population (Part 1 only)

CCI [redacted]

– Lytic lesions as assessed by skeletal survey (or similar bone imaging)

7. STUDY DESIGN

7.1. Overview

This is a Phase 2b, single-arm, open-label, multicenter study of Sd (selinexor 80 mg plus dexamethasone 20 mg), both dosed twice weekly, four weeks of each four-week cycle, in patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab. (Note: Refractory is defined as ≤ 25% response to therapy, progression during the previously described therapies, or progression within 60 days after completion of therapy.)

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1.0-3.0) enrolled patients with both quad-refractory MM and penta-refractory MM. Part 2 (protocol V≥4.0) will enroll patients with penta-refractory MM only, but continue all patients enrolled in Part 1.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients and quad-refractory MM patients.

Patients will receive selinexor 80 mg (45 mg/m^2 BSA) plus dexamethasone 20 mg (Sd), both dosed twice weekly, for each week of four-week cycles. Patients will receive treatment until PD, death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

Patients will also receive best supportive care to mitigate selinexor side effects, including blood product transfusions, antimicrobials, and (as appropriate) growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anemia, and/or platelet-stimulating factors for thrombocytopenia.

In select cases (e.g., for patients showing SD or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the body surface area (BSA) for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose > 70 mg/m^2.

In Part 2, MM-specific assessments (i.e., SPEP, UPEP, serum/urine immunofixation, quantitative Ig levels, serum FLC, and bone marrow aspirate) must be confirmed by a central laboratory to confirm CR or sCR, and select VGPR, per IMWG. Additional information is provided in the *Study Manual*.

The Investigator may remove a patient from study treatment using criteria described in Section 10.2. Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

7.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the safety of study treatment and any SAEs that occur during the study. Details on how the DSMB will review safety and response data are provided in the *DSMB Charter*.

The DSMB will be comprised of a minimum of two oncologists (at least one of whom specializes in hematologic oncology) and a statistician. Following their initial meeting, DSMB meetings will occur on a periodic basis in accordance with their charter.

7.3. Independent Review Committee

An Independent Review Committee (IRC), will review disease assessment data to independently assess disease response. The IRC will review data that will be used for the analysis of the primary endpoint. The IRC's assessments of disease response and time to progression (TTP) will be used as the basis for the evaluation of the primary endpoint.

The IRC membership, functioning, and procedures (including resolution of any disagreements with Investigators regarding disease assessments) will be described in the *IRC Charter*.

7.4. Stopping Rules

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 10.

7.5. Study Endpoints

Study objectives and endpoints are provided in Section 6.

7.6. Blinding and Randomization

Not applicable; this is an open-label, single-arm, multicenter study.

7.7. End of Study

The End of Study (EoS) will occur when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).

8. SELECTION OF PATIENTS

8.1. Number of Patients

Approximately 210 patients will be enrolled overall, including ~160 patients with penta-refractory MM (Part 1 [~30] and Part 2 [~130]) and ~50 patients with quad-refractory MM (Part 1 only). See Section 7.1.

8.2. Recruitment

This study will be conducted at multiple sites in the United States and Europe.

8.3. Documentation Requirements

For enrollment consideration, patients may be eligible if they have *documented evidence* of previous treatment for MM that substantiates disease status as follows:

- Refractory to a glucocorticoid
- Refractory to lenalidomide and/or pomalidomide (only 1 required) *and* evidence of prior treatment* with *both* lenalidomide and pomalidomide
- Refractory to bortezomib and/or carfilzomib (only 1 required) *and* evidence of prior treatment* with *both* bortezomib and carfilzomib
- Refractory to daratumumab

* Prior treatment is defined as either refractory, treatment with ≥ 2 cycles, or documented severe intolerance.

Documented evidence will include at least one of the following:

1. Medical records that support start and stop dates (month/year) of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
2. Myeloma marker values (SPEP, UPEP, Immunoglobulin, FLC) at the time of prior treatment start, stop and time of progression (accompanied by #1).
3. Formal, signed physician letter by Investigator (on hospital/clinic letterhead), to be included in the patient's medical and research record, indicating start/stop dates of prior treatment (both dose and schedule), best response on treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).
4. Formal, signed physician letter from referring physician (on hospital/clinic letterhead), to be included in the patient's medical and research record, that includes prior treatment history indicating start/stop dates of prior treatment (both dose and schedule), best response on prior treatment and, if applicable, date of progression (including both dose and schedule at the time of progression).

8.4. Inclusion Criteria

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

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥ 18 years at the time of signing informed consent.
3. Measurable MM based on IMWG guidelines as defined by at least one of the following:
    a. Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA
    b. Urinary M-protein excretion ≥ 200 mg/24 hours
    c. FLC ≥ 100 mg/L, provided that the FLC ratio is abnormal.
    d. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative Ig levels by nephelometry is acceptable.
4. Patients must have previously received ≥ 3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
5. MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and daratumumab. Refractory is defined as ≤ 25% response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
6. Multiple myeloma that is refractory to the patient's most recent anti-MM regimen. (Documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor.)
7. Any clinically significant non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #17) that patients experienced from treatments in previous clinical studies must have resolved to Grade ≤ 2 by Cycle 1 Day 1.
8. Adequate hepatic function within 21 days prior to Cycle 1 Day 1: total bilirubin < 2x upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3x ULN), AST < 2.5x ULN and ALT < 2.5x ULN.
9. Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of ≥ 20 mL/min, calculated using the formula of Cockroft and Gault.
10. Female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception) and have a negative serum pregnancy test at Screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose of study treatment.

11. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
12. Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1 (See Exclusion Criterion #20 for transfusion washout periods for RBCs and platelets):
    a. Total WBC count > 1,000/mm^3
    b. ANC ≥ 1000/mm^3
    c. Platelet count ≥ 75,000/mm^3 (patients in whom <50% of bone marrow nucleated cells are plasma cells) or ≥ 50,000/mm^3 (patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells. (Platelet transfusions < 1 week prior to Cycle 1 Day 1 are prohibited [see below].)
13. Hemoglobin level ≥ 8.5 g/dL. In certain cases, patients with stable baseline hemoglobin level > 8.0 may be included following approval by the Medical Monitor. (Red blood cell transfusions < 2 weeks prior to Cycle 1 Day 1 are prohibited [see below].)
14. Confirmation of patient eligibility for specific key criteria for study participation with the Medical Monitor.

8.5. Exclusion Criteria

1. Active smoldering MM.
2. Active plasma cell leukemia.
3. Documented systemic amyloid light chain amyloidosis.
4. Active central nervous system (CNS) MM.
5. Pregnancy or breastfeeding.
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1, and radio-immunotherapy 6 weeks prior to Cycle 1 Day 1.
7. Active graft vs. host disease (after allogeneic stem cell transplantation) at Cycle 1 Day 1
8. Life expectancy of < 4 months.
9. Major surgery within four weeks prior to Cycle 1 Day 1.
10. Active, unstable cardiovascular function:
    a. Symptomatic ischemia, or
    b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
    c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3, or
    d. Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1.
11. Active, uncontrolled hypertension.

12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
13. Known HIV seropositive.
14. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
15. Prior malignancy that required treatment, or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to enrollment. Cancer treated with curative intent > 5 years previously and without evidence of recurrence will be allowed.
16. Active GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
17. Grade ≥ 3 peripheral neuropathy, and Grade ≥ 2 painful neuropathy, within 21 days prior to Cycle 1 Day 1.
18. Serious, active psychiatric or medical conditions which, in the opinion of the Investigator, could interfere with treatment.
19. Participation in an investigational anti-cancer study within 21 days prior to Cycle 1 Day 1.
20. Receipt of transfusions as follows:
    a. Platelet infusion within 1 week prior to Cycle 1 Day 1.
    b. RBC transfusion within 2 weeks prior to Cycle 1 Day 1.
21. Receipt of the following blood growth factors within 2 weeks prior to Cycle 1 Day 1: Granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), or megakaryocyte growth factor.
22. Known intolerance to or contraindications for glucocorticoid therapy at Cycle 1 Day 1.
23. Prior exposure to a SINE compound, including selinexor.
24. Unable or unwilling to comply with protocol requirements, including providing a 24-hour urine samples at the required study time points.

8.6. Screen Failures

Patients who sign an informed consent form and do not receive study treatment for any reason are defined as screen failures. For all screen failures, the Investigator will enter the screening number, patient initials; and reason(s) for screen failure onto electronic case report forms (eCRFs). Screen failures will be replaced. Screen failures may be re-screened.

8.7. Study Patient Numbers

Each patient will be assigned a unique study number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason.

Patients will be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient identification master log.

8.8. Study Patient Number

Each patient will be assigned a unique study number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients will be identified to Karyopharm only by their assigned number, initials, year of birth (as allowed by national and local regulatory authorities), and sex. The Investigator must maintain a patient identification master log.

9. METHODS OF ASSESSMENT AND ENDPOINTS

9.1. Standard Study Assessments

All assessments should be performed as outlined in Table 1.

9.1.1. Demographic Data

During Screening, patient demographic data will be collected. These data include year of birth, age, gender, race, and ethnicity.

9.1.2. Medical History

A complete medical history will be obtained from each patient. Medical history includes historic MM assessment values (Day -30 and Day -60), baseline symptoms as well as a detailed history of prior procedures for MM and other prior cancer therapies (i.e., transplant, chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery) including start and stop dates, best response, disease progression dates (during or after therapy), as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. Data should be reviewed by the Investigator prior to dosing on Cycle 1 Day 1.

9.1.3. Concomitant Medications

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

Supportive care (such as appetite stimulants, anti-emetics, and anti-diarrheals, etc.) is encouraged (see Section 11.4.2).

9.1.4. Physical Examination

Full physical examinations (PE) during Screening and the EoT Visit will be performed. All other PEs during the study should be symptom-directed PEs. Significant findings that were present prior to the signing of informed consent must be included on the medical history page on the patient's CRF. Significant new findings, including the presence of plasmacytomas,

that begin or worsen after informed consent must be recorded on the Adverse Event or Plasmacytoma page of the patient's CRF.

PEs, unless otherwise noted, will include the following:

- Height (without shoes) in centimeters (cm) measured during Screening only
- Body weight (indoor clothing without shoes) in kilograms (kg)
- Body temperature
- Systolic and diastolic BP and pulse rate measured at each visit after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm at each visit.

Information about the PE must be present in the source documentation at the study site. Clinically relevant findings made after the start of selinexor plus dexamethasone dosing, which meet the definition of an AE, must be recorded on the AE eCRF.

