CLINICAL STUDY PROTOCOL

PROTOCOL INFORMATION

Study Title:	A Phase I Study of the Combination of a Selective Inhibitor of Nuclear Export (SINE), Selinexor with Carfilzomib and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma.
Protocol Number:	University of Chicago IRB #IRB14-0033
Lead Institution:	The University of Chicago Medicine
Lead Principal Investigator:	Dr. Andrzej Jakubowiak [redacted]
Participating Centers:	Multi-institutional trial (4 Total Centers)
Investigational Products:	Drug Company Supplied: Carfilzomib (Kyprolis®) (Amgen) Selinxor (KPT-330) Karyopharm Therapeutics Inc. IND 121533
Protocol Version:	1.0 February 11, 2014 2.0 March 18, 2015 3.0 July 28, 2015 3.1 October 21, 2015 3.2 February 25, 2016 3.3 July 6, 2016 4.0 October 20, 2016 5.0 June 14, 2017 6.0 August 28, 2018 7.0 January 20, 2020 8.0 March 5, 2021

SYNOPSIS

Study Title	A Phase I Study of the Combination of a Selective Inhibitor of Nuclear Export (SINE), Selinexor with Carfilzomib and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma
Objectives	**Primary Objective** 1. Determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of the combination of Selinexor, Carfilzomib, and Dexamethasone in relapsed and relapsed/refractory multiple myeloma **Secondary Objectives** 1. Determine safety and tolerability 2. Determine the efficacy, as measured by the rates of stable disease or better (including minimal response, partial response, very good partial response, complete response, and stringent complete response) **Exploratory Objectives** Analyzing isolated bone marrow plasma cells for presence and the effect of treatment on the levels of: 1) XPO1 2) markers of apoptosis such as PARP and caspase 3, and 3) markers of autophagy including caspase 10 and LC3B 4) total protein levels and nuclear localization of tumor suppressor proteins (e.g. p53, p21, pRB, p73), growth regulatory proteins (e.g. IkB) and oncogenic proteins (e.g. MYC) . Estimate of clinical activity in different risk groups by cytogenetics and gene expression profiling will also be assessed.
Sample Size	Between 15 and 100

Study Design

This is a phase I, open-label study, in which a standard 3+3 dose escalation design will be used. 3-6 patients will be entered into each cohort, for a maximum of 8 cohorts to establish the MTD and schedule. Both Selinexor and carfilzomib will be escalated. Once the MTD is provisionally established, expansion cohorts of 6-12 additional patients will be enrolled at recommended doses and schedules. Enrollment into the two schedules will not be done in sequence.

Twice Weekly Dose Schedule

Patients will be treated with the assigned dose level of Selinexor, carfilzomib and dexamethasone starting with Dose Level 1 at 40mg twice weekly Selinexor for 3 weeks, 20/27 mg/m^2 carfilzomib twice weekly for 3 weeks, and 20 mg twice-weekly dexamethasone for 4 weeks.

Twice Weekly Phase 1 Dose Levels

Patients will be enrolled in cohorts of size 3, beginning at dose level 1. Dose Level -1 and -2 will only be tested if Dose Level 1 exceeds the MTD.

Dose Level[a]	**Selinexor**	**Carfilzomib[b]**	**Dexamethasone**
	Days 1, 3, 8, 10, 15, 17	**Days 1, 2, 8, 9, 15, 16[d]**	**Days 1, 2, 8, 9, 15, 16, 22, 23**
-2	20mg	20 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
-1	20mg	20/27 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
1	**30 mg/m^2 (~40mg)**	**20/27 mg/m^2**	**20 mg (Cycle 1-4) 10 mg (Cycle 5+)**
2a	40mg	20/36 mg/m2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
2b	60mg	20/27 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
3	60mg	20/36 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
4	60mg	20/45 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
5	60mg	20/56 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)

a) Once the MTD is established, an expansion cohort of 6-12 patients will be enrolled at that dose limited to carfilzomib refractory patients.

b) Carfilzomib will be initiated at 20 mg/m^2 on Days 1-2 of cycle 1 at all dose levels and then at the assigned dose level for the remainder of treatment.

c) Dose level 2a and 2b will enroll simultaneously alternating patient between the two dose levels.

d) Carfilzomib treatment Days 1, 2, 8, 9, 15, 16 for cycles 1-8 then Days 1, 2, 15, 16 for Cycles 9+

Weekly Dose Schedule

Patients will be treated with the assigned dose level of Selinexor, carfilzomib and dexamethasone starting with Dose Level 1 at 100mg once weekly Selinexor for 4 weeks, 20/56 mg/m^2 carfilzomib once weekly for 3 weeks, and 20 mg twice-weekly dexamethasone for 4 weeks in C1, 40mg once weekly dexamethasone on C2-4, and 20mg once weekly dexamethasone on C5+.

Weekly Phase I Dose Levels

Patients will be enrolled in cohorts of size 3, beginning at dose level 1. Dose Level -1 will only be tested if Dose Level 1 exceeds the MTD.

Dose Level	**Selinexor[a]**	**Carfilzomib[b,c]**	**Dexamethasone**
	Days 1, 8, 15,22	**Days 1, 8, 15**	**Days 1,2, 8,9 15,16, 22, 23 (C1)** **Days 1, 8, 15, 22 (C2+)**
-1	80mg	20/56 mg/m^2	40 mg (Cycle 1-4) 20 mg (Cycle 5+)
1	**100mg**	**20/56 mg/m^2**	**40 mg (Cycle 1-4)** **20 mg (Cycle 5+)**
2	100mg	20/56/70 mg/m^2	40 mg (Cycle 1-4) 20 mg (Cycle 5+)

a) Once the MTD is established, two expansion cohorts will be enrolled at that dose

b) Carfilzomib will be initiated at 20 mg/m^2 on Day 1 of cycle 1 at all dose levels and then at the assigned dose level for the remainder of treatment.

c) Carfilzomib treatment Days 1, 8, and 15 for all cycles.

Duration of Treatment	Subjects may continue to receive the treatment regimen until disease progression or occurrence of an unacceptable toxicity.

Inclusion / Exclusion Criteria	**Inclusions:** 1. Written informed consent in accordance with federal, local, and institutional guidelines 2. Age ≥18 years 3. ECOG performance status of 0-2 4. Diagnosis of multiple myeloma as per IMWG uniform criteria. 5. Measurable disease by IMWG as defined by at least one of the following: a. Serum M-protein ≥0.5 g/dL b. Urine M-protein ≥200 mg in a 24-hour collection c. Serum Free Light Chain level ≥ 10 mg/dL provided the free light chain ratio is abnormal d. Measurable plasmacytoma. If plasmacytoma measurement is the only measurable disease, subject eligibility must be reviewed with Lead PI prior to signing consent. 6. Relapsed/Refractory multiple myeloma with progressive disease at study entry 7. Subjects must have been treated with at least 2 prior therapies including a proteasome inhibitor and a cereblon-binding agent. a. Subjects who are refractory to carfilzomib may enroll throughout the trial. Carfilzomib refractory status is defined by IMWG criteria: disease that is nonresponsive while on therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course (Rajkumar et al Blood 2011) b. In the twice weekly schedule expansion cohort of the study, enrollment will be limited to patients meeting carfilzomib refractory status c. In the weekly schedule, it will be required that one of the expansion cohorts (20 subjects) enrolls carfilzomib refractory subjects and the other (20 subjects) enrolls carfilzomib/PI naïve/sensitive subjects. 8. Ability to adhere with the study visit schedule and other protocol procedures 9. Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L, hemoglobin ≥ 8 g/dL, platelet count ≥50,000mm^3.

	Screening ANC should be independent of growth factor support for over one week for all patients. Subjects may receive red blood cell transfusions as clinically indicated per institutional guidelines but screening hemoglobin should be independent of red blood cell transfusion for at least 3 days prior to screening. Screening platelet count should be independent of transfusions for at least 14 days 10. Adequate hepatic function within 14 days prior to C1D1: total bilirubin ≤2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 times ULN) and alanine aminotransferase (ALT) ≤2.5 times ULN. In the case of known (radiological and/or biopsy documented) liver metastasis, ALT ≤2.5 times ULN is acceptable 11. Adequate renal function within 14 days prior to C1D1: estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockcroft -Gault: (140-Age) • Mass (kg)/ (72 • creatinine mg/dL); multiply by 0.85 if female 12. Female patients of child-bearing potential must agree to practice abstinence or use dual methods of contraception* during treatment and for 90-days after the last dose of carfilzomib and have a negative serum pregnancy test at screening. 13. Male patients must agree to practice abstinence or use an effective barrier method of contraception* during treatment and for 90-days after the last dose of carfilzomib if sexually active with a female of child-bearing potential. *Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. 14. Male patients must agree not to donate semen or sperm while they are taking Carfilzomib and 90 days after the last Carfilzomib dose. **Exclusions:** Patients meeting any of the following exclusion criteria are not eligible to enroll in this study. 15. Patients who are pregnant or lactating 16. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤2 weeks prior to cycle 1 day 1 (localized radiation to a single site at least 1 week before cycle 1 day 1 is permissible)

	17. Concurrent therapy with approved or investigational anticancer therapeutic other than steroids 18. Major surgery within four weeks before Day 1 19. Unstable angina or myocardial infarction within 4 months prior to randomization, NYHA Class III or IV heart failure, LVEF < 40%, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias including uncontrolled chronic atrial fibrillation/atrial flutter, history of torsades de pointe, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or grade 3 conduction system abnormalities unless subject has a pacemaker 20. Subject has plasma cell leukemia or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis. 21. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization 22. Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within 14 days prior to first dose; patients with controlled infection or on prophylactic antibiotics are permitted in the study 23. Known to be HIV seropositive 24. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen) 25. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas 26. Patients with markedly decreased visual acuity in the opinion of the treating investigator after completion of screening ophthalmologic exam 27. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to randomization

	28. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib) 29. Any underlying condition that would significantly interfere with the absorption of an oral medication 30. Serious psychiatric or medical conditions that could interfere with treatment 31. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment 32. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization 33. Patients with coagulation problems and active bleeding in the last month (peptic ulcer, epistaxis, spontaneous bleeding) 34. Previous selinexor exposure
Response	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains Serum quantitative immunoglobulins (Igs) Bone marrow biopsy is required to confirm response at time of suspected CR or better. Plasmacytoma evaluation should be completed if clinically indicated or to confirm CR
Safety Variables & Analysis	The safety and tolerability of Selinexor and carfilzomib will be evaluated by means of drug related DLT, AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) V 4.03 will be used for grading of AEs. Investigators will provide their assessment of causality as 1) unrelated, 2) unlikely related 3) possibly related, or 4) probably or 5) definitely related for all AEs.

