MM 27

Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

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Date Final:	20 July 2011
Amendment 1:	27 September 2011
Amendment 2:	19 July 2012
Amendment 3:	26 March 2013
Amendment 4:	24 October 2013
Amendment 5:	03 August 2015

Clinical Trial Protocol Approval Page

Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

SCRI INNOVATIONS PROTOCOL NUMBER:	MM 27
TRIAL DRUG:	Panobinostat
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Amendment Number:	4	**Amendment Date:**	24 October 2013
Amendment Number	5	**Amendment Date**	03 August 2015

Study Chair/Coordinating Investigator (Name Printed or Typed)	**Study Chair/Coordinating Investigator Signature** Jesus Berdeja, M.D Sarah Cannon Research Institute	**Date**
Medical Monitor (Name Printed or Typed)	**Medical Monitor Signature** John D. Hainsworth, MD, Chief Scientific Officer Sarah Cannon Research Institute	**Date**
Sponsor Representative (Name Printed or Typed)	**Sponsor Representative Signature** Sheetal Khedkar, Director SCRI Innovations	**Date**

Clinical Trial Protocol Acceptance Form

Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

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Principal Investigator Name (Name Printed or Typed)	**Principal Investigator Signature** <*Insert Site Name and ID info as applicable*> <*Insert Site Location*>	**Date**

History of Amendments for MM 27

Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
1	**27 September 2011**	Exclusion criteria added, "Patient has not recovered from all therapy-related toxicities associated with prior treatments to < Grade 2 CTCAE."	• **Synopsis, Section 3.2 Exclusion Criteria #4**
		Section referring to panobinostat dose modifications for prolonged QTc interval has been modified to remove all references to **centralized readings of ECGs** by Novartis. All cardiac events should be treated according to standards and referred to a specialist if clinically indicated. Treatment decisions at the sites will be based on QTc as determined by the automated machine reading (or as measured and calculated by trained personnel at the site). ~~The centralized readings of ECGs by eRT will use the Fridericia correction: QTcR. Any final decisions concerning any dose modifications or patients discontinuing study drug permanently will be based on QTcF calculations assessed by eRT and evaluated via a discussion between the Study Chair.~~ If a patient	• **Section 6.2**
		References to transmit ECGs in Table 6: Criteria for Dose Reductions, Delays and/or Re-Institution Due to Drug-Related QTcF Abnormalities have been struck.	• **Table 6**
		Modifications to the Section - General Monitoring Principals #7. All ECGs will be reviewed by the treating physician prior to administering the dose of panobinostat. ~~If the QTc interval is > 480 msec, the ECG will be sent to eRT and the SCRI Study Chair via SCRI ORC facsimile for review.~~ ~~#11. Two ECG paper tracings will be printed each time an ECG is performed. One original will remain with the source documentation. The second original will be stored for submission to eRT at the end of each treatment cycle.~~	• **Section 6.2.1**

History of Amendments for MM 27 (continued)

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
1	**27 September 2011**	If any QTc interval is ≥500 msec, the patient must have at a minimum, hourly ECG monitoring until the QTc is <480 msec. In addition to the minimum hourly ECG monitoring, telemetry monitoring is strongly recommended. ~~ECGs must be transmitted to the Sponsor for prompt review.~~ Prior to a patient with a QTc interval >500 msec being discharged to home, that patient must have at least 2 consecutive, hourly ECGs obtained at least 6 hours after dosing that demonstrate a QTc interval of ≤480 msec.	• **Section 6.2.1**

History of Amendments for MM 27 (continued)

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
2	**19 July 2012**	As of December 31, ~~2008~~,***2010*** ~~twenty-two~~ ***32*** clinical studies, including clinical pharmacology, phase I and/or phase II, have either been completed or are ongoing. A total of ~~789~~ ***1589*** patients were enrolled and received at least one dose of panobinostat.	• **Section 1.2.1**
		2) Patients must have measurable disease requiring systemic therapy defined as at least one of the following: • Serum M-protein ≥~~1~~ ***0.5*** g/dl (≥~~10~~ ***5*** g/l) • Urine M-protein ≥200 mg/24 hrs Serum free light chain assay: involved free light chain level ≥10 mg/dl (≥100 mg/l) provided the serum free light chain ratio is abnormal	• **Synopsis,Section 3.1, #2**
		A maximum of ~~three~~ ***four*** dose levels will be evaluated.	• **Synopsis, Section 5,**
		Cycle 2 ~~– 12~~ ***and beyond***	• **Section 5.1, Table 1**
		Phase I Dose Level 3 Cycle 1, Carfilzomib dose is ~~36~~ ***45*** mg/m^2 IV D8, 9 15, 16	• **Section 5.2, Table 2**
		Phase I Dose Level 4 Cycle 1, Carfilzomib dose is ~~36~~ ***45*** mg/m^2 IV D8, 9 15, 16	• **Section 6.4**
		• CrCl changes are mostly transient, reversible, and non-cumulative. All patients should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, ~~must be obtained~~ ***are strongly encouraged*** ~~and reviewed~~ prior to each dose of carfilzomib during Cycles 1 and 2. ***The decision will be at the discretion of the treating physician***. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.	
		All patients must have the following assessments performed before receiving their first dose of protocol therapy ***(labs may be obtained up to 72 hours prior to treatment)***:	• **Section 7.2**
		The physical examination, ~~complete blood counts~~ ***CBCs***, ***CMP, uric acid*** and pregnancy test should be done <7 days prior to initiation of treatment.	

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
2	**19 July 2012**	• CBC, 3-part differential and platelets ***(-3 to Day 1 window allowed)***	• **Section 7.3.2, 7.3.4, 7.3.5**
		• CMP (see Section 7.1.) plus magnesium and phosphorus ***(-3 to Day 1 window allowed)***	
		• Uric acid (if clinically indicated) ***(-3 to Day 1 window allowed)***	
		• ***Vital signs (blood pressure, weight, pulse, and respiratory rate)***	• **Section 7.3.3, 7.3.4**
		• Measurement of vital signs (blood pressure, pulse, and respiratory rate and weight) (~~Day 1 only~~)	• **Section 7.3.5**
		Re-Staging – 4 Weeks***(-7 to Day 1 window allowed)***	• **Section 7.4**
		At any point in this treatment, patients suspected of PD will have response assessed again to confirm disease progression (i.e. 2 sets of response assessments at least 1 week apart). The outcomes will be reviewed by the study chair before the patient is removed from the study.	
		MR – Minimal Response	• **Section 9, Appendix C**
		Minimal Response (MR) should be reported for patients with relapsed refractory myeloma. When reported, the specific rate of MR should be distinguished from PR or better.	
		MM 27 is a ~~combined~~ Phase I/II study of carfilzomib in combination with panobinostat in the treatment of relapsed/refractory multiple myeloma.	• **Synopsis,Section 10**

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
3	**26 March 2013**	A maximum of four dose levels ~~**will be**~~ **were evaluated**. ~~Approximately 24 patients will be enrolled during the Phase I portion to establish the MTD~~ **No DLTs were seen during the Phase I portion.** *In the Phase II portion of this study, patients with relapsed/refractory multiple myeloma will receive treatment with the* ***dose level 4*** panobinostat and carfilzomib combination ~~established during Phase I~~. Patients will be reevaluated for response to treatment after each cycle (4 weeks). Patients with objective response or stable disease will continue treatment, with subsequent reevaluations every 4 weeks, until disease progression or unacceptable toxicity occurs. ***A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at dose level 5 of the combination of carfilzomib and panobinostat (see Table 3).*** ***If dose level 5 is found to be tolerable, then additional patients will be recruited into an expansion cohort, which will be open at all sites - a maximum total of 36 patients (including the ones recruited into the parallel Phase I study) will be treated at this dose level. Sites will be notified about the expansion cohort and patients will enter in the dose level confirmed in their enrollment confirmation from SCRI.*** Up to ~~54~~ **80** eligible patients will be treated in the Phase I/II study. The treatment schema for the study is shown in Figure 12.	• **Section 5**
		Addition of ***Table 3. Parallel Dose Escalation Study – Dose Level 5*** ***A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at dose level 5 of the combination of carfilzomib and panobinostat.*** ***Patients will enter in the dose level confirmed in their enrollment confirmation from SCRI.***	• **Section 5.2**