9.1.5. ECOG Score

An ECOG Score Assessment (see Appendix 1) will be performed during Screening, Day 1 of each cycle, and the EoT visit.

9.2. Multiple Myeloma Disease Specific Assessments

Patient response will be assessed by the procedures summarized in Table 4 and graded according to the IMWG response criteria summarized in Table 10 (Appendix 3). Per IMWG, quantitative Ig levels by nephelometry may be used in place of SPEP for routine M-protein measurements for patients with IgA or IgD myeloma. Also, per IMWG, response may be confirmed if the patient fails to provide 24-hour urine sample collection after Screening activities occur. All MM assessments outlined in this protocol are required to be performed at each study visit, prior to dosing. If MM assessments are collected at unscheduled times, those results must be documented in the eCRF as unscheduled visits. This includes SPEP, UPEP, serum FLC, β_2 microglobulin, quantitative Ig, and serum/urine protein immunofixation. Results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 (±15 days) will also be provided.

SPEP with serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP, with immunofixation, must be collected at each required time point. An aliquot of the blood and urine samples should be retained. If the local laboratory results indicate a CR or sCR, sequential MM disease assessment samples, per IMWG, will be collected. The sequential samples will be split – one aliquot of each sample will be sent to the local lab while the other aliquots, along with the initial assessment aliquots, will be sent to the central laboratory to confirm CR or sCR. If the results do not indicate CR or sCR, then the aliquots may be destroyed. Refer to the *Study Manual* for details.

All disease assessments (SPEP, UPEP, FLC, quantitative Ig, and serum/urine protein immunofixation) should be performed regardless of the diagnosis that is being followed (e.g., 24 hour UPEP collection must be collected at each time point outlined in the protocol even if the patient is being followed by SPEP, Ig or FLC).

Table 4: Multiple Myeloma Disease-specific Assessments

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. If the patient fails to provide the 24-hour urine sample, this should be documented. All attempts should be made to collect the 24-hour urine sample at the required time points. UPEP must be determined from a urine sample collected for 24 hours – no other method is acceptable. UPEP must be performed at each time point outlined in the protocol even if the patient is being followed by SPEP.
Serum FLC	Per IMWG.
Quantitative Ig levels	Per IMWG. For IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage changes apply as for serum M-spike. Only nephelometry can be used for the response assessment, and SPEP and nephelometric values cannot be used interchangeably (Durie et al., 2006).
β_2-microglobulin	For MM staging (Appendix 2), not for assessing response
Skeletal survey	A skeletal survey (using x-rays and/or other clinically appropriate imaging modalities [MRI, whole body CT, or PET/CT]), as determined by the Investigator, will be performed within 45 days of C1 D1 and as clinically indicated, per Investigator discretion, during the study. The skeletal survey should include a lateral radiograph of skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri. Results will be read by the local laboratory. If lytic bone lesions or plasmacytomas are observed at Screening, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline should be re-assessed during the study at a frequency determined by the Investigator, using the same imaging modality that was used at Screening. • For patients without soft tissue plasmacytomas (i.e., bone lesions only), skeletal survey by X-rays or low-dose CT should be performed. Contrast is not required. • For patients with soft tissue plasmacytomas, skeletal survey by X-rays or low-dose CT should be performed (contrast not required) and in addition MRI or CT or PET/CT, usually requiring contrast enhancement, should be performed.
Clinical plasmacytoma	If plasmacytomas are detected at Screening by physical examination/palpation, they should be counted and measured per IMWG guidelines and recorded, and then reassessed and recorded during symptom directed physical examinations.
CCI [redacted]	[redacted]

Procedure	Notes
	CCI [redacted]
CCI [redacted]	[redacted]
FACT-MM	See Section 9.9.2

9.3. Multiple Myeloma Response Criteria

IMWG criteria (*Kumar 2016*) will be used in this study to assess response. All MM assessments are required at each time point as outlined in this protocol (Table 1).

Response will be assessed per IMWG response criteria for multiple myeloma (Appendix 3). Two consecutive samples are required to confirm the response. The time period between samples may be discussed with the Medical Monitor and can occur on the same day, as long as, the samples are analyzed separately.

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

9.4. Safety Assessments

Safety evaluations will be conducted at each visit and will include the procedures summarized below.

9.4.1. 12-Lead ECG

A standard 12-lead ECG will be performed as indicated in Table 1. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG was performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected (QTc) using Bazett's formula or calculated by the Fridericia correction formula (*Bazett 1920, Fridericia 1920*). If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula: QT/(RR^[1/3]), where RR = 60/heart rate.

9.4.2. Ophthalmic Exam

A full ophthalmic examination will be performed prior to the patient's first dose of selinexor. Prior to dilation, best corrected visual acuity (Snellen's Equivalent based on either Snellen chart or ETDRS chart), slit lamp examination including tonometry, following dilation, and fundoscopy. If a cataract is seen during the examination, the cataract will be graded as follows:

- *Lens Opacities Classification System III (LOCS III)* – Patients who enrolled in this study under the original Protocol or Protocol Amendments 1 or 2 and had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the new AOA Grade 1-4 cataract scale. For new patients or patients in whom no cataracts have been detected to date, if cataracts are detected, they will be graded according to the Grade 1-4 scale.
- *American Optometric Association (AOA) Cataract Grading System* – Starting with Protocol Amendment 3, new patients will be evaluated using the AOA grading system until they complete the study. This system is modified from the Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataract, which is available on the AOA website (*www.aoa.org*)(See Appendix 5.)

9.4.3. Clinical Laboratory Assessments

The following clinical laboratory tests should be performed as indicated in Table 1.

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.

- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate (HCO_3^-), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, amylase, lipase, creatine kinase and uric acid.
  - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
  - Thyroid-stimulating hormone (TSH)
- Coagulation parameters will include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

Blood chemistry will be analyzed at each study site by a certified local laboratory and a report of the laboratory values will be provided to the Investigator. 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 medication) or baseline. Any laboratory value that remains abnormal at the EoT Visit and that is considered clinically significant 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 assessed using CTCAE version 4.03.

9.4.4. 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. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 during the study and at the EoT Visit (serum hCG).

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

9.5. Pharmacokinetic [redacted] Procedures

9.5.1. Blood Sampling and Processing

As of protocol version 5.0, these samples are no longer collected.

9.6. Pharmacokinetic Endpoints

Pharmacokinetic analysis of selinexor plasma levels will be performed on blood samples from patients enrolled in Part 1 only. Pharmacokinetic endpoints to be evaluated include selinexor maximum plasma concentration and time-to-peak plasma concentration.

Plasma samples will be analyzed via a validated high performance liquid chromatography/ tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications. CCI [redacted] Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan, to be completed prior to database lock.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.8. Efficacy Procedures

9.8.1. Objective Disease Assessment

Procedures for confirming response are listed in Table 4.

9.9. Efficacy Endpoints

The primary efficacy objective/endpoints are provided in Section 6.1; secondary efficacy endpoints are presented in Section 6.2.

9.9.1. Response Criteria

Disease response will be assessed using IMWG (*Kumar 2016*). There is no maximum treatment duration. Disease response will be assessed centrally by an independent IRC (Section 7.2). Definitions of individual response criteria are provided in Appendix 3.

9.9.2. Quality of Life Assessment

Health-related QoL and potential for improvement over the course of the study will be assessed by the FACT-MM patient-reported outcome questionnaire that is specifically relevant to MM. Additional information on the FACT-MM is provided in Section 13.3.4.

Patients should complete the FACT-MM assessment *before* they undergo any study related procedure, including other study related evaluations, discussions with medical personal, physician and study treatment administration.

10. DISCONTINUATION CRITERIA

10.1. Early Discontinuation of the Study

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

The DSMB will inform the sponsor if a safety signal is detected (see Section 7.2). The sponsor, in conjunction with appropriate regulatory authorities, would then decide if the trial should be modified or terminated. If this occurs, the sponsor will notify IRB/REB/ECs and investigators.

10.2. Early Discontinuation of Individual Patients

The Investigator may remove a patient from study treatment at his/her discretion for any of the following reasons:

- Disease progression defined according to IMWG for progression of MM, including confirmatory analysis to document progression. Disease progression must be confirmed by the IRC prior to discontinuation of the study treatment
- Unacceptable AE(s) or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator

Reasons for discontinuation must be clearly documented in the source and in the study CRFs, including reasons for patient withdrawal and Investigator decision to discontinue the patient.

Patients may discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

11. TREATMENT

Selinexor study medication will be in the form of a coated, immediate-release tablet for oral administration. Selinexor tablets will be supplied as single-strength (20 mg) tablets in wallet-size blister packs. Dexamethasone 20 mg will be given with each dose of selinexor. Additional information is provided in Section 11.1.3.

11.1. Dosing and Administration

11.1.1. Dose Modifications

All dosing modifications should be discussed with the study Medical Monitor prior to implementing the dosing change.

11.1.2. Labeling

All drug containers will be labeled in accordance with current International Conference on Harmonization (ICH), GCP, and regulatory agency-specific requirements (e.g., FDA, MHRA). Medication labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of the US.

11.1.3. Dosing Information

Selinexor will be administered as a fixed oral selinexor dose of 80 mg twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday, etc.) on Weeks 1-4 of each four-week cycle. For doses on non-clinic days, the patient will be provided with doses by the hospital pharmacy to take home.

Dexamethasone 20 mg will be given with each dose of selinexor. For patients with partial intolerance to glucocorticoids (as determined by the Investigator), a minimum dose of 10 mg dexamethasone is permitted. If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis. Dexamethasone will be provided to take home in the form of tablets.

In select cases (e.g., for patients showing SD, MR, or PR and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after discussion with the sponsor. The dose level for an individual patient may be escalated based on efficacy considerations after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the BSA for the patient should be calculated. Patients with may have their dose increased if it would result in a dose >70 mg/m^2 [redacted]

Selinexor should be given with, or within 30 minutes of, solid food consumption (to optimize tolerability) together with at least 120 mL (4 ounces) of fluids (water, juice, etc.) For details of drug formulation, preparation, and administration, please refer to Appendix 4.

Selinexor tablets should be swallowed whole and should not be crushed to avoid increased risk of dermatologic toxicity if the powder comes in contact with skin.

Compliance to study treatment will be assessed by the Investigator or delegate at each patient visit and recorded in source documents after discussion with the patient and drug accountability. The date will be recorded as per study drug schedule. The Investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons. The Investigator / designee will attempt to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

Patients may receive a study treatment holiday at any time during the four-week cycles, following prior consultation with the Medical Monitor.