1.5.3 Study Population and Sample Size

Up to 100 patients with relapsed or relapsed/refractory multiple myeloma will be the included in this trial.

1.5.4 Assessment for Response

Disease assessment for response will include Serum Protein Electrophoresis (SPEP), Urine Protein Electrophoresis (UPEP), Serum Free Light Chains (SFLC) and Immunoglobulins (Igs). Bone marrow procedures should be completed at the time of suspected Complete Response (CR). Additionally, for subjects who have a plasmacytoma or disease measured by imaging at baseline, plasmacytoma evaluations and radiographic imaging should be completed as per standard of care and in accordance with IMWG response criteria for multiple myeloma. Patients who achieve stable disease, PR, or CR will continue therapy until disease progression. Patients with disease progression will discontinue the treatment regimen and be removed from protocol.

2 Objectives

2.1 Primary Objective

- Determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of the combination of Selinexor, Carfilzomib, and Dexamethasone in relapsed and relapsed/refractory multiple myeloma

2.2 Secondary Objectives

- Determine safety and tolerability

- Determine the efficacy, as measured by the rates of stable disease or better (including minimal response, partial response, very good partial response, complete response, and stringent complete response)

2.3 Exploratory Objectives

- In order to confirm the biological effects of synergy that we have demonstrated in vitro, we also plan to perform an exploratory evaluation of pharmacodynamics. We propose analyzing isolated bone marrow plasma cells for the presence and the effect of treatment on the levels of: 1) XPO1 2) markers of apoptosis such as PARP and caspase 3, and 3) markers of autophagy including caspase 10 and LC3B 4) total protein levels and nuclear localization of tumor suppressor proteins (e.g. p53, p21, pRB, p73), growth regulatory proteins (e.g. IkB) and oncogenic proteins (e.g. MYC) . Bone marrow samples for this evaluation will be collected prior to initiation of treatment and on day 15 of cycle 1. We will also study the effects of treatment on XPO1 expression in peripheral blood mononuclear cells (PBMCs) at day 1 and day 15 of cycle 1, and at the time of progression/relapse.

3 Investigational Plan

3.1 Overview of Study Design and Dosing Regimen

This is a multi-center, open-label, investigator-initiated phase I study to determine the maximum tolerated dose (MTD) as well as safety and tolerability of oral Selinexor in combination with carfilzomib in patients with relapsed and relapsed/refractory multiple myeloma.

The study employs a 3+3 dose escalation design. In this design, 3-6 patients will be entered into each cohort, for a maximum of 7 cohorts. Both Selinexor and carfilzomib will be escalated. Once the MTD is provisionally established, an expansion cohort of 6-20 additional patients will be enrolled at that dose. Based on current patterns, we anticipate that at least half of the enrolled patients out of the total enrolled patients into this trial will be carfilzomib-refractory (i.e. from enrollment in both dose escalation and in the expansion phase of the trial). The RP2D will be defined as the highest dose such that <30%DLTs occur in 12-20 patients in the respective cohorts.

Enrollment into the two schedules will not be done in sequence.

Phase 1 Twice Weekly dosing:

After the initial screening visit and registration in the study, patients will receive Selinexor twice weekly on days 1 and 3 of each week for 3 weeks (Monday/ Wednesday or Tuesday/ Thursday; Days 1, 3, 8, 10, 15, 17 of 28-day cycles). Selinexor will be given orally at a starting dose of 40mg

Carfilzomib dosing will start at 20 mg/m^2 IV on days 1 and 2 of cycle 1 followed by dose escalation to 27-56 mg/m^2 on Days 8, 9, 15, 16 of Cycle 1 and all subsequent cycles. All doses of carfilzomib will be given as 30 minute infusions.

Dexamethasone dosing will be 20 mg PO/IV on days of Carfilzomib: Days 1, 2, 8, 9, 15, 16 **and** 22, 23 for Cycles 1-4. Starting at Cycle 5, dexamethasone dosing will be reduced to 10 mg PO on Days 1, 2, 8, 9, 15, 16, 22 and 23.

Phase 1 Weekly Dosing:

After the initial screening visit and registration in the study, subjects will receive Selinexor once per week on day 1 of each week for 4 weeks (Days 1, 8, 15, and 22 of 28-day cycles). Selinexor will be given orally at a starting dose of 100mg. Dose modifications will be applied based on toxicities per the treating investigator's discretion after discussion with the lead PI.

In the first 3 subjects, carfilzomib dosing will start at 20 mg/m^2 IV on day 1 of cycle 1 followed by dose escalation to 56 mg/m^2 on Days 8 and 15. From cycle 2+ carfilzomib will be given at 56mg/m^2 weekly for 3 weeks. If there are no DLTs in the first 3 patients observed after C1, an additional 3 patients will be enrolled and treated with carfilzomib at 20mg/m^2 on C1D1 and escalated to 56 mg/m^2 in cycle 1 day 8 and finally to 70mg/m^2 in cycle 1 day 15. Carfilzomib will be given at 70mg/m^2 weekly for 3 weeks in 28 day cycles from cycle 2+. If there are no DLTs observed after cycle 1 in the first 6 subjects, two additional cohorts will enroll simultaneously at the highest tolerated dose. Each cohort will enrol 20 subjects total; the first will only allow carfilzomib refractory subjects, while the second carfilzomib/PI naïve/sensitive subjects. See section 6.2.1 "Dose Escalation Rules (for Phase 1 Weekly Dosing Cohort)" for more details. All doses of carfilzomib will be given as 30-minute infusions. Dose modifications will be applied based on toxicities per the treating investigator's discretion after discussion with the lead PI.

Dexamethasone dosing will be 20 mg PO on days of Carfilzomib: Days 1, 2, 8, 9, 15, 16 **and** 22, 23 in Cycle 1. From cycles 2-4, dexamethasone will be given PO as a single 40mg dose weekly (Days 1, 8, 15, and 22). Starting at Cycle 5, dexamethasone dosing will be reduced to 20 mg PO on Days 1, 8, 15, and 22. Dose modifications will be applied based on toxicities per the treating investigator's discretion after discussion with the lead PI.

Treatment responses will be assessed by serum free light chains (SFLC), quantitative immunoglobulin levels (Igs), and serum and urine monoclonal protein starting at Cycle 2 Day 1 and then at the beginning of each subsequent cycle. Subjects with stable disease or better will continue treatment until disease progression or the development of unacceptable toxicities. All patients will then undergo a final visit (end of treatment visit).

3.1.1 Number of Centers

A total of up to 5 centers: The University of Chicago Medical Center is the lead center plus 4 additional MMRC sites.

3.1.2 Definition of Treatment Cycle and Duration

Each treatment cycle is 28 days.

Twice Weekly Dosing Cohort

Selinexor will be taken orally twice weekly on days 1 and 3 of each week for weeks 1-3. Every effort should be made to keep selinexor dosing on weekdays particularly during cycle 1. Therefore, recommended dosing days are Monday/Wednesday, Tuesday/Thursday or Wednesday/Friday. Selinexor dosing will therefore take place on Days 1, 3, 8, 10, 15, 17. Carfilzomib will be administered on Days 1, 2, 8, 9 15, and 16. Dexamethasone will be taken on Days of Carfilzomib administration 1, 2, 8, 9, 15, 16, and also days 22 and 23. No treatment will be administered on Days 24-28.

Study drug administration may be delayed for toxicity according to protocol Section 9.2.

Weekly Dosing Cohort

Selinexor will be taken orally once weekly on day 1 of each week for weeks 1-4. Every effort should be made to keep selinexor dosing on weekdays particularly during cycle 1. Selinexor dosing will therefore take place on Days 1, 8,15, and 22. Carfilzomib will be administered on Days 1, 8, and 15. Dexamethasone will be taken on Days of Carfilzomib administration 1, 8, and 15, and also on day 22 (and on days 2, 9, 16, and 23 of cycle 1 only). No treatment will be administered on Days 24-28.

Study drug administration may be delayed for toxicity according to protocol Section 9.2.