History of Amendments for MM 27 (continued)

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
3	**26 March 2013**	***If dose level 5 is found to be tolerable, then additional patients will be recruited at this dose level into an expansion cohort of 30 patients for Phase II for a total of 60 Phase II patients (30 patients for dose level 4 and 30 patients for dose level 5). A maximum of up to 80 total patients may be enrolled in this study (including patients from the dose escalation Phase I studies).***	• **Section 5.3**
		• Patients should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis. In addition, patients ~~should~~ ***may*** receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone (or imethroprim/sulfamethoxazole if fluoroquinoles are contradicted) ***if clinically indicated*****.**	• **Section 5.2**
		Addition to Table 4 Panobinostat and Carfilzomib Dose Level Modifications: Carfilzomib IV. 15mg/m2, 20mg/m2, 27mg/m2, 36mg/m2, 45mg/m2, ***56mg/m^2***	• **Section 6**
		MM 27 is a Phase I/Phase II study of carfilzomib in combination with panobinostat in the treatment of relapsed/refractory multiple myeloma. The total number of patients expected to be accrued is up to ~~54~~**80.** The Phase II efficacy objective is to evaluate the overall response in patients with relapsed/refractory multiple myeloma treated at the optimal dose level ***in the first 4 dose levels*** **established** during the Phase I portion, ***as well as the overall response in patients at dose level 5 if this dose level is found to be tolerable and patients are recruited into the expansion cohort. The response rates in the two dose levels will be evaluated separately***.	• **Synopsis,Section 10.1**

History of Amendments for MM 27 (continued)

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
3	**26 March 2013**	Following additions made: Efficacy will be evaluated for patients treated at the optimal dose level ***from the first 4 dose levels*** during Phase I together with those entered in the Phase II dose expansion portion of the study, and ***at dose level 5 (if this dose level is found to be tolerable and patients are recruited into the expansion cohort). The data from the two dose levels will be evaluated separately, and no formal statistical comparisons will be made between the two dose levels.***	• **Section 10.4**

History of Amendments for MM 27 (continued)

Amd #	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
4	**24 October 2013**	A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at ***additional*** dose level***s*** of the combination of carfilzomib and panobinostat (see Table 3). If ***additional*** dose levels ***are*** found to be tolerable, then additional patients will be recruited into an expansion cohort which will be open at all sites - a maximum total of 36 patients (including the ones recruited into the parallel Phase I study) will be treated at this dose level.	• **Section 5**
		Dose Level 6 added as follows: Carfilzomib Cycle 1 = ***20 mg/m^2 IV D1,2/ 56 mg/m^2 IV D 8, 9, 15, 16*** Cycle 2 to Progression = ***56 mg/m^2 IV D 1, 2, 8, 9, 15, 16*** Panobinostat Cycle 1 = ***20 mg D 1, 3, 5, 15, 17, 19*** Cycle 2 to progression = ***20 mg D 1, 3, 5, 15, 17, 19***	• **Table 3**
		Window for Holidays and Vacations ***For holidays and vacations it is preferred to plan ahead and adjust D1 of treatment +/- 48 hours of the cycle the patient plans to be gone for treatment so that the patient follows the treatment schedule per protocol. If it is not possible to adjust D1, the carfilzomib infusion days may be adjusted +/- 48 hours after cycle 1 for a holiday or vacation. There is no window allowed during cycle 1 and for the panobinostat doses except for D1 with the window described above.***	• **Section 5.1.3**
		A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at ***additional*** dose ***levels*** of the combination of carfilzomib and panobinostat.	• **Section 5.2**
			•

History of Amendments for MM 27 (continued)

Amd	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
4	**24 October 2013**	If ***a*** dose ***level in the parallel Phase I*** study is found to be tolerable, then additional patients will be recruited at this dose level into an expansion cohort of 30 patients for Phase II for a total of 60 Phase II patients (including 30 patients for dose level 4). ~~and 30 patients for dose level 5).~~ A maximum of up to 80 total patients may be enrolled in this study (including patients from the dose escalation Phase I studies).	• **Section 5.3**
		At any point in this treatment, patients suspected of PD will have response assessed again to confirm disease progression (i.e. 2 sets of response assessments at least 1 week apart). The outcomes will be reviewed by the study chair before the patient is removed from the study. ***After the second set of response assessments, if disease progression is confirmed, the date of the first set of response assessments should be recorded as the progression date***	• **Section 7.4**
		The Phase II efficacy objective is to evaluate the overall response in patients with relapsed/refractory multiple myeloma treated at the optimal dose level in the first 4 dose levels established during the Phase I portion~~, as well as~~. ***In addition***, the overall response in patients at ***any additional*** dose level ~~is found to be tolerable and patients are recruited into the expansion cohort~~ will be evaluated.	• **Section 10.1**
		Efficacy will be evaluated for patients treated at the optimal dose level from the first 4 dose levels during Phase I together with those entered in the Phase II dose expansion portion of the study, and at ***any additional*** dose ***level*** (if ~~this dose level is~~ found to be tolerable and patients are recruited into the expansion cohort).	• **Section 10.4**
		SCRI and SCRI Oncology Research Consortium have been updated to ***SCRI Development Innovations, LLC (SCRI Innovations)*** as appropriate.	• **Global Change**

History of Amendments for MM 27 (continued)

Amd	Amd Date	Revision(s) Made	Refer to this Section in the Protocol
5	**03 August 2015**	Moved hydration and safety guidelines for carfilzomib from Section 6.4	• **Section 5.1.2**
		Deleted duplicate concomitant medication information	• **Section 5.4**
		Added hypertensive events to Table 8	• **Section 6.3**
		Added management guidelines for carfilzomib-related events	• **Section 6.4**
		Amended to refer to the most current carfilzomib Investigator's Brochure.	• **Section 8.2.5**
		Updated precautions and risks for carfilzomib	• **Section 8.2.6**
		Amended response criteria for Progressive Disease as follows: Increase of ≥ 25% from the nadir in at least one of the following criteria: • serum M-protein (absolute increase must be ≥0.5 g/dL ~~and absolute value must be ≥1 g/dL~~)	• **Appendix C**

SYNOPSIS

Title of Study:	A Phase I/II Study of the Combination of Panobinostat and Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma	
Protocol Number:	MM 27	Study Phase: I-II
Study Centers:	Multicentered	
Objectives:	Primary Objectives: • To establish the optimal doses of carfilzomib in and panobinostat that can be administered to patients with relapsed/refractory multiple myeloma. (Phase I) • To evaluate the overall response in patients with relapsed/refractory multiple myeloma treated with the combination of panobinostat and carfilzomib. (Phase II) Secondary Objectives: • To evaluate time-to-progression (TTP) • To evaluate progression-free-survival (PFS) • To evaluate overall-survival (OS) • To evaluate safety	
Study Design:	This is an open-label, non-randomized Phase I/II study of patients with relapsed or refractory multiple myeloma. The Phase I study will determine the MTD of the combination of carfilzomib and panobinostat. The Phase I portion will follow a standard dose escalation design, beginning with dose level 1 (see Table 2). Patients will be assessed for dose-limiting toxicity (DLT) at each visit during Cycle 1 prior to receiving treatment. Dose modifications will not be permitted during Cycle 1 unless a patient experiences a DLT (see Section 5.2.2.). Treatment cycles will be administered at 28-day intervals. Panobinostat will be administered orally three times weekly during weeks 1 and 3 of each cycle (Days 1, 3, 5, 15, 17, 19). Carfilzomib will be administered intravenously on Days 1, 2, 8, 9, 15, and 16 of each cycle. During Cycle 1, the carfilzomib dose will be escalated after the Day 2 dose, if well tolerated. A maximum of four dose levels will be evaluated. Approximately 24 patients will be enrolled during the Phase I portion to establish the MTD. In the Phase II portion of this study, patients with relapsed/refractory multiple myeloma will receive treatment with the panobinostat and carfilzomib combination established during Phase I. Patients will be reevaluated for response to treatment after each cycle (4 week). Patients with objective response or stable disease will continue treatment, with subsequent reevaluations every 4 weeks, until disease progression or unacceptable toxicity occurs.	
Number of Patients:	Up to 80 eligible patients will be treated in this study.	