11.1.4. Dose Modifications for Patients with VGPR

In an effort to improve long-term disease control and tolerability, this protocol allows for dose reductions in patients with very good anti-tumor activity of selinexor. Thus, for patients who achieve ≥ VGPR for ≥ 6 months and who, in the opinion of the Investigator may benefit from dose reduction(s), the following modifications may be considered: (a) The dose of dexamethasone may be reduced by 40% or (b) the dose of selinexor may be reduced by 20 mg or (c) the frequency of selinexor may be reduced to once weekly, after consultation with the Medical Monitor. In general, dexamethasone should always be given on the day(s) of selinexor dosing. Patients whose doses are reduced under this schema should have appropriate MM markers monitored at least every two weeks (e.g., with FLC) so that dose may be re-escalated to their initial dose if evidence of progression occurs. These monitoring studies may be done at local laboratories.

11.1.5. Dose Reduction Guidelines for Toxicity

Toxicity will be graded according to CTCAE v.4.03 criteria; the therapy modifications described below are applied according to this severity grading.

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

Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. If drug-related toxicity requires a treatment delay of more than 28 days, the patient is taken off protocol treatment.

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

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from ~6 mg/m^2 to ≥ 60 mg/m^2. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, dose reductions and/or schedule modifications will be allowed as described in Table 5 and Table 6. Patients should also be treated aggressively with supportive care to reduce toxicities.

For all Grade ≥ 3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained, provided that the patient can continue to take the agent by mouth.

Table 5: Pre-specified Dose/Schedule Modifications for Adverse Events Related to Study Drug

	Dose Level	Selinexor Dosing
	1	100 mg BIW (total dose of 200 mg per week)
Starting Dose	**0**	**80 mg BIW (total of 160 mg per week)**
Dose Reductions	-1	60 mg BIW (120 mg total per week)
	-2	100 mg total per week: 100 mg one day OR divided as 60 mg and 40 mg on separate days
	-3	80 mg total per week: 80 mg one day OR divided as 40 mg per day on 2 days
	-4	60 mg total per week: 60 mg one day OR divided as 40 mg one day and 20 mg on another day
	-5	40 mg total per week: 40 mg one day OR divided as 20 mg per day on separate days

Abbreviation: BIW = twice weekly

Table 6: Supportive Care and Dose Adjustment Guidelines

Please note the following recommendations:

- After consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained for all hematological or non-hematological AEs that are NOT related to selinexor.
- For all selinexor-related AEs, if the prescribed dose reductions/interruptions in Table 8 result in a stabilization of ≥ 4 weeks, a re-escalation may be considered after approval from the Medical Monitor.

Toxicity and Intensity	Selinexor Dose Modification
Fatigue (common)	
Grade 1 or Grade 2 lasting ≤ 7 days	Maintain dose. Rule out other causes of fatigue, particularly dehydration and anemia. If found to be anemic, consider transfusing for hemoglobin < 8 g/dL. Institute supportive care medications per institutional guidelines and NCCN CPGO. Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting > 7 days or Grade 3	Rule out other causes of fatigue, particularly dehydration and anemia. If found to be anemic, consider transfusing for hemoglobin < 8 g/dL. Institute supportive care medications per institutional guidelines and NCCN CPGO. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level when resuming selinexor. (Table 5). Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.

Toxicity and Intensity	Selinexor Dose Modification
Anorexia or Weight Loss	
Grade 1 anorexia Grade 1 weight loss Grade 2 anorexia	Maintain dose. Rule out other causes and consider a repeat nutritional consultation and nutritional supplements (e.g., Ensure ®, Boost®, etc.). Institute supportive care medications per institutional guidelines and NCCN CPGO.
Grade 2 weight loss Grade ≥ 3 anorexia or weight loss	Rule out other causes and consider a repeat nutritional consultation and nutritional supplements (e.g., Ensure ®, Boost®, etc.). Institute supportive care medications per institutional guidelines and NCCN CPGO. Interrupt dosing with selinexor until improves to Grade 1 or baseline and weight stabilizes, then reduce selinexor by 1 dose level when resuming selinexor (Table 5). Consult Medical Monitor to discuss persistent or ≥ second occurrence of weight loss after stabilization.
Nausea, Acute (common)	
Grade 1 or 2 (If intolerable or persistent Grade 2 not responsive to supportive care, follow guidelines for Grade 3 below)	Maintain dose. Rule out other causes of nausea. Implement additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists using institutional guidelines and NCCN CPGO.
Grade 3	Rule out other causes of nausea. Implement additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists using institutional guidelines and NCCN CPGO. Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and restart selinexor at 1 dose level lower (Table 5).
Hyponatremia (common)	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels 120 to <130 mmol/L without symptoms	Correct for hyperglycemia as outlined under Grade 1. Treat hyponatremia per institutional guidelines. If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that intravenous saline and/or salt tablets (1-3 times daily) are provided. If Grade 3 is persistent or worsens or does not respond to treatment, hold selinexor until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.
Grade 3 with sodium levels 120 to <130 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Correct for hyperglycemia as outlined under Grade 1. Treat hyponatremia per institutional guidelines. Delay/hold selinexor until resolved to Grade 1 or baseline then reduce selinexor dose by 1 level (Table 5).

Toxicity and Intensity	Selinexor Dose Modification
Diarrhea (common)	
Grade 1	Maintain selinexor dosing. Rule out other causes including drug effects. Initiate anti-diarrheal treatment per institutional guidelines.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines. Interrupt selinexor until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level (Table 5).
Grade 3 or 4	Delay selinexor until resolved to Grade 1 and the patient is clinically stable, then reduce selinexor dose by 1 dose level (Table 5).
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 Thrombocytopenia without bleeding	Consider platelet growth factors per institutional guidelines. Do not interrupt/hold selinexor but dose reduce as below: For patients on 80 mg BIW (starting dose, Dose Level 0): Do not hold selinexor. Dose reduce to 100 mg total dose per week (Dose Level –2) but dosed at QW schedule until recovery to Grade ≤ 2 or baseline and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg). For patients on all other dose levels: Do not hold selinexor. Dose reduce by one dose level but dose the patient at the total weekly dose as QW until further recovery to Grade ≤ 2 or baseline and then resume the total weekly dose scheduled as BIW. For example, patients who were on dose level –2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level –3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade ≤ 2 or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW. *For ≥ second occurrence or worsening thrombocytopenia despite measures above: Hold selinexor until recovery to Grade ≤ 2 or baseline and resume at 1 dose level lower dosed at QW schedule. CCI [redacted]

Toxicity and Intensity	Selinexor Dose Modification
Grade 4 Thrombocytopenia without bleeding	Strongly consider platelet growth factors and transfuse per clinical practice/institutional guidelines. Delay or hold selinexor dosing until platelets recover to Grade ≤ 3 and see below: For patients on 80 mg BIW (starting dose, Dose Level 0): Hold selinexor until recovery to Grade ≤ 3, then dose reduce to 100 mg total dose per week (Dose Level -2) but dosed at QW schedule until further recovery to Grade ≤ 2 or baseline and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg). For patients on all other dose levels: Hold selinexor until recovery to Grade ≤ 3, then dose reduce by one dose level but dose the patient at the total weekly dose at the QW schedule until further recovery to Grade ≤ 2 or baseline and then may resume the total weekly dose scheduled as BIW. For example, patients who were on dose level –2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level –3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade ≤ 2 or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW. *For ≥ second occurrence or worsening thrombocytopenia despite measures above: Hold selinexor until recovery to Grade ≤ 2 or baseline and resume at 1 dose level lower dosed at QW schedule. **If the occurrence falls on Day 1 of a cycle, delay the start of the cycle and check platelet counts weekly until recovery to Grade ≤ 3 and follow the guidelines above. CCI [redacted]
Grade ≥ 3 Thrombocytopenia with bleeding	Delay/hold dosing until the bleeding has stopped and the patient is clinically stable. When resuming selinexor, see below: For patients on 80 mg BIW (starting dose, Dose Level 0): Upon recovery to Grade ≤ 2 or baseline, dose reduce to 100 mg total dose per week (Dose Level -2) but dosed at the QW schedule until further recovery to Grade ≤ 1 and then may resume the total weekly dose scheduled as BIW (100 mg divided as 60 mg and 40 mg). For patients on all other dose levels: Upon recovery to Grade ≤ 2 or baseline, dose reduce by one dose level, but dose the patient at the total weekly dose at the QW schedule until further recovery to Grade ≤ 1 or baseline and then may resume the total weekly dose scheduled as BIW. For example, patients who were on dose level –2 (100 mg QW or divided as 60 mg and 40 mg) and need to de-escalate to dose level –3 (80 mg total per week), should be dosed at 80 mg QW until platelets recover to Grade ≤ 1 or baseline and then may resume the same total weekly dose of 80 mg total as a divided schedule of 40 mg BIW.

Toxicity and Intensity	Selinexor Dose Modification
	**If the occurrence falls on Day 1 of a cycle, delay the start of the cycle and check platelet counts weekly until the bleeding has stopped, recovery to Grade ≤ 3 and the patient is clinically stable and follow the guidelines above. CCI [redacted]
Neutropenia	
Grade 3 or 4 Neutropenia with fever (febrile neutropenia) or without fever	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils weekly until recovery to Grade ≤ 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming. If the occurrence falls on Day 1 of a cycle, delay start of a cycle and check neutrophils weekly until recovery to Grade ≤ 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for any hemoglobin < 8 g/dL. If possible, maintain selinexor dose as long as patient is clinically stable, but if dose reduction or interruption is desired, discuss with the Medical Monitor.	
Other Selinexor-Related Adverse Events	
Grade 1 or 2	Maintain dose. Rule out other causes. Initiate treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Interrupt selinexor until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade ≥ 3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

Abbreviations: 5-HT3 = 5-hydroxytryptamine; BIW = twice weekly; NCCN CPGO = National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology; QW = once weekly

11.1.5.1. Selinexor Dose Reduction for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction. Creatinine clearance must be > 20 mL/min in order to initiate therapy with Sd. If creatinine clearance declines during treatment and is believed to be unrelated to selinexor, the dose of selinexor may be maintained provided that the patient's condition is closely monitored. If creatinine clearances decline to < 20 mL/min and this is felt to be related to selinexor, then the selinexor dose should be reduced by one level. If creatinine clearance returns to > 20 mL/min for 4 weeks, then the dose of selinexor can be returned to previous level. If dialysis is implemented during Sd treatment, then Sd should always be given after dialysis.