3.1.3 Treatment Phase

Treatment will be continued until progression of disease according to IMWG criteria, unacceptable toxicities occur in individual subjects or consent is withdrawn.

3.1.4 End of Treatment Visit

Patients that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, 30 days (± 7 days) after the last dose of study medication.

3.2 Study Duration

The study is planned to start in Q3 2014 with respect to first patient in (FPI). With an expected accrual rate of 2-4 patients per month across 4 centers, and a total number of up to 48 patients planned, the anticipated enrolment period is 8-16 months. Hence the last patient in will be included not prior to Q3 2015. The length of treatment period will be approximately 12-18 months. Patients will be followed for survival for 2 years after their end of treatment visit or until death, whichever occurs first. During the dose escalation phase, the first full cycle for at least 3 patients must be examined before dose escalation meaning a minimum of 84 days of active treatment.

4 Patient Selection

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study. No enrollment waivers will be granted.

1. Written informed consent in accordance with federal, local, and institutional guidelines
2. Age ≥18 years
3. ECOG performance status of 0-2 (Appendix 2)
4. Diagnosis of multiple myeloma as per IMWG uniform criteria
5. Measurable disease by IMWG as defined by at least one of the following:
    a. Serum M-protein ≥0.5 g/dL
    b. Urine M-protein ≥200 mg in a 24-hour collection
    c. Serum Free Light Chain level ≥ 10 mg/dL provided the free light chain ratio is abnormal
    d. Measurable plasmacytoma. If plasmacytoma measurement is the only measurable disease, subject eligibility must be reviewed with Lead PI prior to signing consent

6. Relapsed/Refractory multiple myeloma with progressive disease at study entry
7. Subjects must have been treated with at least 2 prior therapies including a proteasome inhibitor and a cereblon-binding agent
    a. Subjects who are refractory to carfilzomib may enroll throughout the trial. Carfilzomib refractory status is defined by IMWG criteria: disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course (Rajkumar et al Blood 2011)
    b. In the twice weekly dosing cohort of the study, enrollment will be limited to patients meeting carfilzomib refractory status
    c. In the weekly dosing cohort, it will be required that one of the expansion cohorts (20 subjects) enrolls carfilzomib refractory subjects and the other (20 subjects) enrolls carfilzomib/PI naïve/sensitive subjects.
8. Ability to adhere with the study visit schedule and other protocol procedures
9. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, hemoglobin $\geq$ 8 g/dL, platelet count $\geq$50,000mm^3. Screening ANC should be independent of growth factor support for over one week for all patients. Subjects may receive red blood cell transfusions as clinically indicated per institutional guidelines but screening hemoglobin should be independent of red blood cell transfusion for at least 3 days prior to Cycle 1 Day 1. Platelet count should be independent of transfusions for at least 14 days for eligibility
10. Adequate hepatic function within 14 days prior to Cycle 1 Day 1: total bilirubin $\leq$2 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 times ULN) and alanine aminotransferase (ALT) $\leq$2.5 times ULN. In the case of known (radiological and/or biopsy documented) liver metastasis, ALT $\leq$2.5 times ULN is acceptable
11. Adequate renal function within 14 days prior to Cycle 1 Day 1: estimated creatinine clearance of $\geq$ 30 mL/min, calculated using the formula of Cockroft and Gault: (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female
12. Female patients of child-bearing potential must agree to practice abstinence or useuse dual methods of contraception* during treatment and for 90-days after the last dose of carfilzomib and have a negative serum pregnancy test at screening
13. Male patients must agree to practice abstinence or use an effective barrier method of contraception* during treatment and for 90-days after the last dose of carfilzomib if sexually active with a female of child-bearing potential.

    *Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal.
14. Male patients must agree not to donate semen or sperm while they are taking Carfilzomib and 90 days after the last Carfilzomib dose.

4.2 **Exclusion Criteria**

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study. No enrollment waivers will be granted.

1. Patients who are pregnant or lactating
2. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤2 weeks prior to cycle 1 day 1 (localized radiation to a single site at least 1 week before cycle 1 day 1 is permissible)
3. Concurrent therapy with approved or investigational anticancer therapeutic other than steroids
4. Major surgery within four weeks before Cycle 1 Day 1
5. Unstable angina or myocardial infarction within 4 months prior to randomization, NYHA Class III or IV heart failure, LVEF < 40%, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias including uncontrolled chronic atrial fibrillation/atrial flutter, history of torsades de pointe, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
6. Subject has plasma cell leukemia or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
7. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization
8. Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within 14 days prior to first dose; patients with controlled infection or on prophylactic antibiotics are permitted in the study
9. Known to be HIV seropositive
10. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen)
11. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
12. Patients with markedly decreased visual acuity in the opinion of the treating investigator after completion of screening ophthalmologic exam
13. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to randomization
14. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
15. Any underlying condition that would significantly interfere with the absorption of an oral medication
16. Serious psychiatric or medical conditions that could interfere with treatment

17. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
18. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization
19. Patients with coagulation problems and active bleeding in the last month prior to Cycle 1 Day 1 (peptic ulcer, epistaxis, spontaneous bleeding)
20. Previous Selinexor exposure

5 Subject Enrollment and Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 4. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should call the study coordinator at (773) 834-3095 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

Please refer to the eligibility checklist form for submission guidelines. Sites should make all enrollment requests at least 72 hours before the anticipated Cycle 1 Day 1. Treatment may not start until the approved enrollment form is sent back to the site. The University of Chicago will assign a study-number to each subject within the Velos eResearch.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the above CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.

The date the patient receives treatment for the first time will be considered the patient's "Enrolled/OnStudy Date." The patient's subject ID will be assigned and a confirmation of

registration will be issued by the CRA on this date. Subjects that sign consent and do not go "On Study" will be recorded in the database with the date they signed consent and the reason for not going "On Study" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

6 Treatment Plan

Please refer to the Study Calendar (Appendix 6) for an overview.

After screening, eligibility determination and enrollment, subjects will receive carfilzomib, Selinexor, and dexamethasone in 28-day cycles until progression, unacceptable toxicity or subject withdraws consent.

A subject is considered to be off-treatment following a 30-day safety follow-up period after the last treatment. Long-term follow-up for survival will be 2 years from End of Treatment visit.

6.1 Study Procedures

6.1.1 Screening Procedures

The screening period is 21 days in length. The screening period starts on the date that the patient signs the Informed Consent Form. Refer to the study calendar (Appendix 6)

Signed written informed consent	Obtained prior to any study specific assessments (may be obtained within 30-days of Day 1)
Demographics and medical history	• Age, gender, ethnic background • Details on myeloma diagnosis • Details on prior cancer therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities • Previous and concurrent relevant diseases • Current symptoms and/ or residual toxicities from prior therapies
Pregnancy test (if applicable) (Day - 7 to -1)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years. In case the sampling date for the serum pregnancy test exceeds 7 days before treatment start, a urine test is required for confirmation
Physical examination and vital signs	• Body height and weight • BSA • ECOG Performance Status (Appendix 2) • Blood pressure, pulse, temperature • Physical examination
Ophthalmologic exam	Full ophthalmologic exam. Prior to dilation: best corrected visual acuity and slit lamp examination including tonometry. Following dilation: fundoscopy and a slit lamp examination to document lens clarity If a cataract is seen during the exam, cataract will be graded

	according to the Lens Opacities Classification System III (LOCS III) (Appendix 8)
Oxygen Saturation	Pulse oximetry is performed for patients at rest on breathing room air
Cardiac evaluation	12-lead ECG required at screening
Echocardiogram	Required at screening
Urinalysis	Required at screening. Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology (CBC)	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, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, amylase, lipase, creatinine kinase, urate, LDH, TSH
Coagulation	Required at screening. Prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT)
CRP & β2 microglobulin	Required at screening only
TSH & BNP	Required at screening
Myeloma Disease Assessment - laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains (SFLC) • Serum quantitative immunoglobulins (Igs) All of the above assessments are required at screening regardless of the disease classification.
Bone Marrow Biopsy	Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for conventional cytogenetics and fluorescent *in situ* hybridization. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening (Section 7)

Plasmacytoma Evaluation	May be performed by physical exam or imaging, whichever is clinically indicated and at the treating investigator's discretion.
Skeletal Survey	May be within 30 days of planned treatment start (does not need to be repeated if within 30 days). Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Exams outside of 30 days may be considered for enrollment after approval from Lead PI
Chest radiograph	Both, posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any adverse events during the study.
Neurotoxicity Assessment	Includes Neurotoxicity Questionnaire (Appendix 5)
Adverse Events and Concomitant medication	Only SAEs considered related to study procedure need to be reported. Concomitant medication currently used
Nutritional Assessment	Optional and if clinically indicated

6.1.2 **Treatment Phase Procedures**

The following assessments should be performed on Day 1 of each cycle unless otherwise noted. Please refer to section 6.1.6 for details of response evaluation to be completed at any time throughout the trial when a CR or better is suspected.