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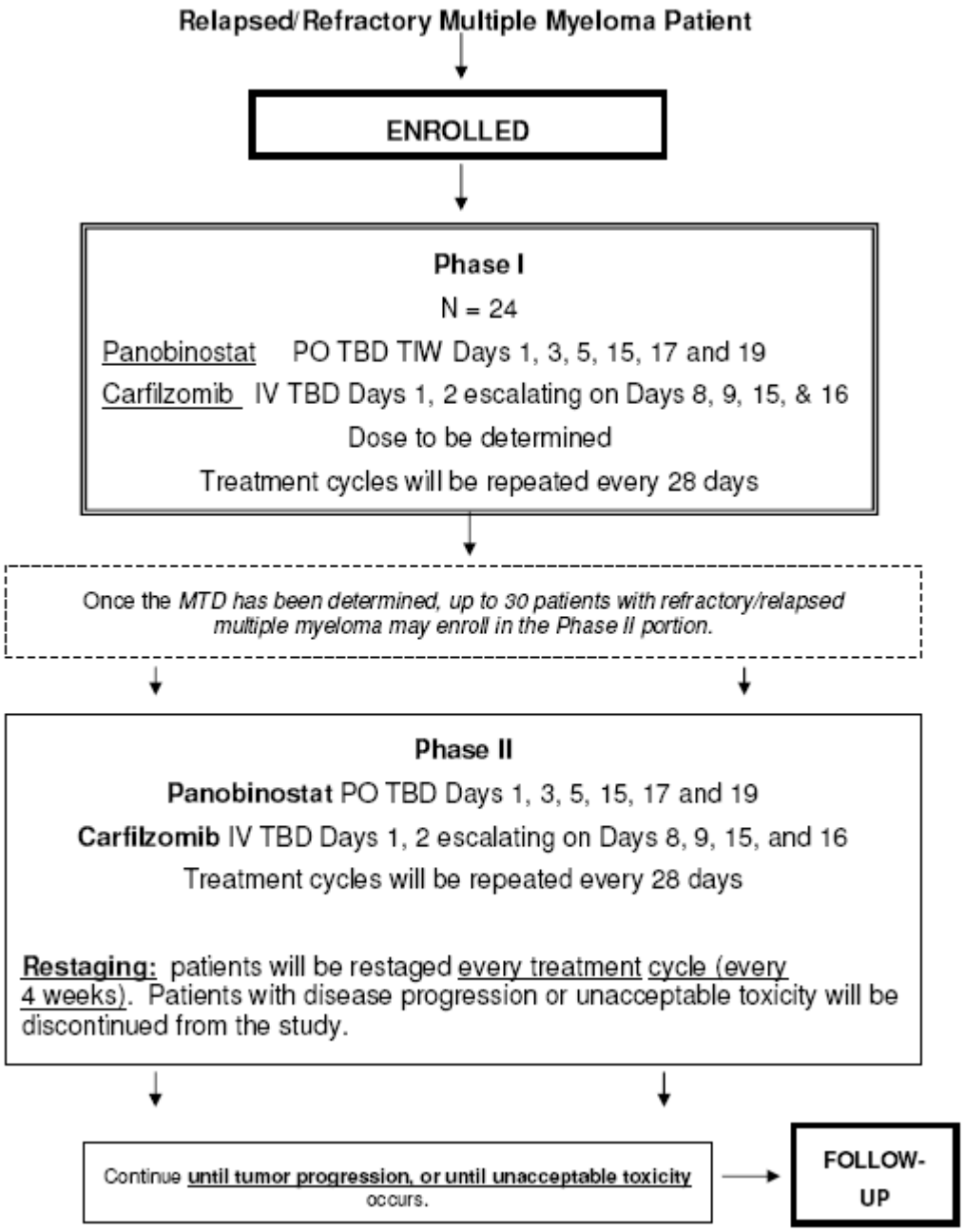
Drug Supply:	Panobinostat and Carfilzomib for use in the study will be provided to the Sponsor, SCRI Development Innovations, LLC (SCRI Innovations). Panobinostat will be provided to SCRI Innovations by Novartis Pharmaceuticals. Carfilzomib will be provided to SCRI Innovations by Onyx Pharmaceuticals. Supplies will be requested through SCRI Innovations.
Study Drug(s), Schedule, and Mode of Administration:	

SYNOPSIS

Inclusion Criteria:	1. Eligible participants must have multiple myeloma using standard criteria (Appendix B). 2. Patients must have measurable disease requiring systemic therapy defined as at least one of the following: • Serum M-protein ≥0.5 g/dl (≥5 g/l) • Urine M-protein ≥200 mg/24 hrs • Serum free light chain assay: involved free light chain level ≥10 mg/dl (≥100 mg/l) provided the serum free light chain ratio is abnormal 3. Must have progressed during or after at least one previous treatment regimen. Patients who have received previous high dose therapy/autologous stem cell transplantation are eligible. 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. (see Appendix A). 5. Must meet the following laboratory criteria: • Absolute neutrophil count (ANC) ≥1000/μL; • Platelets ≥70,000/μL; • AST or ALT and alkaline phosphatase (ALP) must be ≤2.5 x ULN, or ≤5 x ULN in patients with plasmacytomas of the liver; • Total bilirubin ≤1.5 x the institutional ULN; • Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥50 ml/min; • Serum potassium, calcium, magnesium WNL (These may be corrected prior to starting therapy, to make the patient eligible.) 6. Ability to swallow oral medications. 7. Baseline MUGA or ECHO must demonstrate left ventricular ejection fraction (LVEF) ≥ the lower limit of the institutional limits of normal. 8. Male or females ≥18 years of age. 9. Female patients must not be of child-bearing potential or must agree to use adequate contraceptive measures. 10. Male patients willing to use adequate contraceptive measures. 11. Willingness and ability to comply with the trial and follow-up procedures. 12. Ability to understand the nature of this trial and give written informed consent.
Exclusion Criteria:	1. Currently receiving or have received systemic cancer therapy (chemotherapy, biologic therapy) ≤21 days of initiating study therapy. For patients receiving small molecule targeted therapy, study treatment may begin >21 days after last dose or >5 half lives of previous treatment, whichever is shorter. Patients must have completed radiation therapy ≥7 days prior to starting study treatment. Patients must have recovered from or come to a new chronic stable baseline from all treatment-related toxicities. Dexamethasone or other high-dose steroid therapy must be stopped ≥7 days prior to starting study treatment. 2. Previous treatment with HDAC, DAC, HSP90 or valproic acid for treatment of cancer. 3. Requires valproic acid for any medical condition during the study ≤5 days prior to first panobinostat treatment. 4. Patient has not recovered from all therapy-related toxicities associated with prior treatments to < Grade 2 CTCAE.