11.1.5.2. Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have Sd treatment withheld until the infection has clinically resolved or the patient is clinically stabilized. Dexamethasone should be adjusted per institutional guidelines, and adrenal suppression considered. After the infection has resolved clinically, or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics or other anti-microbial agents for prolonged periods while re-initiating their selinexor regimen at the discretion of the Investigator.

11.1.5.3. Conditions Not Requiring Selinexor Dose Reduction

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

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

11.1.5.4. Missed or Vomited Doses

Note: A maximum of 2 doses of selinexor may be given per week.

Missed Doses

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

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

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

Vomited Doses

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

11.1.5.5. Dose Escalation

In select cases (e.g., for patients showing stable disease or partial response and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg after discussion with the Medical Monitor. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the BSA for the patient should be calculated.

CCI [redacted]

CCI [redacted] Patients will be followed as long as possible or until disease progression and death.

11.2. Study Drug Storage

Selinexor tablets should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at or below 86°F (30°C) (i.e., room or refrigerated temperature). Room temperature storage is preferred. The tablets should not be stored at freezer temperatures or frozen.

Selinexor tablets (20 mg) will be supplied in plastic film blisters with an aluminum foil lidding packaged in a secondary paper wallet with childproofing. See Appendix 4 for detailed information on selinexor preparation, storage, stability, and administration.

Dexamethasone tablets should be stored as recommended on the product label.

11.3. Study Drug Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (including lot/kit numbers) in a drug accountability log. Drug accountability will be noted by the clinical research associate (CRA) during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

As appropriate during the course of the study, and at study close out, the Investigator will return all used and unused study treatment and a copy of the completed drug accountability log to the CRA.

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

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of unused material.

All drug supplies provided by Karyopharm Therapeutics Inc. must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm Therapeutics Inc. or designee for destruction. Drug supplies will be counted and reconciled at the site before being returned. The study site will be required to maintain a log of the temperature where the study medication is stored.

11.4. Concomitant Treatments

11.4.1. Required 5-HT3 Antagonists

In order to minimize nausea, unless contraindicated, all patients must receive 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued two or three times daily, as needed. Alternative anti-emetic agents may be used if the patient does not tolerate 5-HT3 antagonists.

11.4.2. Supportive Care

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations for 2103 adult patients evaluable for safety as of the 31 March 2017 safety data cutoff point, the main side effects associated with selinexor are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding. In addition to dexamethasone included in the standard treatment plan, and required 5-HT3 prophylaxis (Section 11.4.1), supportive care including anti-nausea/anti-emetic therapy, acid suppression (proton pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as described below:

- Appetite stimulants: megesterol acetate at a dose of 80-400 mg daily.
- Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for antiemesis and anorexia/cachexia [palliative care])
- Neurokinin 1 receptor antagonist (NK1R antagonist): aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

11.4.3. Infection

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

11.4.3.1. Other Glucocorticoid Side Effects

The management of common glucocorticoid side effects is well documented. Aggressive use of proton-pump inhibitors (PPIs), anti-hypertensives and other agents is strongly encouraged in order to maintain the use of dexamethasone in combination with selinexor in this study.

Patients with documented osteopenia or osteoporosis should continue to take dexamethasone with selinexor as indicated in the study. Standard precautions such as use of bisphosphonates should be instituted unless contraindicated.

11.4.4. Concomitant Medication and Treatment

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

11.4.4.1. Permitted Concomitant Medication

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

11.4.5. Restricted Medications

Medications: Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with glutathione (GSH), ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen up to 1 gram and selinexor up to 55 mg/m^2 (approximately 80-100 mg). Therefore, there are no longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days of selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

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

11.4.6. Prohibited Medications

Concurrent therapies: Concurrent therapy with any non-study anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

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Medications: Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during this study as these products may enhance the metabolism of selinexor. Please see Appendix 6 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

11.4.7. Contraception Requirements

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential must agree to use 2 methods of contraception (1 highly effective and 1 effective) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

Highly effective methods include:

1. Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
2. Intrauterine device or intrauterine system

3. Vasectomy or tubal ligation

Effective methods include:

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

Of particular note,

- No barrier method by itself achieves a highly effective standard of contraception
- The proper use of diaphragm or cervical cap includes use of spermicide and is considered 1 barrier method.
- The cervical cap and contraceptive sponge are less effective in parous women.
- The use of spermicide alone is not considered a suitable barrier method for contraception.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable (i.e., effective), but not highly effective, birth control methods.
- Male and female condoms should not be used together as they can tear or become damaged.

Alternatively, the following fulfill the contraception requirements:

1. A sexual partner who is permanently surgically sterilized or post-menopausal.
2. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient) is an acceptable method of contraception. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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

Please see Section 4.4.1 for additional safety information related to pregnancy.

11.4.8. Radiation Treatment

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

11.5. Treatment Compliance

The Investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration.

Patients will be asked to bring their study medication container with them at each visit and compliance with protocol-defined study drug intake will be checked by pill count.

Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study medication will be assessed by the Investigator or delegate and recorded in source documents. The date will be recorded as per study drug schedule. The Investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs for verification with the reasons.

The Investigator or designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again.

12. ADVERSE EVENTS

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Any treatment-emergent abnormal laboratory result or test result (e.g., PE, ECG, Echo, vitals, etc.), which is clinically significant, (i.e., meets one or more of the conditions listed below), should be recorded as a single diagnosis on the AE page in the eCRF:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the Investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

AEs should be reported for their actual grade and duration.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious.” Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The severity of the AE will be graded according to the CTCAE Grading Scale (see the CTCAE web page at *http://ctep.cancer.gov* for details). For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.

The Investigator will make a judgment regarding the AE's relationship to study drug, as outlined below in Table 7.

Table 7: Classification of Adverse Events by Causality

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

12.1. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

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

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

Progression of the malignancy (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period (see below). Sudden and unexplained death should be reported as an SAE.

12.1.1. AE and SAE Follow-up

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related must be followed until resolution or until stabilization.

12.1.2. Post-Study Adverse Events and Serious Adverse Events

All unresolved AEs should be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the Investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study.

Prior to the conclusion of the study at the site, the Investigator should notify the Karyopharm Pharmacovigilance Department (see Section 12.1.3.1) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

After study conclusion, the Investigator should notify Karyopharm Therapeutics Inc., or its designee, of any death or AE he or she is aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. Karyopharm Therapeutics Inc. should also be notified if the Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

12.1.3. Serious Adverse Event Reporting

12.1.3.1. Reporting Requirements

ALL SAEs occurring in any patient, must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of first knowledge of the event by the principal investigator or assigned site personnel. The following information will be requested from the investigational site:

- Protocol number
- Site and/or investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved

- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of the SAE's relationship to investigational product
- Outcome of the event, if available

This information will be captured in the SAE report form and/or the study specific safety database and will be forwarded to:

- Pharmacovigilance Department
- Karyopharm Therapeutics Inc.
- Email: pharmacovigilance@karyopharm.com
- North American sites, Fax to US: +1-617-334-7617
  European sites, Fax to Germany: +49-89-9218-5650

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

All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics committee (EC), as applicable. Reporting of SAEs by the Investigator to the IRB or EC will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

In addition, Karyopharm Therapeutics Inc. will communicate all cases of cerebellar toxicities of Grade 3 or higher to the regulatory authority, IRBs and investigators, in the format of an expedited Safety Report within 7 days of awareness of the event.

12.2. Overdose

An overdose is defined as a deliberate or accidental administration of study medication to a study patient at a dose above that which is assigned to that individual patient according to the study protocol. In the event of drug overdose, the Investigator and Karyopharm Medical Monitor should be notified immediately and the patient observed closely for AEs. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment documented in the patient's medical record. In addition to documenting the overdose in the patient's records, the overdose must be reported to Karyopharm Pharmacovigilance on an SAE report form. Any AE or SAE observed as a consequence of the overdose will be handled as described in Section 12.2, as appropriate.

As selinexor is metabolized by GSH conjugation, it is conceivable that hepatic GSH depletion can occur in case of overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as SAM 400 mg orally 1-4 times a day, or other drugs that can replace GSH, should be considered.

Medication errors, and uses of the study medication outside what is foreseen in the protocol, including misuse and abuse of the product must also be reported to Karyopharm Pharmacovigilance on an SAE report form.

12.3. Pregnancies

Pregnancy *per se* is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication.

Each pregnancy in a patient or partner of a patient on selinexor must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

The avoidance of fathering a child is recommended for 3 months following the discontinuation of selinexor therapy. No information is currently available regarding the effects of selinexor on fertility, gestation or subsequent child development.

Any pregnancy within 3 months post-study should be reported to the study investigator and the sponsor's designee.

13. STATISTICAL METHODS

13.1. General Considerations

13.1.1. Statistical and Analytical Plans

This is a Phase 2b, single-arm, open-label, multicenter study of selinexor 80 mg with dexamethasone 20 mg (Sd), both given orally twice weekly for each week of four-week cycles, to patients with MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab.

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1-3) enrolled patients with both penta-refractory MM and quad-refractory MM. Part 2 (protocol V≥4.0) will enroll patients with penta-refractory MM only, but continue all patients enrolled in Part 1.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients and quad-refractory MM patients.

Hypothesis testing will be used for the primary efficacy endpoint data, in order to evaluate if selinexor plus dexamethasone provides statistically significant improvement in efficacy over a minimally acceptable level of 10% ORR. No formal hypothesis-testing will be used for other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

CCI [redacted]

13.1.3. Disposition of Patients

A tabulation of patient disposition will be presented, including the number in each analysis population, the number with non-evaluable disease according to the IMWG criteria, the number censored at each of the PFS and OS analyses, the number lost to follow-up, the number that withdrew prior to completing the study, and reason(s) for withdrawal. This tabulation will be presented separately for each study part and by quad-refractory MM and penta-refractory patient populations in Part 1.

13.1.4. Blinding and Randomization

This is an open-label, single-arm study, therefore blinding and randomization are not applicable.

13.1.5. Dose Adjustment

The dose level for an individual patient may be escalated, based on efficacy considerations, after a minimum of 2 cycles of study therapy. Reasons for dose escalation can include, for example, a response of SD or PR with acceptable safety. Dose reduction can take place, based on the guidelines in Section 11.1.5. CCI

13.2. Analysis Datasets

13.2.1. Populations to be Analyzed

13.2.1.1. Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population will consist of Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to participate in the study), and received at least 1 dose of study treatment (partial or complete). This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause, including those related to study drug or disease. This population (Part 2 patients with penta-refractory MM only) will be used for the primary analysis of efficacy.