Complete Physical examination and vital signs (Symptom-directed Physical Exam Day 8, 15; Vital signs on each treatment day with Carfilzomib and/or Selinexor)	• Body weight • BSA • ECOG Performance Status • Blood pressure, pulse, temperature • Pulse oximetry • Physical Exam
Ophthalmologic exam	Only if clinically indicated during treatment. Prior to dilation: best corrected visual acuity and slit lamp examination including tonometry. Following dilation: fundoscopy and a slit lamp examination to document lens clarity If a cataract is seen during the exam, cataract will be graded according to the Lens Opacities Classification System III (LOCS III) (Appendix 8)
Cardiac evaluation	12-lead ECG only if clinically indicated
Echocardiogram	During treatment only if clinically indicated

Urine analysis (week 1-4 only)	Only if clinically indicated: Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology (Day 1, 8, 15 before carfilzomib administration; Day 22*)	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, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated **Cycle 2+ an additional CBC may be drawn the 4th week of each cycle to assess pancytopenias and initiate concomitant treatments including growth factors and transfusion support prior to starting next cycle*
Complete clinical chemistry (Day 1, 8, 15 before carfilzomib administration)	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, amylase, lipase, uric acid, LDH • *Magnesium and phosphorous are required Day 1, 8, 15 of cycle 1 only and as clinically indicated* • *LDH and uric acid are required Day 1, 8, 15 of cycle 1 and then Day 1 of Cycle 2+* • *Amylase, lipase required Day 1 of every other cycle starting with Cycle 2 (Cycle 2, 4, 6, 8 etc.)*
Limited clinical chemistry (on day days 2, 9, 16 if clinically indicated)	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, LDH
Coagulation	Only if clinically indicated: Prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
Pregnancy Test	Cycle 1 Day 1 only or unless indicated
Myeloma Disease Assessment - laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs)

	Only those assessments used to follow the myeloma disease are required past screening. All assessments are required for confirmation of response.
Neurotoxicity Assessment	Including Neurotoxicity Questionnaire (Appendix 5)
Adverse events	Assessed on an ongoing basis
Concomitant Medications	Pre-treatment concomitant medications (refer to section 6.1.3). All other con-meds assessed on an ongoing basis
Study Treatment	Section 6.2.1 and Appendix 6 • Twice weekly dosing Cohort: Selinexor (Days 1, 3, 8, 10, 15, 17); Carfilzomib (Days 1, 2, 8, 9, 15, 16), Dexamethasone (Days 1, 2, 8, 9, 15, 16, 22, 23) • Weekly dosing cohort: Selinexor (Days 1, 8, 15, 22); Carfilzomib (Days 1, 8, 15), Dexamethasone (Cycle 1, Days 1, 2, 8, 9, 15, 16, 22, 23; Cycles 2+ Days 1, 8, 15, 22)
Correlative Samples	For patients who give consent, Cycle 1 Day 15 bone marrow aspirate and blood samples (Section 7)

6.1.3 **Pretreatment Preparation**

6.1.3.1 Hydration

IV hydration will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (eg, ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

6.1.3.2 Pre-treatment Concomitant Medications

The following are required concomitant medications to be started on Cycle 1 Day 1 or up to 24 hours prior to Cycle 1 Day 1:

- Valacyclovir 500 mg PO QD or equivalent HZV prophylaxis, continuing for the duration of treatment. Additional prophylaxis is at the Treating Investigator's discretion.
- Patients must receive prophylactic treatment to prevent anorexia and nausea associated with Selinexor, which includes:
    - Megesterol acetate 160-400 mg daily, beginning 0-3 days before the first dosing day of Selinexor

    AND

    - 5-HT3 antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued twice daily (bid) – three times a day (tid) as needed (prn).

- Additional standard supportive care agents may be used as needed (prn).

- **Megesterol acetate and a 5-HT3 antagonist are mandatory during Cycle 1 but may be tapered or discontinued at the Treating Investigator's discretion in Cycle 2 or later in patients who tolerate Selinexor well in Cycle 1.**

The following are alternative concomitant medications:

-Ondansetron 8 mg PO q 8 hours (scheduled, not PRN 1st cycle)

- Olanzapine 2.5 mg PO day of Selinexor and for 2 days after

- rolapitant 180 mg PO every 2 weeks

The following are **recommended/optional** medications to be started on Cycle 1 Day 1 or up to 24 hours prior to Cycle 1 Day 1:

Aspirin (enteric-coated) 325 mg PO QD or low molecular weight heparin at prophylactic doses for the duration of treatment. (Subjects with known high thrombotic risk, eg, prior thrombosis, DVT, etc, should receive full anticoagulation at the Treating Investigator's discretion.) Anticoagulation should be held in patients with **platelets <50,000/mm^3, those at risk of platelets dropping to Grade 3 thrombocytopenia or with active bleeding.**

6.1.4 Study Drug Administration

6.1.4.1 Carfilzomib Administration

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. The dose will be calculated using the subject's actual BSA at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Dose adjustments do not need to be made for weight gains/losses of ≤ 10%. Subjects with a Body Surface Area (BSA) of greater than 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m2 dose level), 59.4 mg of carfilzomib (at the 27 mg/m^2 dose level), 123.2mg (at the 56 mg/m^2 dose level), or 154mg (at the 70 mg/m^2 dose level).

In the Twice Weekly cohorts for Cycle 1 Days 1 and 2, the dose of carfilzomib must be 20 mg/m^2 followed by the assigned dose for the remainder of treatment.

In the weekly dosing cohorts, 3 subjects will be treated with carfilzomib at 20/56 mg/m^2, if there are no DLTs after cycle 1, 3 more subjects will be enrolled and treated at 20/56/70 mg/m^2. Specifically, this indicates that in cycle 1 carfilzomib will be escalated from 20 mg/m^2 on day 1 to 56 mg/m^2 on day 8 and 70 mg/m^2 on day 15. On Cycle 2 day 1 and for the remainder of the treatment, carfilzomib will be given at the highest dose (56 mg/m^2 for the first 3 subjects and 70 mg/m^2 for the second 3 subjects). If no DLTs are observed after cycle 1 in the first 6 subjects, two additional cohorts of 20 subjects total each will begin enrolling simultaneously: one will require carfilzomib refractory subjects, while the other will require carfilzomib/PI naïve/sensitive subjects. Please see section 6.2.1 "Dose Escalation Rules (for Phase 1 Weekly Dosing Cohort)" for more details.

Carfilzomib will be given as an IV infusion over 30 minutes on **Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle of Cycles 1-8 and then Days 1, 2, 15, 16 of Cycles 9+ (Twice Weekly dosing cohort) and Days 1, 8, and 15 for all cycles (Weekly dosing cohort).** If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration. The dose will be administered at a facility capable of

managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1. During these observation times, post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) may be given per the treating investigator's discretion. Subjects should be monitored periodically during this period for evidence of fluid overload. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Refer to Table 7.3 for guidance regarding dose reduction in subjects with compromised renal function. Refer to section 6.7 for safety guidance with Carfilzomib administration.

Doses of carfilzomib may be rescheduled up to 2 days if the scheduled day falls upon a holiday or with approval from Lead Principal Investigator. If day 2 of Carfilzomib dosing is delayed (i.e., Day 2, 9, 16) 4 mg of dexamethasone premedication is required to be used prior to second treatment. Missed doses will not be replaced during a cycle.

6.1.4.2 Selinexor Administration

Tablets for Selinexor oral administration will be supplied in two (2) strengths: 10 and 25 mg of active ingredient per tablet. Bulk bottles of 50 tablets per bottle will be supplied for each of the two strengths.

In the twice weekly dosing cohort selinexor will be administered twice weekly (Monday/ Wednesday or Tuesday/ Thursday; Days 1, 3, 8, 10, 15, 17) orally at a starting at Dose Level 1 of 40mg Due to overlapping toxicity, the starting dose of Selinexor will be 5 mg below the current best tolerated dose.

In the weekly dosing cohort selinexor will be administered once weekly (Days 1, 8, 15, and 22) orally at a dose of 100mg in the first 3 subjects enrolled. Please see section 6.2.1 "Dose Escalation Rules (for Phase 1 Weekly Dosing Cohort)" for details of dose reduction and increase depending on DLT evaluation.

Selinexor is to be taken within 30-minutes of solid food consumption together with 240 mL (8 ounces) of water.

On Days coinciding with Carfilzomib administration, Selinexor should be taken at least 4 hours after the carfilzomib dose. Selinexor dose should be taken close to the same time each day. If Selinexor is missed during any cycle, it should be taken as soon as possible and within 24 hours of the scheduled time. In the twice weekly dosing cohorts of this protocol, if Day 1, 8, or 15 is missed, the subsequent dose on Day 3, 10, or 17 respectively should be adjusted to ensure 72 hours between doses

During cycle 1, Selinexor must be taken in clinic on Days 1, 8, 15. Dosing on Days 3, 10, 17 during Cycle 1 of the twice-weekly cohorts, or on Day 22 of cycle 1 of the weekly cohorts may be self-administered at home but research staff must follow-up with subject compliance via a phone call. At home dosing may commence after 1 full cycle is completed and with approval of the Treating Investigator.

6.1.4.3 Dexamethasone Administration

Dexamethasone will be administered between 30 minutes and 4 hours preceding the carfilzomib (on days that they coincide), as follows:

Twice Weekly Dosing Cohorts:

• Cycles 1 – 4: 20 mg PO or IV per dose Days 1,2, 8,9, 15,16, 22, 23

• Cycles 5+: 10 mg PO or IV per dose Days 1,2, 8,9, 15,16, 22, 23

Weekly Dosing Cohorts:

• Cycle 1: 20 mg PO per dose Days 1,2, 8,9, 15,16, 22, 23

• Cycles 2-4: 40 mg PO per dose Days 1, 8, 15, 22

• Cycles 5+: 20 mg PO per dose Days 1, 8, 15, 22

Dexamethasone given on days without carfilzomib may be self-administered by the subject on an outpatient basis.