SYNOPSIS

Exclusion Criteria:	5. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib). 6. Patients with pleural effusions requiring thoracentesis or ascites requiring paracentesis ≤14 days prior to study entry. 7. Patients using medications that have a risk of prolonging the QT interval or inducing Torsade de Pointes if treatment cannot be discontinued or switched to a different medication prior to receiving study drug (see Appendix F). 8. Patients with > grade 2 diarrhea. 9. Patients with impaired cardiac function, including any of the following conditions: • History or presence of sustained ventricular tachyarrhythmia. • Any history of ventricular fibrillation or Torsade de pointes. • Bradycardia defined as HR <50 bpm. Patients with pacemakers are eligible if HR ≥50 bpm. • Screening ECG with a QTc >450 msec. • Right bundle branch block + left anterior hemiblock (bifascicular block). • Patients with myocardial infarction or unstable angina ≤6 months prior to starting study drug. • Other clinically significant heart disease (e.g. CHF NY Heart Association class III or IV (Appendix D), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen). 10. Infection requiring IV antibiotics. 11. Patients with > grade 2 peripheral neuropathy. 12. Women who are pregnant or lactating. 13. Any concurrent medical illness that may impair the ability of the patient to tolerate study treatment and comply with the requirements of the study. 14. Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study. 15. Use of any non-approved or investigational agent ≤30 days prior to administration of the first dose of study drug. Patients may not receive any other investigational or anti-cancer treatments while participating in this study. 16. Presence of other active cancers, or history of treatment for invasive cancer ≤ 5 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
Statistical Method:	MM 27 is a Phase I/II study of carfilzomib in combination with panobinostat in the treatment of relapsed/refractory multiple myeloma. The total number of patients expected to be accrued is 80. The Phase I objective is to establish the optimal dose of carfilzomib with panobinostat that can be administered to patients with relapsed/refractory multiple myeloma. In this part of the trial, the optimal dose combination to be administered will be determined as described in Section 5.2. Since 3-6 patients will be treated in each cohort, the maximum number of patients treated in this phase will be 24.

SYNOPSIS

Statistical Method:	The Phase II efficacy objective is to evaluate the overall response in patients with relapsed/refractory multiple myeloma treated at the optimal dose level in the first 4 dose levels established during the Phase I portion. In addition, the overall response in patients at any additional dose levels will be evaluated. The response rates in the two dose levels will be evaluated separately. When used in the treatment of patients with relapsed/refractory multiple myeloma, the historical carfilzomib overall response rate is approximately 18%. It is hypothesized that the overall response rate for the treatment regimen of carfilzomib plus panobinostat is greater than that for patients treated with carfilzomib alone. A sample size of 27 achieves 80% power to detect an increase in the overall response rate to 36% (representing a 100% relative improvement) based on a one-sided test of proportion at an alpha level of 0.10. The sample size will be increased by 10% to account for potential non-evaluable patients and adjusted relative to the actual number of patients in the Phase I portion who are treated at the optimal dose level.

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1. INTRODUCTION

1.1. Background

Multiple myeloma accounts for approximately 20,000 new cancer diagnoses in the US each year (Jemal et al. 2010). Although myeloma patients usually benefit from initial therapy, sooner or later, treatment will be required for refractory or resistant disease.

1.2. Panobinostat

Panobinostat (LBH589) is a potent histone deacetylase (HDAC) inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule and a solution for intravenous (IV) injection. Both the oral and IV formulations are currently being investigated in ongoing phase I and phase II studies in advanced solid tumors and hematological malignancies.

1.2.1. Overview of the Clinical Experience

In clinical studies, both oral and intravenous (IV) formulations of panobinostat are being explored for further development. As of December 31, 2010, 32 clinical studies, including clinical pharmacology, phase I and/or phase II, have either been completed or are ongoing. A total of 1,589 patients were enrolled and received at least one dose of panobinostat. These patients constitute the safety population.

The most common adverse events seen have been grades 1 and 2 nausea, diarrhea, and neutropenia. Additional common toxicities have included fatigue and vomiting. With the exception of thrombocytopenia, grades 3 and 4 adverse events were uncommon. The occurrence of thrombocytopenia appears to be related to the underlying disease (incidence is higher in patients with malignancies that involved the bone marrow e.g., acute myeloid leukemia, chronic myeloid leukemia, multiple myeloma, myelodysplastic syndrome, etc.) as well as the mode and interval of administration, with oral every other week schedules producing the least amount of toxicity.

The most common electrocardiogram (ECG) findings adjudicated by central review included post-baseline increase in frequency of sinus tachycardia, T-wave changes (flat, biphasic, inverted), as well as depressed ST segment findings.

The most frequently encountered laboratory abnormalities were thrombocytopenia, neutropenia, some degree of anemia, and fluctuations in electrolytes that might not be clinically relevant.

Thyroid function, as monitored by the measurement of TSH and free T4, did not reveal overt hyper- or hypothyroidism, with fluctuations in TSH values being within normal limits.

1.2.2. Single Dose Panobinostat Administration and ECG Monitoring

In the initial Phase I study utilizing the IV formulation of panobinostat administered on consecutive days, significant QTcF interval abnormalities were noted, with one patient experiencing Torsade de pointes. With the introduction of the oral formulation and the three-times-weekly (TIW) administration, extensive monitoring has been conducted in all clinical trials of panobinostat.

As of December 31, 2009 cardiac safety data were available for 532 patients receiving TIW dosing and 70 patients TIW every other week (QOW). All of these patients underwent intensive pre- and post-dose ECG recording to monitor the occurrence of QTcF changes as well as to capture other ECG abnormalities. There is increasing evidence that the most common finding is a QTcF increase of ≤60 msec (CTCAE grade 1) from baseline in both schedules. QTcF prolongation to >480 msec has been mostly observed at the highest oral dose of 60 mg given TIW. There were no cases of Torsade de pointes with either schedule for oral panobinostat.

To date, an increase from of ≤60 msec (CTCAE grade 1) was observed in 98 patients (16.7%) in TIW schedule. An increase of >60 msec from baseline in 12 patients (2%) is less frequently reported. QTcF prolongation translating in an absolute value above baseline to ≤480 msec or to ≤500 msec occurred in 61 patients (10.4%) and in 5 patients (0.8%), respectively. Absolute QTcF prolongation above 500 msec was reported in 3 patients (0.5%) treated at doses of 20 and 60 mg (2 and 1 patients, respectively).

To date, an increase from baseline of ≤60 msec (CTCAE grade 1) was observed in 15 patients out of 70 patients (21.4%) in the TIW QOW schedule. An increase of >60 msec from baseline in 4 patients (5.7%) was less frequently reported. QTcF prolongation translating in an absolute value above baseline to ≤480 msec or to ≤500 msec occurred in 9 out of 70 patients (12.9%) and in 1 out of 70 patients (1.4%), respectively. Absolute QTcF prolongation above 500 msec was not observed.

Across all doses in both schedules, the most frequent ECG findings were T-wave abnormalities (flat, inverted, or biphasic T-waves) and depressed ST segment. An increased frequency of sinus tachycardia was also observed.

In addition, an assessment of grade 3 or 4 cardiovascular events of clinical relevance (angina pectoris, cardiac failure, cardiac arrest, CHF, pericardial effusion, DVT, and pulmonary embolism) was conducted for both dose schedules. The events are described by disease group.

In Group 1 (N= 229) treated with 20 mg TIW, angina pectoris was reported in 4 cases (1.7%), cardiac failure, CHF and DVT in 2 cases (0.9%) each, cardiac arrest and pericardial effusion in 1 case (0.4%) each. At 40 mg, TIW pericardial effusion and pulmonary embolism were reported in 2 cases (1.3%) each (N=153). None of these

events were noted in the few patients (N=5) treated at the dose of 60 mg TIW. For group 2 at the dose of 20 mg TIW (N=64), DVT and pulmonary embolism, cardiac failure and pericardial effusion were noted in 1 instance (1.6%) each. A second event of cardiac failure was reported at the dose of 30 mg TIW in 8 treated patients (12.5%).

For group 1 at 50 mg TIW QOW (N=15), cardiac failure and CHF were reported in 1 case (6.7 %) each. For group 2 at 45 mg TIW QOW (N-9), MI was reported in 1 case (11.1%).

Given the nature of the disease under treatment, patients with such events have many risks factors such as underlying cardiovascular disease and concomitant medications. As such, it is yet to be determined whether panobinostat is causally related to these cardiovascular adverse events.