13.2.1.2. Per-Protocol Population

A per-protocol (PP) population will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance ≥ 70%,
- Have at least one adequate post-baseline response assessment unless died or withdrew from study before that.
- No major protocol violations that would compromise the assessment of efficacy. The list of major protocol violations that affect statistical analysis will be finalized before database lock.

Major violations will be determined independently of knowledge of response to therapy, prior to database lock and study analysis. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the assessment of efficacy.

13.2.1.3. Safety Population

The safety population will consist of all patients who have received at least one dose of study treatment and have any post-baseline safety information.

13.2.1.4. Sub-group Efficacy Analyses

The subgroup comparisons of interest will be evaluated per the Statistical Analysis Plan (SAP) (version 1.0).

13.3. Data Analysis and Presentation

Summary tabulations will be presented separately for each study part and by penta-refractory MM patients and quad-refractory MM patients in Part 1 for disposition as noted above, and for demographic, baseline, efficacy and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

13.3.1. Demographic Characteristics

Demographic characteristics will be summarized for the mITT, PP, and Safety populations and will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

13.3.2. Baseline Characteristics and Medical History

Baseline characteristics include: performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight. Baseline data will be tabulated using summary statistics for the mITT, PP, and Safety populations; no formal hypothesis testing will be performed.

Medical history and physical examination results at baseline will be tabulated for the same analysis populations.

13.3.3. Primary Endpoint

The primary statistical analysis of efficacy will be performed on ORR (achievement of PR, VGPR, CR or sCR) for the mITT population. For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using a two-sided 95% confidence interval, calculated for the rate of ORR, and statistical significance will be declared if the lower bound of this interval is greater than 10%.

13.3.4. Secondary Endpoints

The following secondary efficacy endpoints will be analyzed separately for mITT and PP populations.

- Duration of response (DOR = Duration from first observation of at least PR to time of disease progression [PD] or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least

MR to time of disease progression or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any causes other than disease progression)

- Disease Control Rate (DCR = CBR + stable disease [SD; for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of disease progression) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy
- Time to Next Treatment (TTNT = Duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)

Time-to-event endpoints (including duration of response, PFS, TTP, and OS) will be assessed using Kaplan-Meier (KM) methods, including an estimate of the median, as well as the 25^{th} and 75^{th} percentiles, along with two-sided 95% CIs. Duration of CBR will be regarded as descriptive adjuncts to the analyses of response rates. Clinical benefit (CBR) and disease control (DCR) rates will be statistically evaluated using two-sided 95% confidence intervals.

QoL will be assessed using the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM). This instrument combines the General version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (“Not at all”) to 4 (“Very much”), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit. The QoL analysis will be based on changes in the total TOI score from Baseline using paired T-tests. A secondary analysis of QoL will be performed in a similar manner using the total of all subscales. All 5 individual subscale total scores will be summarized over time using descriptive statistics.

Additionally, the following analyses of safety and tolerability secondary endpoints will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part.

- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the PK properties of selinexor in this patient population (Part 1 only).

CCI [redacted]

13.3.6. Pharmacokinetic CCI [redacted] Data

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor concentration. Selinexor concentration data will be analyzed for Part 1 patients only in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, concomitant medications, and treatment. CCI [redacted]

13.3.7. Safety Data

Safety analyses will be performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 penta-refractory MM patients, Part 1 quad-refractory MM patients, and Part 2 penta-refractory MM patients. The original dose level for each patient will be used for safety analysis; no separate categories for dose escalation or reduction will be conducted in the primary analysis of safety. CCI [redacted].

13.3.7.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and Preferred Term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset, or worsening of a pre-existing condition, on or after the first dose of study treatment through 30 days following the last dose of study treatment, 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. No formal hypothesis-testing of AE incidence rates will be performed.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE (preferred term). The number and percentage of patients with any treatment-emergent adverse events (TEAE) will be summarized for each treatment group, classified by SOC and preferred term. The number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner.

The Investigator will judge the causal relationship between the occurrence of an AE and the study drug as not related, unlikely related, possibly related, or related. In the event a patient repeatedly experiences episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

All reported SAEs will be tabulated.

All AEs (treatment-emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient and day on study. In addition, separate by-patient listings will be provided for the following: deaths; SAEs; and AEs leading to withdrawal.

13.3.7.2. Laboratory Data

Clinical laboratory values will be expressed using conventional units International System of Units (SI) units. The actual value and change from baseline (Day 1, prior to the first administration of study drug) to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the Screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE v.4.03 criteria (e.g., 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 and Baseline to last on-study values relative to CTCAE classification ranges will be produced.

13.3.7.3. Vital Signs, Physical Examinations, and ECOG Performance Status

The actual value and change from baseline (Day 1) to each on-study evaluation will be summarized for vital signs. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will be produced. By-patient listings of all vital sign measurements and ECOG performance status scores will be presented in data listings.

Physical examination results at Screening, and physical examination results changes during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

13.3.7.4. Electrocardiogram Results

Electrocardiogram results will be summarized descriptively, including heart rate and PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula) intervals. If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula: QT/(RR^[1/3]), where RR = 60/heart rate. Actual values and changes from baseline will be reported for each study visit.

Electrocardiogram data for each patient will be provided in a data listing.

13.3.7.5. Ophthalmic Examinations

Ophthalmic examination findings will be summarized descriptively by visit. All ophthalmic examination findings will be presented in the data listings.

13.3.7.6. Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

13.3.8. Procedures for Handling Missing Data

The procedures for handling missing data will be performed per the SAP (version 1.0).

13.4. Changes in the Conduct of the Study or Planned Analysis

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

14. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

14.1. Regulatory and Ethical Compliance

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

14.2. Institutional Review Boards/Ethics Committees

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

procedures found in this protocol and to give access to all relevant data and records to Karyopharm, Quality Assurance representatives, designated agents of Karyopharm, IRBs/IECs/REBs and regulatory authorities as required.

14.3. Regulatory Authority Approval

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

14.4. Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR.

14.5. Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be provided by Karyopharm, and approved by Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB 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, Karyopharm should be notified of this action and the IRB/IEC/REB at the study site should be informed according to local regulations (e.g., the UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

14.6. Informed Consent

Eligible patients may only be included in the study after providing written consent (witnessed, where required by law or regulation) on an IRB/IEC/REB approved ICF.

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

Karyopharm will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Karyopharm or their designee must agree to any investigator suggested changes to this ICF before their submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Karyopharm or designee after IRB/IEC/REB approval. CCI [redacted] Each patient's informed consent document will reflect that samples collected may be used for pharmacogenomic investigations.

14.7. Patient Confidentiality and Disclosure

The Investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Karyopharm or their designees. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

14.8. Collection, Auditing Study Documentation, and Data Storage

14.8.1. Study Documentation, Record Keeping and Retention of Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

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

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

14.8.2. Auditing Procedure

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority may conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

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

In the event that a major compliance or regulatory issues arises, the Sponsor may conduct an audit without prior warning.

14.9. Disclosure of Information

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

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

14.10. Discontinuation of the Study

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

14.11. Reporting and Publication of Study Documentation

Karyopharm assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.clinicaltrials.gov. In addition, upon study completion and analysis of the resulting clinical data, the results of the study will be:

- Reported to appropriate, competent regulatory authorities in full compliance with International Conference on Harmonization (ICH) E3: Structure and Content of Clinical Study Reports. A primary clinical study report (CSR) may be written based on all available patient efficacy and safety data for the primary analysis; a final CSR may be submitted when all evaluable patients have completed the long-term follow up period, died, progressed, withdrawn consent, discontinued due to toxicity, or been lost to follow up. PK results may be reported in either CSR.
- Submitted for publication and/or posted in a publicly accessible database of clinical study results. Publication will be in a relevant peer- reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

CCI [redacted]

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APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA

Table 8: Eastern Cooperative Oncology Group (ECOG) 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 (e.g., 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 2. INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA

Table 9: International Staging System for Multiple Myeloma

Stage	Characteristics
Stage I	β_2-microglobulin <3.5 mg/L, albumin ≥3.5 g/dL
Stage II	β_2-microglobulin <3.5 mg/L and albumin <3.5 g/dL, or β_2-microglobulin 3.5-5.5 mg/L irrespective of the serum albumin
Stage III	β_2-microglobulin ≥5.5 mg/L

Source: Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412-3420

APPENDIX 3. INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA, MYELOMA

Table 10: International Myeloma Working Group Response Criteria (Kumar 2016)

Standard IMWG Response Criteria[1,2,3]	
Response Subcategory	**Response Criteria**
Complete response (CR)	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas (SPDs), and < 5% plasma cells in bone marrow aspirates
Stringent complete response (sCR)	CR as defined above plus normal FLC ratio[4] 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[5]
Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hr
Partial response (PR)	≥ 50% reduction of serum M-protein plus reduction in 24-hr urinary M-protein by ≥ 90% or to < 200 mg/24 hr. If the serum and urine M-protein are not measurable, 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 and serum FLC assay are not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[6]
Minimal response (MR)	≥ 25% but < 49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50–89%. In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[6]
Stable disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the TTP estimates. Not meeting criteria for CR, VGPR, PR, MR, or PD.
Progressive disease (PD)[7,8]	Any 1 or more of the following criteria: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of ≥ 0.5 g/dL;

Standard IMWG Response Criteria[1,2,3]	
Response Subcategory	**Response Criteria**
	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 hr); In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); 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[6] 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
Clinical relapse	Clinical relapse requires 1 or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD[6] of the measurable lesion; Hypercalcaemia (> 11 mg/dL); Decrease in haemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from CR (to be used only if the endpoint is disease-free survival)	Any 1 or more of the following criteria: Reappearance of serum or urine M-protein immunofixation or electrophoresis; Development of ≥ 5% plasma cells in the bone marrow; Appearance of any other sign of progression (i.e,. new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)

Standard IMWG Response Criteria[1,2,3]	
Response Subcategory	**Response Criteria**
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any 1 or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cell on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥ 5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Abbreviations: ASCT = autologous stem-cell transplantation; CR = complete response; CRAB features = calcium elevation, renal failure, anemia, lytic bone lesions; CT = computed tomography; DOR = duration of response; FDG = fluorodeoxyglucose; FLC = free light chain; hr = hour; Ig = immunoglobulin; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGF = next-generation flow; NGS = next-generation sequencing; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; TTP = time to progression; VGPR = very good partial response.