If day 2 of Carfilzomib dosing is delayed (i.e., Day 2, 9, 16) 4 mg of dexamethasone premedication is required to be used prior to second treatment. Missed doses will not be replaced during a cycle.

Missed doses of dexamethasone will not be made up.

6.1.5 **End of Treatment and Long-term Follow-up**

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug. Following the end of treatment, subjects will be followed for survival for 2 years.

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

Pregnancy test (if applicable)	A serum pregnancy test will be performed in pre-menopausal women and women who are post-menopausal for < 2 years to exclude that a pregnancy occurred under treatment
Physical examination and vital signs	• Body weight • ECOG Performance Status • Blood pressure, pulse, temperature • Physical examination • Pulse oximetry
Cardiac evaluation	12-lead ECG if clinically indicated
Urinalysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein if clinically indicated
Hematology	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, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated

Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, amylase, lipase, urate, LDH
Myeloma Disease Assessment– laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs)
Adverse events and concomitant medication	Record through 30-days after last treatment. All SAEs considered related to treatment must be followed until resolution.
Bone Marrow Biopsy	If indicated, refer to section 6.1.6 Response Evaluation

6.1.6 **Response Evaluation**

The first response assessment should be completed at Cycle 2 day 1. If at any time throughout the treatment a complete response or better is suspected, a complete disease assessment should be performed to confirm response according to IMWG criteria:

Myeloma Disease Assessment – laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs)
Bone Marrow Biopsy	Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for conventional cytogenetics and fluorescent *in situ* hybridization. For subjects who give consent for correlative samples, an additional aspirate sample should be collected at Cycle 1 Day 15, at time of complete response (if applicable), and time of progression (Section7). Note: Cycle 1 Day 15 aspirate samples is for research purposes only and it is not required of the site to submit sample locally for pathology assessment. If Cycle 1 Day 15 sample is submitted as SOC, treatment does not have to be discontinued if progressive disease is shown on Cycle 1 Day 15 bone marrow. The first response evaluation should be after one full cycle of treatment (i.e. Cycle 2 Day 1).
Radiographic Imaging	If indicated

Plasmacytoma Evaluation	If indicated. May be performed by physical exam or imaging, whichever is clinically indicated and at the treating investigator's discretion. Additionally, for subjects who have a plasmacytoma or disease measured by imaging at baseline, plasmacytoma evaluations and radiographic imaging should be completed as per standard of care and in accordance with IMWG response criteria for multiple myeloma.

Progressive disease requires 2 consecutive assessments made at any time before classification of relapse or progression and/or institution of new therapy when clinically possible.

6.1.7 **Treatment Compliance**

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

6.1.8 **Instructions for Initiation of a New Cycle**

A new course of treatment may begin on the scheduled Day 1 of a new cycle if all of the following are met:

- ANC $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 30 \times 10^9$/L
- Any other study drug-related adverse event must have resolved to grades as specified in protocol (see Section 5.4)
- Serum uric acid and creatinine levels must return to baseline prior to carfilzomib doses during Cycles 1 and 2

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly, and a new treatment cycle will not be initiated until the toxicity has resolved, as described above.

If either carfilzomib or selinexor are held for the remainder of the previous cycle or the new cycle is delayed due to residual toxicity on the planned Day 1 of the next cycle, then the new cycle will be started at 1 dose decrement.

If a delay of starting a new cycle is greater than 21 days, the subject should be discontinued from treatment, unless continuing treatment is mutually agreed upon by the site Lead Principal Investigator at the University of Chicago and the Principal Investigator at the treating institution.

Dexamethasone may be discontinued without the subject discontinuing study treatment.

6.2 **Treatment Assignments**

6.2.1 **Dose Levels to be Tested in Phase 1**

The MTD for the phase I trial will be determined using the standard "3+3" design with the following modification: If, at a given dose level, 3 patients have been enrolled, no DLTs have as yet been observed but all three have not yet completed their first cycle of treatment, and an additional patient(s) become available for enrolment, expansion to 6 patients will be allowed. Then, if 0 or 1 of 6 patients experience a DLT, the dose will be escalated; otherwise if 2 or more DLTs

are observed among the 6 patients the MTD will have been exceeded. Table 6.1 summarizes the Dose Levels. Dose Level -1 and -2 will only be tested if Dose Level 1 exceeds the MTD.

Table 6.1 Phase 1 Twice Weekly Dosing Cohort Dose Levels

Dose Level[a]	Selinexor	Carfilzomib[b]	Dexamethasone
	Days 1, 3, 8, 10, 15, 17	**Days 1, 2, 8, 9, 15, 16 (Cycles 1-8)** **Days 1, 2, 15, 16 (Cycles 9+)**	**Days 1, 2, 8, 9, 15, 16, 22, 23**
-2	20mg	20 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
-1	20mg	20/27 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
1	**30 mg/m^2 (~40mg)**	**20/27 mg/m^2**	**20 mg (Cycle 1-4)** **10 mg (Cycle 5+)**
2a	40mg	20/36 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
2b	60mg	20/27 mg/m2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
3	60mg	20/36 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
4	60mg	20/45 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)
5	60mg	20/56 mg/m^2	20 mg (Cycle 1-4) 10 mg (Cycle 5+)

a) Once the MTD is established, an expansion cohort of 6-12 patients will be enrolled at that dose limited to carfilzomib refractory patients.

b) Carfilzomib will be initiated at 20 mg/m^2 on Days 1-2 of cycle 1 at all dose levels and then at the assigned dose level for the remainder of treatment.

c) Dose level 2a and 2b will enroll simultaneously alternating patient between the two dose levels.

Table 6.2 Phase 1 Weekly Dosing Cohort Dose Levels

Subjects will be enrolled in a 3+3 design into this cohort. Dose modifications will be applied as necessary (See dose modifications section).

Dose Level	Selinexor[a]	Carfilzomib[b,c]	Dexamethasone
	Days 1, 8, 15,22	**Days 1, 8, 15**	**Days 1,2, 8,9 15,16, 22, 23 (C1)** **Days 1, 8, 15, 22 (C2+)**
-1	80mg	20/56 mg/m^2	40 mg (Cycle 1-4) 20 mg (Cycle 5+)
1	**100mg**	**20/56 mg/m^2**	**40 mg (Cycle 1-4) 20 mg (Cycle 5+)**
2	100mg	20/56/70 mg/m^2	40 mg (Cycle 1-4) 20 mg (Cycle 5+)

a) Once the MTD is established, two expansion cohorts will be enrolled at that dose

b) Carfilzomib will be initiated at 20 mg/m^2 on Days 1-2 of cycle 1 at all dose levels and then at the assigned dose level for the remainder of treatment.

c) Carfilzomib treatment Days 1, 8, and 15 for cycles 1-8 then Days 1 and 15 for Cycles 9+

Dose Escalation Rules (for Phase 1 Twice Weekly Dosing Cohort)

Patients will be enrolled in cohorts of size 3, beginning at dose level 1. If 0 of 3 patients experience a DLT, the dose will be escalated for the next cohort. If 1 of 3 patients experience DLT, 3 more patients will be added at the same dose. Then, if no additional DLTs are observed (i.e., 1 of 6), the dose will be escalated for the next cohort. If 2 or more DLTs are observed at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD provided at least 6 patients have been studied at that dose. (If only 3 patients have been studied, 3 more will be added.) Expansion to 6 patients per cohort will be allowed if, at a given dose level, 3 patients have been enrolled, no DLTs have as yet been observed but all three have not yet completed their first cycle of treatment, and an additional patient(s) become available for enrolment. Then, if 0 or 1 of 6 patients experience a DLT, the dose will be escalated; otherwise if 2 or more DLTs are observed among the 6 patients the MTD will have been exceeded.once the MTD is reached, that dose cohort will be expanded to 12 carfilzomib-refractory patients to provide further safety data. If 3 or fewer of the 12 patients experience DLT, the twice weekly dosing cohort will terminate, with the given dose declared the RP2D; however, if 4 or more DLTs are observed, further dose de-escalation will occur.

Dose Escalation Rules (for Phase 1 Weekly Dosing Cohort)

Patients will be enrolled in cohorts of size 3, beginning at dose level 1. If 0 of 3 patients experience a DLT, the dose will be escalated for the next cohort of 3 patients treated at dose level 2. If 1 of 3 patients at DL1 experiences a DLT, 3 more patients will be added at the same dose. Then, if no

additional DLTs are observed (i.e., 1 of 6), the dose will be escalated for the next cohort. If 2 or more DLTs are observed at dose level 1, 3 patients will be treated at dose level -1. If there are no DLTs at DL-1, this dose will be used for the dose expansion cohort. If there is one DLT, 3 additional patients will be studied and if no further DLTs occur this dose will be used for the dose expansion cohort. If there are 2 or more DLTs, expansion of the weekly dosing schedule with further dose de-escalation may be considered.

Expansion to 6 patients per cohort will be allowed if, at a given dose level, 3 patients have been enrolled, no DLTs have as yet been observed but all three have not yet completed their first cycle of treatment, and an additional patient(s) become available for enrolment. Then, if 0 or 1 of 6 patients experience a DLT, the dose will be escalated; otherwise if 2 or more DLTs are observed among the 6 patients the MTD will have been exceeded. Once the MTD is reached, that dose cohort will be expanded to a total of 20 carfilzomib-refractory patients and 20 carfilzomib naïve/sensitive patients to provide further safety data. If 5 or fewer of the 20 patients (in each cohort) experience a DLT (<30%), the trial will terminate, with the given dose declared the RP2D; however, if 6 or more DLTs are observed, further dose de-escalation will occur.