1.2.3. Phase Ib Study in Patients with MM

The primary objective of the CLBH589B2207 trial is to determine the maximum-tolerated dose (MTD) of oral panobinostat when combined with bortezomib in patients with relapsed or refractory MM. A total of 38 patients have been enrolled into five completed dose cohorts: (I) 10 mg panobinostat (TIW) + 1.0 mg/m^2 bortezomib (IV, Days 1, 4, 8, 11) q 21-days, (II) 20 mg panobinostat + 1.0 mg/m^2 bortezomib, (III) 20 mg panobinostat + 1.3 mg/m^2 bortezomib and (IV) 30 mg panobinostat + 1.3 mg/m^2 bortezomib, (V) 25 mg panobinostat +1.3 mg/m^2 bortezomib. Enrollment into Cohort VI at 20 mg panobinostat + 1.3 mg/m^2 bortezomib has enrolled 1 patient as of the 09-Oct-03 cutoff. In Cohorts I-V, the median number of prior therapies was two (range 1-7); 30 patients had at least one prior auto-SCT. Out of 22 bortezomib pre-treated patients 13 were refractory to prior bortezomib therapy (10 PD and 3 SD on bortezomib according to IMWG'08). Median time on study was longest in Cohort 3 at 109 days (range 7- 424) (Anderson et al. 2010).

The combination of panobinostat and bortezomib was safe and tolerated in Cohorts I, II, III and IV. Dose-limiting toxicities (DLT) were reported in cohorts II (one patient with Grade 4 afebrile neutropenia) and cohort IV (4 DLTs: 2 Grade 4 TCPs, requiring 2 consecutive platelet transfusions), Grade 3 pneumonia and Grade 3 fatigue. In cohort V, the dose of panobinostat was de-escalated to 25 mg. In this Cohort, one DLT has been seen to date (Grade 4 thrombocytopenia, Grade 3 asthenia, Grade 3 dizziness).

Hematological AEs have been common, including Grade 3/4 TCP (30 in 38 patients), neutropenia (23) and anemia (6). Non-hematological AEs (all grades) included diarrhea (23), fever (17), nausea (18), fatigue (16), and asthenia (13). A total of 2,200 ECGs have been analyzed: no QTcF prolongations from BL >60 msec nor absolute QTcF time duration >480 msec were noted. No QTcF prolongation ≥Grade 1 were seen.

Although Grade 3/4 TCP occurred frequently it was manageable with dose reduction/interruption and platelet transfusion. TCP (Grade 4) was to be managed by platelet transfusions before study drug dose omission/reduction was allowed. Thrombocytopenia as the DLT in three patients in cohorts IV and V. No patients experienced hemorrhagic events in association with Grade 3/4 TCP. A detailed review

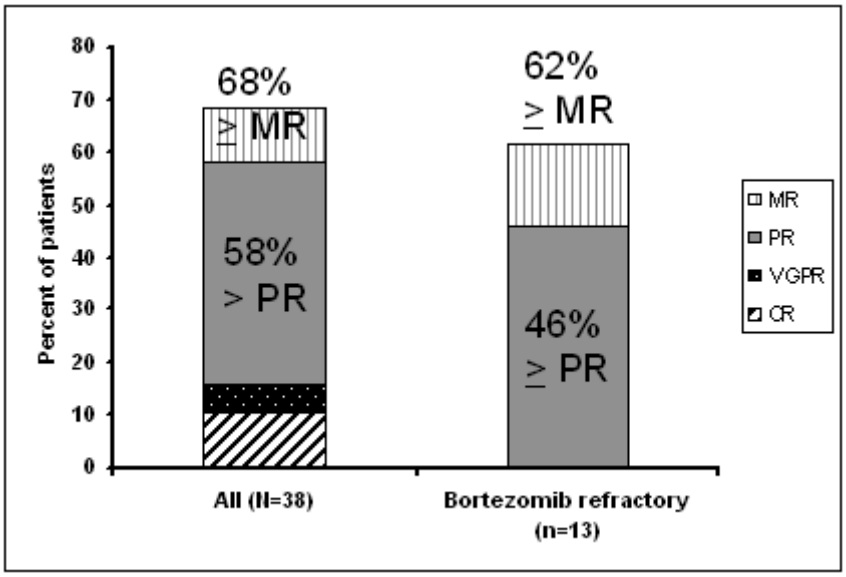
of dose reductions and interruptions as well as timing of dose modifications and platelet transfusions relative to time to and duration of TCP in patients enrolled in cohorts I - IV revealed the following findings:

The majority of patients experienced TCP within the first 2 cycles. This resulted in dose reductions, interruptions and/or dose delays. The time course of TCP appeared predictable with the platelet count nadir in most cases occurring at the end of the second week, or during the 3rd, i.e. last week of the first or second treatment cycle. No dose relationship was seen with a similar number of Grade 3/4 TCP episodes during the three first cohorts. A similar number of patients receiving platelet transfusions (n=1/7, 5/7, and 3/8 in cohorts I, II, and III), and administrations of platelet transfusion (n=15 in cohorts I-V). With 109 days (compared to 52 and 76 days in cohorts I and II) median panobinostat exposure time was longest in cohort III in spite of dose reductions/interruptions. Anecdotal cases have been reported in which patients were clinically benefiting from panobinostat, but were unable to maintain the QW dosing schedule even after dose reduction.

Clinical efficacy was observed in all 5 cohorts with 26 responses (MR or better) in 38 evaluable patients. For 22 patients, the best response was at least PR (58%) including 2 VGPR, and immunofixation (IF) - negative CR in 4 pts. Responses were seen in the subset of patients refractory to prior bortezomib suggesting a strong clinical correlate of the preclinical synergism of the combination of panobinostat and bortezomib: 8 of 13 bortezomib-refractory patients responded, including 6 with a PR (46%) and 2 with a MR (Figure 1). One patient had received bortezomib as part of an induction regimen prior to autologous SCT, and experienced a VGPR (cohort I).

According to the protocol Dex could be introduced in cycle 2 (or 3) and this was done in 9 patients including 8 out of 18 responders (2 in cohort I, 2 in cohort II, 1 in cohort III and 3 in cohort IV). Five patients received Dex after first documentation of response and 3 patients before. Eleven of 18 patients with a response did not receive Dex at all, including several patients refractory to bortezomib. In cohort III all 8 patients experienced a clinical benefit with 7 responding [immunofixation-negative CR (n=2), PR (n=3) including one bortezomib refractory patient, MR (n=2) including one bortezomib refractory patient] and one with SD. Dose modifications did not affect efficacy since the highest number of responders seen to date was in cohorts III, IV and V where a higher dose of bortezomib (1.3 mg/m^2 biweekly) were used.

Figure 1. CLBH589B2207 Response Rates for All Patients and Bortezomib Refractory



1.3. Carfilzomib

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib (Demo et al. 2007 and Arastu-Kapur et al. 2008).

1.3.1. Carfilzomib Phase 2 Single Agent Experience

Two Phase 2 clinical studies are ongoing with carfilzomib in multiple myeloma (MM) patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM. In both studies, patients were treated with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 every 28 days. In these studies there were four cases of suspected or documented tumor lysis syndrome (TLS) prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia, gastrointestinal, and dyspnea. There were reported cases of increased in serum creatinine that were primarily < Grade 2. A very low rate of treatment-emergent peripheral neuropathy (2.2% Grade 3/4), was observed in PX-171-003-A0 despite the fact that 78% of patients had Grade 1/2 neuropathy upon study entry (Jagannath et al. 2009).

Patients in the PX-171-003-A0 study had progressive myeloma and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug

(usually lenalidomide). In this study, 18% of patients had partial responses, with 7% minor responses and 41% stable disease. The median time to progression on the PX-171-003-A0 study was 5.1 months with duration of response of 7.4 months (Jagannath et al. 2009).