Source: Kumar, 2016

[1] All response categories require 2 consecutive assessments made any time before starting any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

[2] Per IMWG, quantitative Ig levels by nephelometry may be used in place of SPEP for routine M-protein measurement for patients with IgA or IgD myeloma. Also, per IMWG, response may be confirmed if the patient fails to provide 24-hour urine sample collection after screening activities occur. See "Practical considerations for application of IMWG consensus criteria" section of the guidelines (page e340; Kumar, 2016).

[3] Derived from international uniform response criteria for MM (*Durie 2011*). MR definition and clarifications derived from Rajkumar (*Rajkumar 2011*). When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the CR criteria listed previously. VGPR in such patients requires a ≥ 90% decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for SD, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as DOR.

[4] All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, United Kingdom).

[5] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[6] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.
[7] Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. For purposes of calculating time to progression and PFS, patients who have achieved a CR and are MRD-negative should be evaluated using criteria listed for PD. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.
[8] In the case where a value is felt to be a spurious result per Investigator discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

Questions regarding interpretation of these criteria may be addressed by consulting the, "Practical considerations for application of IMWG consensus criteria," section of the guidelines (page e340, *Kumar 2016*).

APPENDIX 4. SELINEXOR FORMULATION AND ADMINISTRATION

Description of Selinexor (KPT-330)

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

The chemical name is: (*Z*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-*N*′-(pyrazin-2-yl)acrylohydrazide

The *molecular formula* is: $C_{17}H_{11}F_6N_7O$.

The *molecular weigh*t is: 443.31

Form

Selinexor will be supplied and administered as 20 mg, coated, immediate-release tablets.

Storage and Stability

Selinexor tablets (20 mg) will be supplied in plastic film blisters with an aluminum foil lidding packaged in a secondary paper wallet with childproofing. Selinexor should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s), with temperature at or below 30˚C (86˚F). Room temperature storage is recommended, refrigerated is suitable. Tablets should not be stored frozen.

Selinexor tablets are currently in on-going stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.

Handling

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

Availability

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

Preparation

No special preparation required.

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

Administration

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

Patients in the present study will receive selinexor 80 mg (45 mg/m^2 BSA) plus dexamethasone (20 mg), both twice weekly, during Weeks 1-4 of each four-week cycle.

Accountability

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

Destruction and Return

At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

APPENDIX 5. LENS OPACITIES CLASSIFICATION SYSTEM

For patients enrolled under protocol version 3.0, if a cataract is seen during the slit lamp examination to document lens clarity, the cataract will be graded according to the grading system shown below.

Table 11: Lens Opacities Classification System

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

Source: Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts (CPG8). American Optometric Association at www.aoa.org.

APPENDIX 6. GLUTATHIONE (GSH)-, S-ADENOSYLMETHIONINE (SAM)-, OR N-ACETYLCYSTEINE (NAC)-CONTAINING PRODUCTS (REPRESENTATIVE LIST)

Table 12: Glutathione (GSH)-, S-Adenosylmethionine (SAM)-, OR N-Acetylcysteine (NAC)-Containing Products (Representative List)

Glutathione (GSH)		N-acetylcysteine (NAC)		S-adenosylmethionine (SAM)	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	glutathione	Antidote for acetaminophen overdose	acetylecysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	glutathione L-cysteine vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		
(Mega-) Liposomal Glutathione	glutathione				
Lypospheric GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				

APPENDIX 7. SUMMARY OF CHANGES

Amendment 1

Amendment Rationale

The primary purpose for this amendment is to:

- Address the following FDA deficiency and comments provided in an e-mail message with the subject: "IND-114042 KPT-330-Deficiency and Comments", dated: 21Jan2014:
    - Deficiency:

      - To be eligible for the trial, patients should have returned to ≤ Grade 2 non hematological toxicities from previous treatment.
    - Comments:

      - The primary endpoint should be per central independent review committee including radiology review.

      - Time-to-event endpoints such as PFS/OS and Patient Reported Outcomes are not evaluable in non-controlled trials.

The revised protocol Version 2.0, dated 05Feb2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 1.0, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes

- Internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 1.0 dated 15 Apr 2014 to Version 2.0 dated 05 Feb 2015 (**Modified sections**: Global)

Specific Content Changes

Synopsis

Table 1.1

- Changed the Screening Period from 14 days to 21 days prior to C1 D1
- Removed mention of randomization
- [redacted]

Section 7.2 Data Monitoring Committee

- Added sub-sections to clarify the roles of the DMC for reviewing safety and response data (the latter was added in response to comments by the FDA.

Section 8.3 Inclusion Criteria

- Added resolution of hematologic toxicities from previous treatments to ≤ Grade 2 in response to a deficiency reported by the FDA

Section 9.2.5 Survival Follow-Up

- SPEP, UPEP and FLC every 3 months to assess durability of response was added to be consistent with the SOA

Section 10.5 Skeletal Survey

- Modified to include central read.

Section 10.8 Pharmacokinetic Endpoints

- Table 10.1 was revised to reflect PK [redacted]

Section 12.4 Concomitant Treatments

- Redundant wording for restricted medications was deleted

Section 14.3.4 Secondary Endpoints

- Text was revised to clarify that PFS, QoL and OS will not be tested for statistical significance, in response to comments from the FDA.

Amendment 2

Amendment Rationale

The primary purposes for this amendment were to:

1. Revise the study target patient population from "quad-refractory" to "dual-refractory" as shown in the following modified inclusion criteria:

   From: Patients must have "MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib."

   To: "Patients must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib" *and have* "MM double refractory to previous treatment with both the PI and IMiD drug classes"

2. Change the study treatment (selinexor plus dexamethasone) dose schedule from "twice weekly for three weeks of every four-week cycle" to "twice weekly for every week of each four-week cycle."

The revised protocol Version 3.0, dated 25 September 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 2.0, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes

- Revisions were made to harmonize procedures and assessments with those in clinical protocol KCP-330-017 (STOMP): A Phase 1b/2 Study of Selinexor (KPT-330) in Combination with Backbone Treatments for Resistant/Refractory Multiple Myeloma.
- Internal changes were made to improve clarity and eliminate inconsistencies across sections (**Modified sections**: Global)
- Updated the version number and date of protocol from Version 2.0 dated 05 February 2015 to Version 3.0 dated 25 September 2015 (**Modified sections**: Global)

Specific Content Changes

Title

From: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Low-Dose Dexamethasone in Patients with Multiple Myeloma Quad-refractory to Previous Therapies

To: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Dexamethasone in Patients with Multiple Myeloma Double-refractory to Previous Therapies

Indication

From: Multiple myeloma quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide

To: Multiple myeloma refractory to prior treatment with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

Synopsis

Objectives

- Revised the Primary Objective for selinexor to be dosed four weeks (instead of three weeks) of each four-week cycle
- Moved the following objective from Exploratory Objectives to Secondary Objectives:

  "Determine ORR, DOR, PFS, and OS in the sub-group of patients with free light chain (FLC) MM"
- Revised objectives to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs (i.e., one drug in each class).
- CCI [redacted]

Background and Study Rationale

- Updated reported (preliminary) information on all four treatment groups in KCP-330-001 (i.e., selinexor ≤ 30 mg/m^2, selinexor ≥ 35 mg/m^2, selinexor 45 mg/m^2 + dexamethasone 20 mg, and selinexor 60 mg/m^2 + dexamethasone 20 mg) all as of 15 Dec 2014.

Methodology

- Changed the selinexor plus dexamethasone dose schedule from "twice weekly for three weeks of every four-week cycle" to "twice weekly for four weeks of every four-week cycle.

Inclusion/Exclusion Criteria

- Revised to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs.

Study Duration

- Added an End-of-Study definition: The study will end when all patients have completed the one-year Follow-up Period (i.e., when the last patient has expired, been followed for 12 months after last dose of study drug, been lost to follow-up, or has withdrawn consent, whichever occurs first).

Criteria for Evaluation

- Changed the causality assessments
  From: 1) unrelated, 2) possibly related, or 3) related.
  To: 1) not related, 2) unlikely related, 3) possibly related, or 4) related.
- Added a list of the IMWG response criteria

Table 1.1

- Reorganized the table for clarity and consistency of table, footnotes and Section 9 (Study Day Procedures), including:

- Added column for "Safety Follow-up Call"
- Added columns for "Cycle 2 Day 15" and "Cycles ≥ 3"
- Organized multiple study procedure rows under "Clinical Labs" and "Multiple Myeloma Specific Procedures"
- Revised wording for MM disease-specific assessments
- Revised study schedules for MM disease-specific assessments
- Added row for "Blood draws for PK analysis"

CCI [redacted]

Section 1 Overview

- Updated overall selinexor clinical study information for > 1,000 patients who received selinexor as of 31 May 2015, as stated in the mostly recently issued Selinexor *Investigator's Brochure*, version 5, released on 12 August 2015.

Section 2 Multiple Myeloma

- Revised estimated mortality to 11,000 deaths anticipated due to MM in the US in 2015 as stated in *http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics*

Section 4.3 Clinical Experience

- Provided additional summary information about preliminary results seen with selinexor and selinexor plus dexamethasone in the MM arm of the ongoing study KCP-330-001 (as of 01 Dec 2015), as presented in *Chen et al. ASH 2014*

Section 5 Rationale for the Study

- Revised study target patient population from "quad-refractory" to "dual-refractory"

Section 5.1 Rationale for Selinexor Dose Schedule

- Changed the study treatment dose schedule from "twice weekly for three weeks of every four-week cycle" to "twice weekly for four weeks of every four-week cycle."

Section 6.1 Primary Objective

- Revised study target patient population from "quad-refractory" to "dual-refractory"

Section 6.2 Secondary Objectives

- Moved the following objective from Exploratory Objectives to Secondary Objectives:

  "Determine ORR, DOR, PFS, and OS in the sub-group of patients with free light chain (FLC) MM"

- Revised objectives to state that patients must have been *exposed* to lenalidomide, pomalidomide, bortezomib, and carfilzomib, but their disease must only be shown to be refractory to the drug classes PIs and IMiDs.

CCI [redacted]

Section 7.1 Overview

- Revised study summary to reflect the changes summarized above (i.e., dual-refractory target patient population and study treatment will be dosed for four weeks per four-week cycle)

Section 8.3 Inclusion Criteria

- Changed:

  From: Patients must have "MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib."

  To: "Patients must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib" *and have* "MM double refractory to previous treatment with both the PI and IMiD drug classes"

- Added:

  Confirmation of patient eligibility for study participation with the Medical Monitor

Section 9 Study Plan and Procedures

- Modified procedures and assessments to be consistent with Table 1.1 (Schedule of Assessments and Study Activities)
- Added a definition of End-of-Study (EoS): one year after the last patient to be enrolled has been treated for one year.