6.3 **Definition of Dose Limiting Toxicities**

Subjects will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 (Appendix 3).

A DLT is defined as any of the below treatment emergent toxicities with attribution to one or more of the study drugs that occur during Cycle 1. Toxicities that occur in subsequent cycles will be handled through dose modifications (Section 6.4) but will not figure into the definition of MTD.

During cycle 1, a subject may not miss more than 1 planned dose of selinexor in order to be included in DLT assessment. Missed doses due to drug-related toxicities occurs when the subject does not take the dose on the planned calendar day (+24 hour window), and the dose will not be made up.

Non-hematologic:

- ≥ Grade 2 neuropathy with pain despite best supportive care
- Grade 3 nausea, vomiting, or diarrhea lasting for ≥3 days despite maximal antiemetic/antidiarrheal therapy
- Grade 3 fatigue and grade 3 anorexia lasting for > 7 days despite best supportive care
- Any Grade ≥ 3 toxicity despite best supportive care with the following exceptions:
    - Electrolyte abnormalities that are reversible and asymptomatic
    - Hair loss
    - ALT, AST or alkaline phosphatase levels in the setting of baseline Grade 2 elevations from disease

- Any non-hematologic toxicity requiring a dose reduction within Cycle 1
- Greater than 7 day delay in the initiation of Cycle 2 due to drug related toxicity persisting from Cycle 1 or drug related toxicity newly encountered on Day 1 of Cycle 2.

Hematologic:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting for > 7 days
- Febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 38.3ºC or a sustained temperature of ≥38°C for more than one hour.)
- Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L) lasting > 7 days despite dose delay
- Grade 3-4 thrombocytopenia associated with bleeding

- Any hematologic toxicity requiring a dose reduction within Cycle 1
- Greater than 7 day delay in the initiation of Cycle 2 due to drug related toxicity persisting from Cycle 1 or drug related toxicity newly encountered on Day 1 of Cycle 2.

Subjects who experience a DLT but are otherwise benefiting from treatment on this trial may continue on protocol after review with the Lead Principle Investigator.

Section 10.2 describes the dose escalation analysis plan.

6.4 Dose Modification Guidelines

6.4.1 Toxicity Management Guidelines

Carfilzomib will be withheld from subjects with:

- Grade 4 lymphopenia persisting for > 14 days, if lymphopenia was not pre-existing
- Grade 4 thrombocytopenia with active bleeding

For toxicities ≥ Grade 3 hematologic or non-hematologic toxicities, selinexor dosing may be maintained if the toxicity is considered not related to selinexor treatment.

Any AE of Grade 3 or greater should be considered to be at least possibly related to treatment with Selinexor.

If either carfilzomib or selinexor is reduced according to the guidelines in Table 6.2 or Table 6.3 but is later determined that the adverse event in question is not related to one or both of the drugs, re-challenging at the previous higher dose level is acceptable. This must first be reviewed and approved by the Lead Principal Investigator. If dexamethasone is held, selinexor should also be held until dexamethasone treatment has resumed.

The following table outlines the dose reduction guidelines for carfilzomib and Selinexor for thrombocytopenia and neutropenia:

Table 6.2 Dose Modification Guidelines for Hematologic Toxicities

Hematologic Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Thrombocytopenia Grade 3 (PLT < 50,000 -25,000/mm^3) without bleeding	No dose reductions required however subjects should receive supportive measures in accordance with institutional guidelines. Contact the Lead Principal Investigator to discuss the need to hold anticoagulation.	Platelet growth factors and/or transfusions per institutional guidelines. Platelet growth factors may require 2-4 weeks to take effect. Monitor platelet counts at least weekly. Consider holding anti-platelet agents. Begin (or maintain) once weekly selinexor dosing at the same dose level until resolved to Grade ≤ 2. Then return to twice weekly dosing (if applicable).

Hematologic Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Thrombocytopenia[a] Grade 4 (PLT < 25,000/mm3) without bleeding	Interrupt carfilzomib, follow CBC weekly. After first occurrence, treatment may resume at full dose when returns to Grade ≤3. If platelets fall again, interrupt carfilzomib, follow CBC weekly, and resume treatment at one dose decrement when returns to Grade ≤3 Contact the Lead Principal Investigator to discuss the need to hold anticoagulation.	Transfuse platelets per institutional guidelines. Strongly recommended use of platelet growth factors and/or transfusions. Platelet growth factors may require 2-4 weeks to take effect, and should be maintained until platelets are consistently >75,000/mm^3. Monitor platelet counts at least weekly. Consider holding anti-platelet agents. Hold selinexor dose until Grade ≤ 3 and follow above guidelines if Grade > 2
Thrombocytopenia Grade ≥3 with bleeding	Interrupt carfilzomib until resolved to ≤ grade 2 without bleeding, then dose reduce by 1 level	Transfuse platelets per institutional guidelines. Strongly recommended use of platelet growth factors and/or transfusions. Platelet growth factors may require 2-4 weeks to take effect, and should be maintained until platelets are consistently > 75,000/mm^3. Monitor platelet counts at least weekly. Consider holding anti-platelet agents. Hold dosing until Grade ≤ 2 and restart selinexor at 1 dose level reduction. if no bleeding for one cycle may consider dose escalation.
Neutropenia Grade 3 (ANC <1000-500/mm^3) *Use of GCSF is permitted in place of a dose reduction if neutropenia is the only toxicity that requires dose reduction. This does not apply when related to a DLT.	Temporarily discontinue carfilzomib and repeat CBC weekly. If resolved to ≤Grade 3 within the cycle, restart carfilzomib at same dose level and complete the cycle. For second occurrence, which resolves to ≤ grade 3 within the cycle, reduce carfilzomib and by one dose level and complete the cycle.	Implement and maintain neutrophil growth factors per institutional guidelines until neutrophils are consistently > 1,500/mm^3. If appropriate, initiate prophylactic anti-microbial agents. Maintain Dose.

Hematologic Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
	If not resolved to ≤ grade 2 within the cycle, start new cycle with one level dose reduction of carfilzomib when the criteria for a new cycle are met. Alternate drug dose reductions may be considered for subsequent occurrences if toxicity can be managed in this way.	
Neutropenia Grade 4 (ANC < 500/mm^3) *Use of GCSF is permitted in place of a dose reduction if neutropenia is the only toxicity that requires dose reduction. This does not apply when related to a DLT.	Temporarily discontinue carfilzomib and repeat CBC weekly. If resolved to ≤Grade 3 within the cycle, restart carfilzomib at same dose level and complete the cycle. For second occurrence, which resolves to ≤ grade 3 within the cycle, reduce carfilzomib and by one dose level and complete the cycle. If not resolved to ≤ grade 2 within the cycle, start new cycle with one level dose reduction of carfilzomib when the criteria for a new cycle are met. Alternate drug dose reductions may be considered for subsequent occurrences if toxicity can be managed in this way.	Implement growth factors per institutional guidelines. Reduce selinexor dose by one level. After implementation of growth factors, for patients who achieve neutrophil levels > 1,500/mm^3 for > 4 weeks (in the presence or absence of growth factors), selinexor dose may be re-escalated, with frequent monitoring is implemented.
Febrile Neutropenia (ANC <1000/mm3 with a single temperature of >38.3°C C or a sustained temperature of ≥38° C for more than one hour.)	Temporarily discontinue carfilzomib and repeat CBC weekly. If resolved to ≤ grade 2 within the cycle restart carfilzomib at same dose level and complete the cycle. For second occurrence, which resolves to ≤ grade 2 within the cycle, reduce carfilzomib by one dose level and complete the cycle. If not resolved to ≤ grade 2 within the cycle, start new cycle with one level dose reduction of carfilzomib when the criteria for a new cycle are met.	Implement and maintain neutrophil growth factors per institutional guidelines until neutrophils are consistently > 1,500/mm^3. Initiate appropriate broad-spectrum anti- microbial agents. Hold selinexor until fever resolves and patient is clinically stable. Restart dosing one dose level below. After implementation of growth factors, for patients who achieve neutrophil levels > 1,500/mm^3 for > 4 weeks, selinexor dose may be re-escalated, provided frequent monitoring is implemented.
Lymphopenia	Hold Carfilzomib if not pre-existing	≥ Grade 3 lymphopenia considered clinically significant

Hematologic Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Grade 4 lasting greater than 14 days		will require dose interruption until resolved to ≤ grade 2, then reduce by 1 dose level.
Anemia ≥Grade 3	Subjects should receive supportive measures in accordance with institutional guidelines	≥ Grade 3 anemia interruption of study treatment until resolved to ≤Grade 1. Blood transfusion should be considered as per site guideline. Second occurrence or clinically significant anemia interruption of study treatment until resolved to ≤Grade 1 then reduce by 1 dose level

a) Grade 4 thrombocytopenia without evidence of bleeding, carfilzomib dosing may occur at the discretion of the investigator. However, subjects should receive supportive measures in accordance with institutional guidelines.