A "stepped up" dosing schedule, referred to as 20/27 mg/m^2, has subsequently been incorporated into the PX-171-003 study in order to maximize the clinical benefit of carfilzomib. Patients receive 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. The study completed enrollment of 266 patients by the end of 2009 and may form the basis for an accelerated approval NDA filing by the end of 2010. To date, this dosing schedule has been well tolerated (Alsina et al. 2007). An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 2.2%, most likely due to hydration and very low dose dexamethasone. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 15% Grade 1/2 and one (0.7%) Grade 3/4 event reported to date on PX-171-003-A18. In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date (Jagannath et al. 2009)

In the PX-171-004 study, a first cohort of patients received 20 mg/m^2. The subset of patients (N=54) that had not previously received bortezomib had an overall response rate (ORR) of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR) (Wang et al. 2009 and Seigel et al. 2009). The median time to progression (TTP) was 7.6 and 5.3 months in these two groups, respectively.

1.3.1.1. Carfilzomib PX-171-007 Trial

The PX-171-003-A1 study enrolled 269 patients with relapsed and refractory multiple myeloma by the end of 2009. The Phase I single agent carfilzomib dose escalation study was ongoing as of July, 2009 with over 65 solid tumor patients starting treatment in the initial Phase II at the 36 mg/m^2 dose. A review of the tolerability of 36 mg/m^2 carfilzomib in these patients indicates that this regimen was very well tolerated with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m^2 carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m^2 with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

Recently in the PX-171-007 trial, patients have been treated with carfilzomib given as a 30-minute infusion in order to minimize C_{max}-related infusion events. The PX-171-007 trial was amended and does of 20/36 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m^2 for all subsequent doses), 20/45, 20/56 mg/m^2 and so forth are being investigated. Doses of 20/56 mg/m^2 are currently being given in two separate cohorts of patients with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose level (20/56 mg/m^2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m^2, dexamethasone was increased from 4mg/dose to 8mg with the 56mg/m^2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56mg/m^2 with tolerability. Patients with advanced, refractory MM being treated at 36mg/m^2 and 45mg/m^2 have shown very good tolerability (>6 months in some cases) with documented minimal and partial responses in these heavily pretreated patients. These data indicate that carfilzomib 30-minute infusion can be given at very high levels, with >95% inhibition of blood proteasome levels achievable and with (at least) acute tolerability. As a result, carfilzomib is now administered as a 30-minute infusion if the dose is ≥36mg/m^2.

In addition to the above observations, a phase I study of carfilzomib in patients with relapsed and refractory multiple myeloma was reported in abstract form at the 2009 American Society of Hematology meeting which demonstrated that carfilzomib can be safely administered to patients with substantial renal impairment (CrCl < 30, including patients on dialysis) without dose adjustment (Badros et al. 2009). These data indicate that carfilzomib does not exacerbate underlying renal dysfunction, and confirm the “pre-renal” etiology of the BUN/creatinine elevations observed with IV bolus carfilzomib.

1.4. Rationale for the Study

Relapsed/refractory MM is an incurable disorder with a poor prognosis. Carfilzomib is a novel proteasome inhibitor with activity in this setting. Panobinostat is a pan-deacetylase inhibitor which has shown synergistic cytotoxicity in vitro and in vivo with proteasome inhibitors. The combination should enhance the activity of both agents against myeloma cells. In the Phase I part of the trial, the optimal doses of the combination of carfilzomib and panobinostat will be determined. Assuming this combination is feasible, the Phase II portion will proceed, using the doses determined in Phase I. This study will be conducted at multiple study sites by the SCRI Development Innovations, LLC (SCRI Innovations).

2. STUDY OBJECTIVES

2.1. Primary Objective

- To establish the optimal doses of carfilzomib and panobinostat that can be administered to patients with relapsed/refractory multiple myeloma. (Phase I)
- To evaluate the overall response in patients with relapsed/refractory multiple myeloma treated with the combination of panobinostat and carfilzomib (Phase II)

2.2. Secondary Objectives

- To evaluate time-to-progression (TTP)
- To evaluate progression-free-survival (PFS)
- To evaluate overall-survival (OS)
- To evaluate safety

3. PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

3.1. Inclusion Criteria

1. Eligible participants must have multiple myeloma using standard criteria (Appendix B).
2. Patients must have measurable disease requiring systemic therapy defined as at least one of the following:
    - Serum M-protein ≥0.5 g/dl (≥5 g/l)
    - Urine M-protein ≥200 mg/24 hrs
    - Serum free light chain assay: involved free light chain level ≥10 mg/dl (≥100 mg/l) provided the serum free light chain ratio is abnormal
3. Must have progressed during or after at least one previous bortezomib-containing treatment regimen. Patients who have received previous high-dose therapy/autologous stem cell transplantation are eligible.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. (see Appendix A).
5. Must meet the following laboratory criteria:
    - Absolute neutrophil count (ANC) ≥1000/µL;
    - Platelets ≥70,000/µL;
    - AST or ALT and alkaline phosphatase (ALP) must be ≤2.5 x ULN, or ≤5 x ULN in patients with plasmacytomas of the liver;
    - Total bilirubin ≤1.5 x the institutional ULN;
    - Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥50 ml/min;
    - Serum potassium, calcium, magnesium WNL (These may be corrected prior to starting therapy, to make the patient eligible.)
6. Ability to swallow oral medications.
7. Baseline MUGA or ECHO must demonstrate left ventricular ejection fraction (LVEF) ≥ the lower limit of the institutional limits of normal.

8. Male or females ≥18 years of age.
9. Female patients must not be of childbearing potential or must agree to use adequate contraceptive measures.
10. Male patients willing to use adequate contraceptive measures.
11. Willingness and ability to comply with the trial and follow-up procedures.
12. Ability to understand the nature of this trial and give written informed consent.

3.2. Exclusion Criteria

1. Currently receiving or have received systemic cancer therapy (chemotherapy, biologic therapy) ≤21 days of initiating study therapy. For patients receiving small molecule targeted therapy, study treatment may begin >21 days after last dose or >5 half lives of previous treatment, whichever is shorter. Patients must have completed radiation therapy ≥7 days prior to starting study treatment. Patients must have recovered from or come to a new chronic stable baseline from all treatment-related toxicities. Dexamethasone or other high-dose steroid therapy must be stopped ≥7 days prior to starting study treatment.
2. Previous treatment with HDAC, DAC, HSP90 or valproic acid for treatment of cancer.
3. Requires valproic acid for any medical condition during the study ≤5 days prior to first panobinostat treatment.
4. Patient has not recovered from all therapy-related toxicities associated with prior treatments to < Grade 2 CTCAE.
5. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
6. Patients with pleural effusions requiring thoracentesis or ascites requiring paracentesis ≤14 days prior to study entry.
7. Patients using medications that have a risk of prolonging the QT interval or inducing Torsade de Pointes if treatment cannot be discontinued or switched to a different medication prior to receiving study drug (see Appendix F).
8. Patients with > grade 2 diarrhea.
9. Patients with impaired cardiac function, including any of the following conditions:
    - History or presence of sustained ventricular tachyarrhythmia.
    - Any history of ventricular fibrillation or Torsade de pointes.
    - Bradycardia defined as HR <50 bpm. Patients with pacemakers are eligible if HR ≥50 bpm.
    - Screening ECG with a QTc >450 msec.
    - Right bundle branch block + left anterior hemiblock (bifascicular block).
    - Patients with myocardial infarction or unstable angina ≤6 months prior to starting study drug.

- Other clinically significant heart disease (e.g. CHF NY Heart Association class III or IV (Appendix D), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).

10. Infection requiring IV antibiotics.
11. Patients with > grade 2 peripheral neuropathy or with uncontrolled pain.
12. Women who are pregnant or lactating.
13. Any concurrent medical illness that may impair the ability of the patient to tolerate study treatment and comply with the requirements of the study.
14. Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study.
15. Use of any non-approved or investigational agent ≤30 days prior to administration of the first dose of study drug. Patients may not receive any other investigational or anti-cancer treatments while participating in this study.
16. Presence of other active cancers, or history of treatment for invasive cancer ≤ 5 years. Patients with stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e. non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

3.3. Withdrawal Criteria

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Patient requests to withdraw from the trial and discontinue treatment
- Patient requests to discontinue treatment
- Pregnancy (see Section 3.3.1)
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Non-compliance/lost to follow-up

Patients who have been discontinued from trial treatment will not be replaced. After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of trial drug. All new AEs occurring during this period must be reported and followed until resolution, or after 30 days (whichever comes first), unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for

this decision in the patients' medical records and as a comment on the Case Report Form (CRF).