Section 10.2 Multiple Myeloma Disease Assessment

- Added Table 6, a summary of the MM disease-specific assessments per IMWG guidelines

Section 10.3.2

- Revised ophthalmic exam to reference both LOCSIII (original protocol) and AOA (added in this amendment)

Section 10.5 Pharmacokinetic Endpoints

- Revised Table 10.2 (Collection Time Points and Sample Volumes for PK [redacted]

Section 12 Treatment

- Table 12.2 (Dose Adjustment Guidelines for Selinexor) – removed dose adjustment guidelines for dexamethasone

Section 13 Adverse Events

- Table 13.1 (Classification of Adverse Events by Causality) – Added a fourth option of "unlikely related" (to treatment with study drug)

Section 15.11 Reporting and Publication of Study Documentation

- Revised to include options for reporting study results in more than one CSR

Amendment 3

Protocol Version 4

Amendment Rationale

The primary purposes for this amendment were to:

1. Expand the population of patients with penta-refractory MM by enrolling approximately 130 additional patients. The overall study population is now ~210 patients.
2. Revise the study design to make the expansion population (Part 2) the mITT population for the primary efficacy analysis (using ORR); ORR for patients enrolled in Part 1 became a secondary analysis.

The revised protocol Version 4.0, dated 11 August 2016 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 3.0, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes

- Revisions were made to simplify the protocol, including the elimination of repetitive references to schedules. (**Modified sections**: Global; Section 9 [in previous versions] was removed in its entirety)
- Added the abbreviation “Sd” to denote selinexor plus low-dose dexamethasone (i.e., selinexor [80 mg] plus dexamethasone [20 mg])
- Internal changes were made to improve clarity and eliminate inconsistencies across sections (**Modified sections**: Global)
- Updated the version number and date of protocol (**Modified sections**: Global)

Specific Content Changes

Title

From: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) plus Dexamethasone in Patients with Multiple Myeloma Double-refractory to Previous Therapies

To: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and an anti-CD38 Monoclonal Antibody (mAb) and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor and an anti-CD38 mAb

Indication

From: Multiple myeloma refractory to prior treatment with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

To: Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody (mAb) (i.e., daratumumab or isatuximab) and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb

Synopsis

– Title and Indication as described above

Objectives (also in Section 6)

– Revised to reflect the change to include the Part 2 expansion and the new primary objective/endpoint for ORR in penta-refractory patients enrolled in Part 2

– Added that the secondary objectives DOR, PFS, DCR, CBR, TTP and OS will be analyzed separately in different patient sub-populations (i.e., Part 1 patients with quad-refractory MM, Part 1 patients with penta-refractory MM, and Part 2 patients with penta-refractory MM).

– [redacted]

Rationale (also in Section 4.3)

– Added a summary of preliminary response results seen thus far in study KCP-330-001 and the current study (KCP-330-012)

Methodology (also in Section 7.1)

– Added a brief description of Parts 1 and 2

Inclusion/Exclusion Criteria (also in Sections 8.4 and 8.5)

– Merged inclusion criteria #3 with #4 to require measurable MM based on modified IMWG guidelines.

– Modified inclusion criteria #5 (now #4) to include either daratumumab or isatuximab

– Modified inclusion criteria #6 (now #5) to include patients with MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib in and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and anti-CD38 mAb (i.e., either daratumumab or isatuximab).

– Modified inclusion criteria #7 (now #6) (multiple myeloma that is refractory to the patient's most recent anti-MM regimen). The new wording in #6 states that "documented severe intolerance to the patient's last therapy is allowed upon approval by the Medical Monitor."

- Adjusted inclusion criterion #13 (now #12), requiring adequate platelet count of ≥ 50,000/mm^3 (patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells) at baseline.
- Added inclusion criteria #13, regarding baseline hemoglobin level ≥ 8.5 g/dL.
- Deleted exclusion criteria #3, MM that does not express either M-protein of FLC is no longer excluded.
- Added exclusion criteria #20 and #21, also to require adequate hematopoietic function at baseline.
- Added exclusion criterion #22, to ensure that patients can tolerate dexamethasone.
- Added exclusion criterion #23, a standard item in protocols.

Documentation Requirements (also in Section 8.3)

- A formal statement was added to describe what documentation is needed to establish that patients are refractory to prior treatments.

Study Numbers (also in Section 13.1.2)

- Revised estimated enrollment for N=122 (for power analysis), and ~130 for enrollment.

Study Duration:

- Revised enrollment period from 15 months to 24 months.

Statistical Methods (also in Section 13)

- Re-stated the statistical assumptions underlying the revised primary endpoint.

Table 1 (Schedule of Assessments)

- Added FLC on C1D15 and C2D15
- Added emphasis that MM-specific lab assessments (i.e., SPEP, UPEP, FLC and quantitative Ig) must be performed at the time of PD to evaluate response. This is an essential requirement of the IMWG and was included in previous versions of this protocol, but its visibility is being increased in this version to support investigatory site staff.
- Reduced size of footnotes and added cross-referencing to protocol sections

List of Abbreviations:

- Deleted abbreviations that were not in use and added several new abbreviations

Protocol, Main Body

Sections 7.2, 7.3 and 9.9.1

- Establish an IRC to perform the central read of response data (for the efficacy analysis) that had been previously included under the Data Safety Monitoring Committee (DSMC) in previous versions of this protocol. The DSMC, now referred to as Data Safety Monitoring Board (DSMB) will retain its role of reviewing all study

safety data. Since this study may be pivotal for a regulatory submission, it is important that the involvement of an IRC was readily apparent.

Section 8.2

- Added Canada and EU for potential investigatory sites.

Previous Section 9.1 – 9.2 (Study Plan and Procedures):

- Deleted to improve overall protocol simplicity

Section 9.1:

- Separated Physical Examinations and ECOG into separate sub-sections

Section 9.2:

- Added confirmatory review of MM-specific assessments by central laboratory to confirm CR and sCR
- Added "modified" to IMWG and added citation of Palumbo 2014
- Table 5: Deleted column containing visit schedule for simplicity
- Added to UPEP that if the patient fails to provide the 24-hour urine sample, this should be documented. All attempts should be made to collect the 24-hour urine sample at the required time points.
- [redacted]

Section 9.3

- Added "modified" to IMWG and added citation of Palumbo 2014

Section 9.4.3:

- Deleted several parameters (e.g., band neutrophils) that were not needed

Section 9.6

- Revised section to indicate blood draws for PK analysis only required in Part 1

Section 10.2

- Added that reasons for discontinuation must be clearly documented in the source and in the study CRFs, including reasons for patient withdrawal and Investigator decision to discontinue patient.

Section 11.1.5:

- Modified Tables 7 and 8 to reflect our current understanding regarding how the selinexor dose should be modified in the presence of AEs during the study

Section 11.2 and Appendix 4:

- Deleted selinexor 10 mg and 25 mg tablet strengths because they are not used in this study

Section 11.4.5:

- Moved Restricted Medications to this section from previous location in Section 9

Section 11.4.6

- Moved Prohibited Medications to this section from previous location in Section 9

Section 12.2:

- Moved "Overdose" to its own sub-section

Section 13.2

- Revised the definition of the mITT population for the primary efficacy analysis to include the statement "consist of Part 2 patients with penta-refractory MM who meet all eligibility criteria," in addition to the existing definition of "who receive at least one dose of study treatment."
- Updated the definition of the per-protocol (PP) population to encompass all patients in the mITT population who have completed at least one cycle of treatment and have no major protocol violations that would compromise the assessment of efficacy.
- [redacted]

Section 15:

- Added Palumbo 2014 to the list of references

Appendix 3:

- Replaced IMWG Response Criteria from Kyle 2009 with comparable table from Palumbo 2014.

Amendment 3.1

Protocol Version 4.1

Amendment Rationale

The primary purpose for this amendment was to remove isatuximab as an allowable anti-CD38 agent for inclusion in the study. Per the FDA, it is not appropriate to include patients who have received isatuximab as the anti-CD38 agent for inclusion in the study because it is not approved at this time.

The revised protocol Version 4.1 (US-specific amendment), dated 06 February 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 4.0, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes (**Modified Sections**: Global)

- Updated the version number and date of protocol
- Updated the number of patients who have received selinexor to the number based on the most recent Investigator's Brochure (14 November 2016)
- Replaced "minor" with "minimal" in regard to response
- Removed the qualifier "modified" from IMWG response criteria because the response criteria were updated to that based on Kumar 2016
- Internal changes to improve clarity

Specific Content Changes

Title (**Modified Sections**: Global)

From: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and an anti-CD38 Monoclonal Antibody (mAb) and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor and an anti-CD38 mAb

To: A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

Indication (**Modified Sections**: Global)

From: Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody (mAb) (i.e., daratumumab or isatuximab) and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 mAb

To: Multiple myeloma (MM) previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab

Protocol Approval Signature Page

- Replaced Michael Kauffman, MD, PhD, Acting Chief Medical Officer, with Humphrey Gardner, M.D., Senior Vice President, Clinical Development, as a signatory.

Inclusion/Exclusion Criteria (also in Sections 8.4 and 8.5)

- Modified inclusion criteria #3d to remove turbidometry as an acceptable method to measure quantitative Ig levels.
- Modified inclusion criteria #4 and #5 to remove isatuximab due to FDA request
- Corrected inclusion criteria #7 to refer to exclusion criteria #17
- Corrected inclusion criteria #12 to refer to exclusion criteria #20
- Changed inclusion criteria #12a to total WBC count > 1,000/mm^3 to update criteria for this patient population.
- Corrected exclusion criteria #17 to add ≥ before Grade 2 painful neuropathy
- Modified exclusion criteria #22 to add or contraindication for before glucocorticoids to further clarify the medical intent of the original language.
- Added a new exclusion criterion immediately after exclusion criteria #22 and moved the previous #23 to #24. The addition of exclusion criteria #23, prior exposure to a SINE compound, including selinexor, provides consistency across Karyopharm protocols.

IMWG Response Criteria (also in Sections 6.1, 9.3, and Appendix 3)

- Updated the IMWG response criteria for myeloma to align with the most recent IMWG criteria (Kumar, Lancet. 2016;17:328-346). The definition for MR was changed from “minor” to “minimal” response to align with the IMWG Consensus Criteria.

Documentation Requirements (also in Section 8.3)

- Removed the requirement to show a patient was refractory to isatuximab to align with feedback on isatuximab from FDA.