Table 6.3 Dose Modification Guidelines for Non-Hematologic Toxicities

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Fatigue grade 2	**Maintain dose level**	Cycle 2+ up to 2 doses of KPT-330 can be held while supportive medications are instituted. .
Fatigue, Grade 3	*If persisting for >14 days:* Hold carfilzomib until resolved to Grade 1 or return to baseline. If not treatment related, carfilzomib may resume at full dose. If event recurs, reduce carfilzomib by 1-dose decrement	Ensure adequate caloric and fluid intake and assess volume status. Interrupt selinexor dosing until resolved to Grade ≤ 2, reduce dose of selinexor by 1 level (*Table 12.1*). If patient's fatigue is Grade ≤ 1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level.
Anorexia Grade 2	**Maintain dose level**	Up to 2 doses of KPT-330 can be held while supportive medications are instituted. .

Toxicity	**Dose Modification for Carfilzomib**	**Dose Modification for Selinexor**
Anorexia, Grade 3	Hold carfilzomib until resolved to Grade 1 or return to baseline. If not treatment related, carfilzomib may resume at full dose. If event recurs, reduce carfilzomib by 1-dose decrement	Interrupt dosing with selinexor until resolution to Grade ≤ 2. Add high calorie supplements. As described above, initiate supportive medications for anorexia. Restart selinexor at 1 dose level reduction (*Table 12.1*) once anorexia resolves to Grade ≤ 2 and follow the guidelines above. If patient's anorexia is Grade ≤1 for 4 weeks, then the dose of selinexor may be increased back to the previous dose level.
Anorexia Grade 4	Hold carfilzomib until resolved to Grade 1 or return to baseline. If not treatment related, carfilzomib may resume at full dose. If event recurs, reduce carfilzomib by 1-dose decrement	Interrupt dosing with selinexor until resolution to Grade ≤ 2 Add high calorie supplements. As described above, initiate supportive medications for anorexia. Restart selinexor at 1 dose level reduction.
Nausea/Emesis, Grade 2	No action required[a]	Implement one or more combinations of anti-nausea medications. If nausea does not resolve to Grade ≤1 inturrept treatment for 2 doses. Persistant grade 2 nausea under best supportive treatment should be modified as grade 3
Nausea/Emesis, Grade 3	No action required[a]	Implement one or more combinations of anti-nausea medications and interrupt dosing of Selinexor. Selinexor may be restarted with one dose level reduction when nausea is Grade ≤2 and adequate caloric and fluid intake have been achieved. If patient's emesis is Grade ≤1 for 2 weeks, then the dose of selinexor may be increased back to the previous dose level.

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Nausea/Emesis, Grade 4	No action required[a]	Interrupt dosing of Selinexor until resolution to grade<2. Restart Selinexor at 1 dose level reduction. Maxsmize anti emetic treatment and insure adequate caloric and fluid intake.
Hyponatremia, Grade 3 Asymptomatic	Hold carfilzomib until resolved to Grade 1 or return to baseline.	Discontinue Selinexor until resolved to grade ≤1 then reduce dose by 1 level. Check renal function, serum and urinary electrolytes, and rule out other causes. If patient's hyponatremia return to baseline for 2 weeks, then the dose of selinexor may be increased back to the previous dose level.
Hyponatremia, Grade 3 Symptomatic or <126meq/L	Hold carfilzomib until resolved to Grade 1 or return to baseline.	Discontinue Selinexor until resolved to grade ≤1 then reduce dose by 1 level. Check renal function, serum and urinary electrolytes, and rule out other causes.
Renal Calculated or measured Creatinine Clearance <30cc/min (Selinexor) or <30cc/min (Carfilzomib)	Hold until CrCl > 30 mL/minute; restart at 1 dose decrement	no dose modification are required
Hyperbilirubinemia ≥Grade 3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Discontinue Selinexor until resolved to Grade ≤2, then reduce one dose level Discontinuation of Selinexor is required if concurrent elevations of total bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed and other causes have been ruled out. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE Grade 2, respectively.

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
AST or ALT increased, or other hepatic toxicities, Grade 3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the treating physician. Frequent monitoring of liver function should then be implemented. 25% dose reduction in case of baseline or treatment emergent mild or moderate hepatic impairment. Withhold carfilzomib until resolved or returned to baseline. After resolution, consider if restarting carfilzomib is appropriate; may be reinitiated at a reduced dose with frequent monitoring of liver function. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.	Delay Selinexor until resolved to ≤ grade 2, then reduce by 1 dose level. Consider addition of S-adenosylmethionine (SAM) 400mg qd-qid. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be re-escalated to original dose. Discontinuation of Selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥CTCAE grade 2, respectively.

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
AST or ALT increased, or **other Hepatic Toxicities** Grade 4	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the treating physician. Frequent monitoring of liver function should then be implemented. 25% dose reduction in case of baseline or treatment emergent mild or moderate hepatic impairment. Withhold carfilzomib until resolved or returned to baseline. After resolution, consider if restarting carfilzomib is appropriate; may be reinitiated at a reduced dose with frequent monitoring of liver function. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.	Delay Selinexor until resolved to ≤ Grade 2, then reduce by 2 dose levels
Treatment Emergent Hypertension including hypertensive crises, Grade 2/3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	No dose adjustment is required. Dexamethasone dose modification should be considered.
Treatment Emergent Hypertension including hypertensive crises, Grade 4	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	No dose adjustment is required. If hypertension is secondary to dexamethasone, it should be stopped and restarted in a lower dose (8mg-12mg).

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Grade ≥ 3 Cardiac Abnormalities including Congestive Heart Failure	Any subject with ≥ grade 3 cardiac toxicities or symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be withdrawn from the study. If no resolution after 2 weeks, the subject will be withdrawn from the study.	N/A
Pericardial Effusion	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	N/A
Pericarditis	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	N/A
Heart problems including rapid, strong or irregular heartbeat **Heart attack, reduced blood flow to the heart, abnormal amount of fluid between the heart and lining around the heart, and swelling/irritation of the lining around the heart**	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction	N/A

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Thrombotic Microangiopathy (TMA)	Monitor for signs and symptoms of TTP/HUS. If TMA is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted at the previous dose. If the condition recurs, permanently discontinue carfilzomib.	N/A
Posterior Reversible Encephalopathy Syndrome (PRES)	If PRES is suspected, hold carfilzomib and consider evaluation with MRI for onset of symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If PRES is excluded, may resume carfilzomib at same dose if clinically appropriate. If PRES recurs, permanently discontinue carfilzomib.	N/A
Pulmonary Complications Grade ≥3 (including Pulmonary Hypertension)	= Grade 2: Carfilzomib attribution, Reduce drug: one level dose reduction ≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤Grade 2. Resume at one level dose reduction	N/A
Pulmonary Toxicities: Interstitial Lung Disease (inc. pneumonitis), Acute Respiratory Failure, and Adult Respiratory Distress Syndrome (ARDS), cough and cough with phlegm	≥ Grade 2 for Pneumonitis ≥ Grade 3 for ARDS ≥ Grade 4 for Respiratory Failure Carfilzomib attribution, hold drug until resolved to ≤Grade 1. Resume at one level dose reduction	N/A

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Blood clot in the lungs, fluid in the lungs, bleeding in the lungs	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction	N/A
Diarrhea Grade 2 (despite maximal anti-diarrheal medication)	No dose adjustment	Reduce Selinexor to one weekly until resolved to ≤ grade 1, then re-start twice weekly at the current dose level. If diarrhea returns as ≥ Grade 2, then reduce Selinexor dose by one dose level and dose once weekly until resolved to ≤ grade 1, then re-start twice weekly at reduced dose level
Diarrhea Grade ≥3 (despite maximal anti-diarrheal medication)	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline. If the diarrhea is clearly established as not related (i.e. C.difficile infection), restarting at the same dose level rather than 1 dose decrement is at the discretion of the treating investigator.	Rule out other causes of diarrhea, including infectious agents, supplements, and laxatives/stool softeners. Delay selinexor until resolved to Grade ≤2, then reinitiate selinexor at one dose level below. If patient is stable and diarrhea resolves (Grade 0 or baseline with or without anti-diarrheal agent(s)) for 4 weeks, then the patient's dose may be re-escalated.
Amylase and/or lipase elevations Grade ≥3, Asymptomatic	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Delay Selinexor until ≤ Grade 2, then restart at 1 dose level reduction. Rule out other causes of amylase/lipase elevation. If levels have not returned to ≤ Grade 2 within 3 weeks, then no further Selinexor may be given and the patient should discontinue permanently from the study. A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any grade 3 elevation of amylase and/or lipase.

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Amylase and/or lipase elevations Grade ≥3, Symptomatic	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Selinexor must be stopped immediately and proper supportive care provided. Evaluate enzyme levels at least twice weekly until resolution to ≤ Grade 1. Clinical manifestations should be monitored as needed until resolution or stabilization of the disease condition. Selinexor may be re-started at 2 dose levels below after resolution to ≤ Grade 1.
Tumor Lysis Syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold carfilzomib until all serum abnormalities have resolved. Take precautionary measures and resume at full dose or one level reduction at the investigators discretion.[b]	N/A
Herpes Zoster Any Grade	Hold carfilzomib until lesions are dry. Reinstitute at full dose	No dose adjustment if clinically stable
Infection Grade ≥3	Hold carfilzomib until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.	Hold Selinexor until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.
Neuropathy Treatment Emergent, Grade 2 with pain	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level. If neuropathy is <grade 1 or baseline for 4 weeks, then the patient's dose may be re-escalated.
Neuropathy Grade 3	Hold treatment until resolved or returned to baseline. Then restart at 1 dose decrement	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level. If neuropathy is <grade 1 or baseline for 4 weeks, then the patient's dose may be re-escalated.
Neuropathy Grade 4	Discontinue carfilzomib	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level
Sepsis	N/A	Selinexor Attribution, discontinue Selinexor.