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to grade 1 or 2, or 30 days after the date of withdrawal (whichever comes first), unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.3.1. Pregnancy

During the course of the trial, all female patients of childbearing potential must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a patient may be pregnant prior to administration of trial drug(s), the trial drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any trial drug(s), and must be discontinued from the trial.

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug(s), the trial drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drug(s) must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the SCRI Innovations study chair as soon as possible. If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form (a paper report form, not available within EDC system) should be completed and faxed to the sponsor or designee. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 11.5.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approvals of this protocol and consent form are required prior to patient enrollment. Registration must occur prior to the initiation of protocol therapy.

Eligible patients will be enrolled through SCRI Innovations. Participating sites may call 1-877-MY-1-SCRI for assistance, or fax a completed and signed Enrollment Form to the SCRI Innovations Enrollment Desk. The SCRI Innovations fax registration number is (866) 699-0258 and is available, Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via fax within 24 hours, or by the next business day.

5. STUDY DESIGN

This is an open-label, non-randomized Phase I/II study of patients with relapsed or refractory multiple myeloma.

The Phase I study will determine the MTD of the combination of carfilzomib and panobinostat. The Phase I portion will follow a standard dose escalation design, beginning with dose level 1 (see Table 2). Patients will be assessed for dose-limiting toxicity (DLT) at each visit during Cycle 1 prior to receiving treatment. Dose modifications will not be permitted during Cycle 1 unless a patient experiences a DLT (see Section 5.2.2.). Treatment cycles will be administered at 28-day intervals. Panobinostat will be administered orally three times weekly during weeks 1 and 3 of each cycle (Days 1, 3, 5, 15, 17, 19). Carfilzomib will be administered intravenously on Days 1, 2, 8, 9, 15, and 16 of each cycle. During Cycle 1, the carfilzomib dose will be escalated after the Day 2 dose, if well tolerated.

A maximum of four dose levels were evaluated. No DLTs were seen during the Phase I portion.

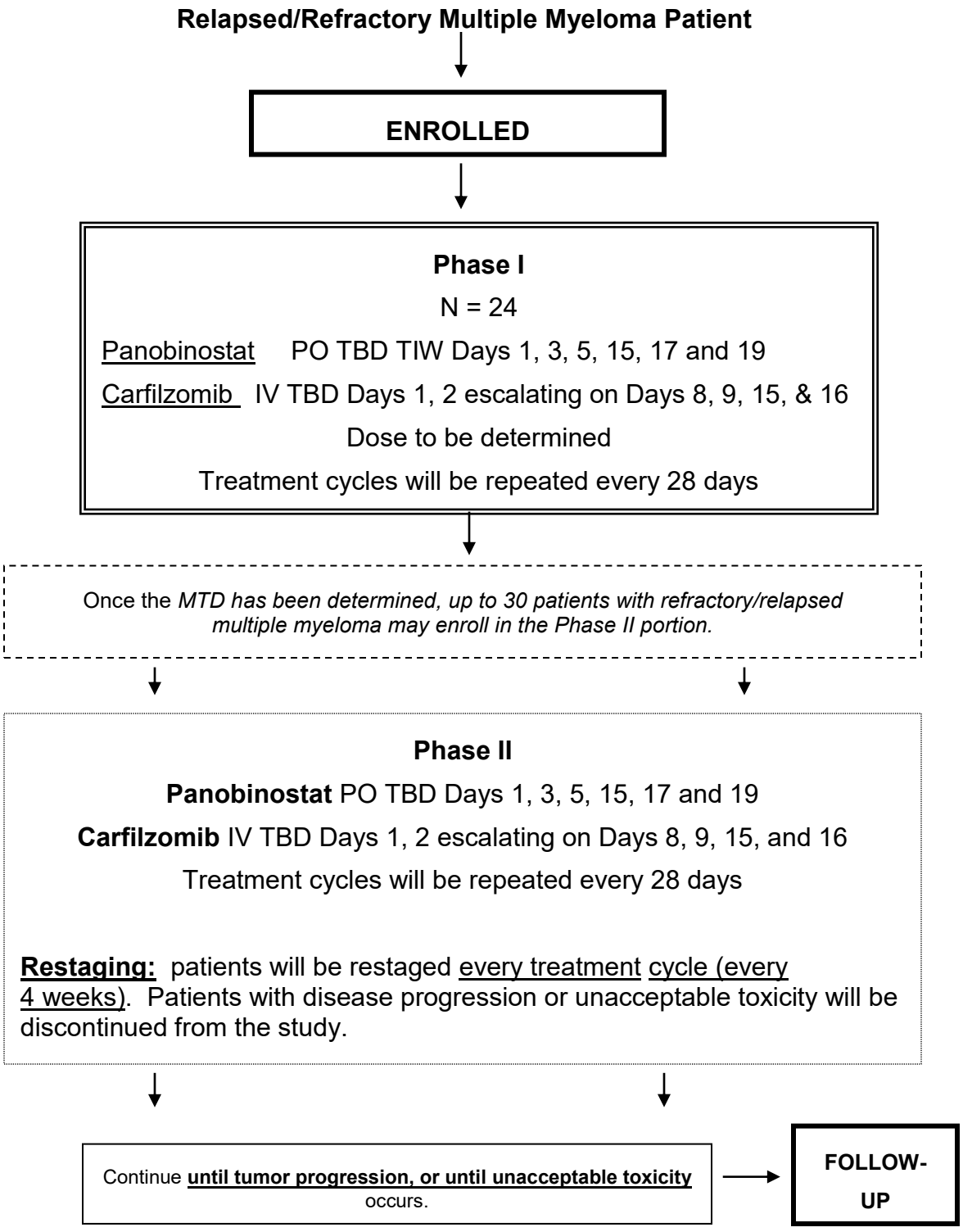
In the Phase II portion of this study, patients with relapsed/refractory multiple myeloma will receive treatment with the dose level 4 panobinostat and carfilzomib combination. Patients will be reevaluated for response to treatment after each cycle (4 weeks). Patients with objective response or stable disease will continue treatment, with subsequent reevaluations every 4 weeks, until disease progression or unacceptable toxicity occurs.

A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at additional dose levels of the combination of carfilzomib and panobinostat (see Table 3).

If additional dose levels are found to be tolerable, then additional patients will be recruited into an expansion cohort which will be open at all sites - a maximum total of 36 patients (including the ones recruited into the parallel Phase I study) will be treated at this dose level. Sites will be notified about the expansion cohort and patients will enter in the dose level confirmed in their enrollment confirmation from SCRI Innovations.

Up to 80 eligible patients will be treated in the Phase I/II study. The treatment schema for the study is shown in Figure 2.

Figure 2 Treatment Schema



5.1. Treatment Plan

Panobinostat and carfilzomib will be administered in the Phase I and Phase II portions of this trial as follows:

5.1.1. Panobinostat

PO TIW during weeks 1 and 3 of each 28-day cycle (i.e. D1, 3, 5, 15, 17, 19)

Dose levels are defined in Table 2.

Panobinostat will be self-administered (by the patient). Patients should be instructed to take their once-a-day oral dose of panobinostat at the same time of each scheduled treatment day. Panobinostat should be taken with a glass of water; the entire dose should be taken over as short a time as possible. Patients should swallow the capsules as a whole and should not chew them. Patients must avoid grapefruit or grapefruit juice and Seville (sour) oranges during the entire study.

If the patient forgets to take his/her dose, the patient may be instructed to take the dose up to 12 hours after the usual time. If more than 12 hours have passed, then the dose should be withheld that day. The patient should be instructed to wait until the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose. No missed doses should be made-up.