Table 1 (Schedule of Assessments and also in Section 9.7.2.4)

– Modified footnote #10 to remove text that scans and accompanying reports will be sent to the central laboratory to reflect current analytical procedures.

[redacted]

List of Abbreviations:

– Added the definitions for 5-HT3, ACS, and FLC (kappa/lamba ratio) for clarification

Protocol, Main Body

Section 1

– Updated text to reflect the current selinexor safety information.

Section 4.4

– Updated the information on ACS to include two pediatric patients to reflect the current selinexor safety information.

Section 7.3 (also in Section 10.2)

– Modified to require that an IRC confirm disease progression prior to a patient discontinuing study treatment to improve the consistency of clinical decisions across the sites.

Sections 9.2 (also in Appendix 3)

– Revised the modifications to the IMWG response criteria modified to allow for quantitative Ig levels by nephelometry to be used in place of SPEP for routine M-protein measurements for patients with IgA or IgD myeloma.

Table 5

– Updated text to clarify UPEP, serum FLC, Quantitative Ig levels, Skeletal survey, and Clinical plasmacytoma assessments.

– Removed the following text for skeletal survey to reflect current analytical procedures: “the scans and accompanying radiology reports will be sent to a central lab. Details regarding the central lab procedures including collection and shipment of data will be described in the Study Manual.”

Section 9.4.1 (also in Section 15)

– Modified to include the Fridericia correction formula for consistency within the protocol and added references for Bazett’s and Fridericia’s formulas.

[redacted]

Table 8

– Added the following text above the table to reflect current guidance: Please note the following recommendations: After consultation with the Medical Monitor and at the

discretion of the Investigator, selinexor dosing may be maintained for all hematological or non-hematological AEs that are NOT related to selinexor. For all selinexor-related AEs, if the prescribed dose reductions/interruptions in Table 8 result in a stabilization of ≥ 4 weeks, a re-escalation may be considered after approval from the Medical Monitor.

- Updated text throughout table to reflect the most recent supportive care information available.

Section 11.2 and Appendix 4

- Modified text to state that selinexor tablets (20 mg) will be supplied in polyvinyl chloride/polychlorotrifluoroethylene/polyvinyl chloride (PVC/PCTFE/PVC) film blisters (or equivalent) with an aluminum foil lidding in a secondary paper wallet with childproofing to reflect current information.

Section 11.4.6

- Removed text to align with the selinexor *Investigator's Brochure*: *Alcohol:* Ethanol should be avoided on selinexor dosing days as it may compete for GSH-mediated metabolism

Section 12.1.1

- Revised text to align with Table 9.

Section 15:

- Added references to the list that were inadvertently removed from previous versions of the protocol.
- Added Durie 2006, Kumar 2016, and Rajkumar 2011 to the list of references
- Removed Kyle 2009 and Palumbo 2014 from the list of references

Appendix 7:

Some of the detailed information in the Protocol Version 4 ROW SOC was not included in the Protocol Version 4 SOC for the US because the Protocol Version 4 ROW SOC was revised after Protocol Version 4 for the US was published.

Amendment 4

Protocol Version 5.0

Amendment Rationale

The primary purpose for this amendment was to address comments received from Regulatory Authorities.

The revised protocol Version 5.0 dated 28 April 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 4.1, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes

- Updated the version number and date of protocol (**Modified sections**: Global)
- Updated the number of patients who have received selinexor to the number based on the most recent Investigator's Brochure (31 March 2017) (Modified sections: Global)
- Internal changes to improve clarity (Modified sections: Global)

Specific Content Changes

Protocol Approval Signature Page

– Replaced Humphrey Gardner, M.D., Senior Vice President, Clinical Development, with Michael Kauffman, MD, PhD, Acting Chief Medical Officer, as a signatory.

Synopsis

– Added the following text to the Background and Study Rationale to align with the most recent IB, "across all patients was 21% and the clinical benefit rate (CBR) is 33%. Similar ORR were seen in the patients with "penta" and "quad" MM, with higher CBR in patients who received 8 vs. 6 doses/cycle consistent with improved disease control with continuous dosing."

– Added the following text, "If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis," to allow for adjustments to the dosing of dexamethasone.

Inclusion/Exclusion Criteria (also in Synopsis and Sections 8.4 and 8.5)

– Modified inclusion criteria #10 to clarify that female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception).

– Modified inclusion criteria #13 to remove "on Cycle 1 Day 1" for hemoglobin level ≥ 8.5 g/dL.

- Modified inclusion criteria #14 to add “key” to specific criteria.
- Corrected exclusion criteria #17 to add ≥ to Grade 2 painful neuropathy

Table 1 (Schedule of Assessments) (also in Section 9.7.2.4)

- Modified footnote #8 to, “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 Cycles ≥ 2 and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study,” to required that testing is performed on Day 1 of Cycles ≥ 2.

[redacted]

[redacted]

List of Abbreviations:

- Removed definition for FLC (kappa/lamba ratio) for clarification
- Added definition for TRAE (treatment-emergent adverse event)

Protocol, Main Body

Section 4.3

- Updated the clinical experience sections to the most recent safety and efficacy information for MM in the KCP-330-001 study and for KCP-330-012 study in the IB.

Section 4.4

- Updated the information on ACS to reflect the current selinexor safety information.

Section 5.1

- Added the following text, “If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis,” to allow for adjustments to the dosing of dexamethasone.

Section 9.2

- Updated text to reflect IMWG requirement for sequential sample to confirm response, “SPEP with serum protein immunofixation, quantitative Ig, serum FLC, and 24-hour UPEP, with immunofixation, must be collected at each required time point. An aliquot of the blood and urine samples should be retained. If the local laboratory results indicate a CR or sCR, a sequential sample, per IMWG, should be collected and analyzed. Aliquots from the initial and subsequent collection will be sent to the central laboratory to confirm the CR or sCR response.”
- Corrected in Table 4 that karyotyping and FISH will be performed at a central laboratory, not a local laboratory.

CCI

- [redacted]

Section 9.3

- Updated text to specify that all MM assessments are required at each time point. Added text to clarify the timing of collection of sequential MM assessment samples, "Two consecutive samples are required to confirm the response. The time period between samples may be discussed with the Medical Monitor and can occur on the same day, as long as, the samples are analyzed separately."

Section 9.4.4

- Added new Section, Pregnancy Testing, with the following text: "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. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 during the study and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study."

Sections 9.5.1, 9.7.2.1, 9.7.2.2 and Table 6

- Replaced text in these sections with, "As of protocol version 5.0, these samples are no longer collected." Table 6 was removed as the PK CCI blood samples are no longer being collected as is it not necessary to continue collecting these samples.

CCI

- CCI

CCI

- [redacted]

Section 11.1.3

- Added the following text, "If any patient is not able to tolerate this dose, then a potential discontinuation or further decrease in dosage would be allowed after a discussion with the Medical Monitor on a case by case basis," to allow for adjustments to the dosing of dexamethasone.

- [redacted]

CCI

- [redacted]

Section 11.2 and Appendix 4

- Modified text to simplify the description of the blister packaging.

Section 11.4.7

- Revised Prevention of Pregnancy language to Contraception Requirements to clarify that female patients of childbearing potential must agree to use 2 methods of contraception (including 1 highly effective and 1 effective method of contraception).

Section 12.1.3.1

- Added the Karyopharm German PV fax number for European sites.
- Revise text to modify reporting suspected unexpected serious adverse reactions to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries in order to ensure safety information is reported to authorities in all countries participating in the study.

Section 14.11

- Clarified the publication language to include the following text, "Publication will be in a relevant peer- reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor."

Section 15

- Added Vogl 2016 to the list of references

Appendix 7:

- Revised Changes to the Protocol for Protocol Version 4.1 to accurately capture changes made to that version of the protocol.

Amendment 5

Protocol Version 6.0

Amendment Rationale

The primary purpose for this amendment was to update statistical language (e.g., definition of analysis populations, CCI [redacted]) and to address inconsistencies.

The revised protocol Version 6.0 dated 13 December 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 5.0, including rationales for these changes, is provided below.

Changes to the Protocol

Administrative Changes

- Updated the version number and date of protocol (**Modified sections**: Global)
- Internal changes to improve clarity (Modified sections: Global)

Specific Content Changes

Protocol Approval Signature Page

– Replaced Michael Kauffman, M.D, PhD, Acting Chief Medical Officer, with Jatin Shah Kauffman, MD, Vice President, Clinical Strategy, as a signatory.

Synopsis

– Objectives: updated for consistency with the Statistical Analysis Plan:

  - Updated definitions of Durations of CBR and DCR.
  - CCI [redacted]

– Statistical Methods: updated the definition of mITT and PP populations, for consistency with SAP, CCI [redacted].

Table 1 (Schedule of Assessments) (also in Section 9.2)

– Modified footnotes #2 and #9 to indicate that results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 (±15 days) will be provided. This information is required to more fully understand history of patient's MM (extent of disease, rate of progression).

Protocol, Main Body

Section 4.1

– Updated the Introduction for clarity and accuracy.

Section 6.2

- Updated definitions of Durations of CBR and DCR,for consistency with the SAP.

Section 7.3

- Deleted the following text, as IRC does not review disease assessments at the time of progression and discontinuation of treatment does not require confirmation of PD by IRC: "…and must review at time of progression. Progression based on site generated disease assessment data must be confirmed by the IRC prior to discontinuing treatment.".

Section 8.2

- Removed Canada from the list of countries where the study is being conducted, to reflect that the study is not being conducted in Canada.

Section 8.8

- Added the following text after date of birth, "(as allowed by regulatory authorities)" to clarify that investigator should provide birth date information in compliance with their regulatory authorities.

Section 9.1.2, 9.2

- Added text to indicate that results of pre-screening MM assessments at Day -30 (window: Screening – 2 weeks) and Day -60 (±15 days) will be provided. This information is required to more fully understand history of patient's MM (extent of disease, rate of progression).
- Text edited in Section 9.2 to clarify sample collection and analysis procedures in the event of a CR or sCR, to align with the lab manual.

CCI [redacted]

CCI [redacted]

Section 13.2.1

- For consistency with Statistical Analysis Plan:
  - Updated the definition of mITT and PP populations
  - CCI [redacted]
  - Updated Sub-group Efficacy Analyses

Section 13.3.4

- Updated the definition of mITT and PP populations, CCI [redacted] for consistency with Statistical Analysis Plan.

Appendix 7:

- Added Summary of Changes for Protocol Version 6.0 to describe changes made to version 5.0.