Toxicity	Dose Modification for Carfilzomib	Dose Modification for Selinexor
Gastrointestinal Perforation	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	N/A
Other Grade ≥ 3	Hold treatment until resolved or returned to baseline. Then restart at 1 dose decrement	Delay dose until resolved to ≤ Grade 1, then reduce by 1 dose level

a) Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals)
b) Refer to section 6.7.2 for guidance and concomitant medications for TLS

Table 6.4 Dose Modification Guidelines for Toxicity Related to Dexamethasone

BODY SYSTEM SYMPTOM RECOMMENDED ACTION	BODY SYSTEM SYMPTOM RECOMMENDED ACTION	BODY SYSTEM SYMPTOM RECOMMENDED ACTION
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with	Hold dexamethasone until symptoms resolve. Restart

BODY SYSTEM SYMPTOM RECOMMENDED ACTION	BODY SYSTEM SYMPTOM RECOMMENDED ACTION	BODY SYSTEM SYMPTOM RECOMMENDED ACTION
	function +/- interfering with activities of daily living)	at 1 dose decrement. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or PO hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.

6.4.2 **Dose Reduction Guidelines**

The following tables summarize the dosing modifications for carfilzomib, selinexor and dexamethasone to manage toxicities. These guidelines pertain exclusively to Cycle 2+. Dose modifications are not permitted in Cycle 1 but rather these toxicities will be counted towards the DLT evaluation. At the treating investigator's discretion, subjects experiencing a DLT during Cycle 1 of the Phase 1 portion of the study may continue on treatment if toxicities recover and can be managed with dose modifications as described in section 6.4.1. The DLT will be counted towards the assessment of MTD.

During the expansion phase, dose modifications may be performed in Cycle 1+.

If the toxicities cannot be managed by dose modification, the subject has to be withdrawn from the trial.

Table 6.5 Carfilzomib Dose Reduction Guidelines

Nominal Dose	Dose -1	Dose -2	Dose -3	Dose -4
20 mg/m^2	15 mg/m^2	11 mg/m^2	n/a	n/a
27 mg/m^2	20 mg/m^2	15 mg/m^2	11 mg/m^2	n/a
36 mg/m^2	27 mg/m^2	20 mg/m^2	15 mg/m^2	11 mg/m^2
45 mg/m^2	36 mg/m^2	27 mg/m^2	20 mg/m^2	15 mg/m^2
56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2	20 mg/m^2
70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2

Table 6.6 Selinexor Dose Reduction Guidelines

Nominal Dose	Dose -1	Dose -2	Dose -3	Dose -4
40mg twice weekly	60 mg total per week: 60 mg on Day 1 OR [40 mg Days 1 and 20 mg on Day 3]	40 mg total per week: 40 mg on Day 1 OR [20 mg Days 1 and 3]	n/a	n/a
60mg twice weekly	80 mg total per week: 80 mg on Day 1 OR [40 mg Days 1 and 3]	60 mg total per week: 60 mg on Day 1 OR [40 mg Days 1 and 20 mg on Day 3]	40 mg total per week: 40 mg on Day 1 OR [20 mg Days 1 and 3]	n/a
100mg once weekly	80 mg total per week: 80 mg on Day 1 OR [40 mg Days 1 and 3]	60 mg total per week: 60 mg on Day 1 OR [40 mg Days 1 and 20 mg on Day 3]	40 mg total per week: 40 mg on Day 1 OR [20 mg Days 1 and 3]	n/a

Table 6.7 Dexamethasone Dose Reduction Guidelines

Nominal Dose	Dose -1	Dose -2	Dose -3	Dose -4
20 mg	12 mg	8 mg	4 mg	n/a
40 mg	20 mg	12 mg	8 mg	4 mg

If either carfilzomib or selinexor is reduced according to the guidelines in Table 6.2 or Table 6.3 but is later determined that the adverse event in question is not related to one or both of the drugs,

re-challenging at the previous higher dose level is acceptable. This must first be reviewed and approved by the Lead Principle Investigator. If dexamethasone is held, selinexor should also be held until dexamethasone treatment has resumed.

6.5 Treatment Discontinuation

Subjects will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary in order to protect their health (see reasons for withdrawal below).

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

- Disease Progression
- Non-compliance with study procedures
- Subject no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Treatment-related toxicity requiring treatment discontinuation
- Incidence or severity of AEs that indicates a potential health hazard to the subject
- For the fourth occurrence of the same Grade ≥3 non-hematological toxicity
- A delay in treatment >21 days unless approved by the Lead Principal Investigator
- Investigator discretion
- Requirement for alternative therapy
- Suspected or positive pregnancy
- Termination of the study by the sponsor

The Lead Principal Investigator should be contacted regarding any impending discontinuation of a study subject. If the reason for withdrawal is the occurrence of an AE, the subject will be followed until such events resolve, stabilize, and, according to the Treating Investigator's judgement, there is no need for further follow-up. The reason for withdrawal from study must be documented in the case report form.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT should be performed, if possible. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, with an explanation of why the patient is withdrawing from the study.

6.5.1 Duration of Follow Up

Long-term follow up will include an assessment for disease progression in subjects who did not progress during treatment. This should occur every 3 months (+/- 30 days) for 2 years from safety follow-up visit (30 days post-last study treatment or ASCT, if applicable).

6.6 Concomitant Medications

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medication(s) must be reported in the case report form (CRF) from time of signing the informed consent form through 30 days following the last dose of study drugs. 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. Patients should minimize the use of products containing acetaminophen, which can interfere with

the metabolism of Selinexor. For combination painkillers containing acetaminophen it is recommended that single agent opiates or aspirin combinations (when clinically acceptable) be substituted.

6.6.1 **Required Concomitant Medications**

All subjects must receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis. All subjects must receive prophylactic treatment to prevent anorexia and nausea including megesterol AND a 5-HT3 antagonist (e.g., ondansetron) according to section 6.1.3.2. Oral hydration is required prior to carfilzomib administration (Section 6.1.3.1)

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential.

6.6.2 **Optional and Allowed Concomitant Medications**

VTE prophylaxis with aspirin is optional but may be considered for all subjects. During cycle 1, allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator.

Glucocorticoids $\leq$ 10 mg oral prednisone (or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma, IBD, etc.) as needed.

Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

Use of Blood Products
Subjects may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the PI, Sponsor and Medical Monitor.

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

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

Radiation Treatment
If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drugs should be held for 3-5 days before the start of palliative radiation therapy and 3-5 days after palliative radiation therapy.

6.6.3 **Prohibited Concomitant Medication**
Although acetaminophen use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with 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 of up to 1 gm and selinexor up to 55 mg/m^2 (total dose 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 on selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 7 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

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

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

Other investigational agents should not be used during the study.

Ethanol ingestion is associated with glutathione depletion, therefore use of products containing ethanol should be minimized or avoided on selinexor dosing days.

6.7 Safety Considerations & Supportive Care

Supportive measures for optimal medical care shall be provided during participation in this clinical trial. Supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers), glucocorticoids, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. As needed and per individual study site institutional guidelines, prophylactic therapies, including antivirals, antifungals, and antibiotics, may be administered to ameliorate risks associated with non-malignant disorders or of immune system compromise.

6.7.1 First Dose Effect (Carfilzomib)

A “first dose effect” has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.

All subjects should be well hydrated (Section 6.1.3.1). Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment.

Should a “first dose” effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.

6.7.2 Tumor Lysis Syndrome

TLS, which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with carfilzomib. All subjects should follow the hydration guidelines outlined in Section 6.1.2.2. If subjects are considered to be at risk for TLS, hydration should be continued into Cycle 2 if clinically indicated.

MM subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

During Cycles 1 and 2, serum electrolytes and chemistries are closely monitored as outlined in Section 6.1.2. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g. serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated as clinically indicated. The Lead Principal Investigator should be consulted if there are further delays.

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of TLS must be reported to Amgen as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

6.7.3 **Renal Function**

Carfilzomib has not been fully characterized in subjects with creatinine clearance < 30 mL/min. It is critical that the subject's renal function is known at the time of dosing. Renal function, serum creatinine, and serum uric acid should be monitored closely during treatment with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Refer to Table 6.3 for guidance regarding dose reduction in subjects with compromised renal function.

6.7.4 **Anorexia**

Based on clinical observations on Schedules 1-3 with over 190 patients treated with Selinexor across this and the companion protocol in advanced hematologic tumor patients (OZM-040), the dose limiting toxicities (DLTs) are primarily related to anorexia with poor caloric and fluid intake leading to weight loss, fatigue and nausea.

Besides the required megase/5-HT3 prophylaxis, supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments may be administered as described below:

1. Appetite stimulants
2. Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for antiemesis and anorexia/cachexia [palliative care]) (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
3. NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

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

All patients will receive nutritional counseling, high caloric beverages (e.g., Ensure®) and prophylaxis with appetite stimulating agent(s), and anti-emetic agents. Patients with proper