5.1.1.1. Panobinostat Administration – Electrolyte Monitoring and Cardiac Precautions

Electrolyte Monitoring

All patients must have an assessment of serum potassium, magnesium, and calcium (total corrected for albumin, or ionized calcium) ≤72 hours prior to the administration of oral panobinostat on Day 1 of Cycle 1 and the results must all be ≥LLN before the first dose of panobinostat is administered. Throughout the study serum biochemistry values including serum potassium, calcium, phosphorus and magnesium will be monitored closely. Whenever serum potassium, calcium, phosphorus and magnesium are assessed, if the value is <LLN, then the patient's potassium, calcium, phosphorus or magnesium should be immediately supplemented following the availability of that laboratory result, in order to minimize the time patients have low values. Patients must then undergo a repeat biochemistry test to demonstrate values ≥LLN. These values must be ≥ LLN before the patient is re-dosed with oral panobinostat.

Patients must be instructed to not take panobinostat if their most recent biochemistry values demonstrate potassium, calcium, phosphorus or magnesium <LLN. At a minimum, potassium, magnesium, phosphorus and calcium will be checked according to the protocol. More frequent testing should be done if clinically indicated (e.g. patient

has had prior low values; patient is taking medications that can result in lowering of their potassium, magnesium, phosphorus or calcium levels.

ECG QTcF Monitoring

Because of the observed QTc prolongation in several patients receiving panobinostat, to be eligible for this trial, the patient must have a mean QTc interval ≤450 at baseline. During Cycle 1 of panobinostat, ECG's will be monitored intensively (see Table 1). Prior to C1D1 and C1D5 dosing of panobinostat, all patients will have 3 12-lead ECGs, separated by 5-10 minutes. Triplicate ECGs, separated by 5-10 minutes, will be repeated approximately 3 hours after panobinostat dosing on C1D1 and C1C5. See Section 6.2.1. for additional ECG monitoring guidelines. Refer to Table 6 for management of prolonged QTc interval.

Beginning Cycle 2, patients will have a single ECG prior to the Day 1 panobinostat dose (assuming no QTc prolongation occurred during Cycle 1).

Table 1. ECG QTcF Monitoring

CYCLE	DAY	ECG(s) Time Point
Baseline		
	Pre-Treatment	Single ECG to Assess Eligibility
Cycle 1		
	Day 1 (day of first study drug administration)	Pre-Dose: 3 ECGs (Sequential ECGs, separated by 5-10 minutes) Post-Dose: 3 ECGs 3 hours (± ½ hour) after dosing (Sequential ECGs, separated by 5-10 minutes)
	Day 5	Pre-Dose: 3 ECGs (Sequential ECGs, separated by 5-10 minutes) Post-Dose: 3 ECGs 3 hours (± ½ hour) after dosing (Sequential ECGs, separated by 5-10 minutes)
Cycle 2 and beyond		
	Day 1	Pre-Dose: Single ECG

If the patient experiences QTcF >480 msec in cycle 1 or in any subsequent cycle, then repeat the monitoring schedule until they have a cycle with no QTc prolongation.

If no significant QTcF prolongation is noted during the first 8 cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion.

5.1.2. Carfilzomib

Cycle 1: TBD mg/m^2 IV Day 1, 2 then TBD mg/m^2 IV Day 8, 9, 15, 16

Cycle 2 and Beyond: TBD mg/m^2 IV Day 1, 2, 8, 9, 15, and 16

Carfilzomib will be administered over 30 minutes (see Section 6.4). Dose levels to be tested are defined in Table 2.

Treatment cycles will be repeated every 28 days. Patients will be evaluated for response to treatment every 4 weeks (i.e. after every cycle). Patients with stable disease or better may continue on study treatment until evidence of disease progression.

Hydration and Fluid Monitoring

Oral hydration - All patients must be well hydrated (i.e., volume replete). Begin oral hydration equal to approximately 30 mL/kg/day (~6–8 cups of liquid per day), starting 48 hours prior to the planned first dose of carfilzomib. Compliance must be reviewed with the patient and documented by the site personnel prior to initiating treatment with carfilzomib; treatment is to be delayed or withheld if oral hydration is not deemed to be satisfactory.

Intravenous Fluids - 250–500 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before *and* after each carfilzomib dose during Cycle 1. If lactate dehydrogenase (LDH) or uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for Cycle 2 and all subsequent cycles until progression disease at the study doctor's discretion to monitor TLS. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Patients should be monitored periodically during this period for evidence of fluid overload.

In patients considered to remain at risk for tumor lysis syndrome at completion of Cycle 1, hydration should be continued into Cycle 2. Patients in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.

5.1.2.1. Carfilzomib Safety Considerations

Based on previous Phase I and II carfilzomib studies, the following observations have been noted:

- 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.

- 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.
- Dexamethasone 4 mg PO/IV will be administered prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose-escalation (for example from 20 mg/m^2 to 27 mg/m^2) cycle. If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (4 mg PO/IV) should be re-started and administered prior to subsequent doses.
- Patients should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis. In addition, patients may receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone (or timethroprim/sulfamethoxazole if fluoroquinoles are contradicted) if clinically indicated.
- CrCl changes are mostly transient, reversible, and non-cumulative. All patients should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, are strongly encouraged prior to each dose of carfilzomib during Cycles 1 and 2. The decision will be at the discretion of the treating physician. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.

5.1.3. Window for Holidays and Vacations

For holidays and vacations it is preferred to plan ahead and adjust D1 of treatment +/- 48 hours of the cycle the patient plans to be gone for treatment, so that the patient follows the treatment schedule per protocol. If it is not possible to adjust D1, the carfilzomib infusion days may be adjusted +/- 48 hours after cycle 1 for a holiday or vacation. There is no window allowed during cycle 1 and for the panobinostat doses except for D1 with the window described above.

5.2. Phase I

The Phase I doses to be tested are defined in Table 2.

Table 2. Phase I Dose Levels

28-Day Cycles	Cycle 1	Cycle 2 to Progression
Dose Level -1		

Carfilzomib	15 mg/m^2 IV D1, 2 /20 mg/m^2 IV D8, 9, 15, 16	20 mg/m^2 IV D 1, 2, 8, 9, 15, 16
Panobinostat	20 mg D 1, 3, 5, 15, 17, 19	20 mg D 1, 3, 5, 15, 17, 19
Dose Level 1		
Carfilzomib	20 mg/m^2 IV D1, 2 / 27 mg/m^2 IV D8, 9, 15, 16	27 mg/m^2 IV D 1, 2, 8, 9, 15, 16
Panobinostat	20 mg D 1, 3, 5, 15, 17, 19	20 mg D 1, 3, 5, 15, 17, 19
Dose Level 2		
Carfilzomib	20 mg/m^2 IV D1, 2 / 36 mg/m^2 IV D8 ,9, 15, 16	36 mg/m^2 IV D 1, 2, 8, 9, 15, 16
Panobinostat	20 mg D 1, 3, 5, 15, 17, 19	20 mg D 1, 3 ,5, 15, 17, 19
Dose Level 3		
Carfilzomib	20 mg/m^2 IV D 1, 2 / 45 mg/m^2 IV D8, 9, 15, 16	45 mg/m^2 IV D 1 ,2, 8 ,9, 15, 16
Panobinostat	20 mg D 1, 3, 5, 15, 17, 19	20 mg D 1, 3, 5, 15, 17, 19
Dose Level 4		
Carfilzomib	20 mg/m^2 IV D 1, 2 / 45 mg/m^2 IV D8, 9, 15, 16	45 mg/m^2 IV D 1 ,2, 8 ,9, 15, 16
Panobinostat	30 mg D 1, 3, 5, 15, 17, 19	30 mg D 1, 3, 5, 15, 17, 19

Table 3. Parallel Dose Escalation Study – Dose Levels 5 and 6

28-Day Cycles	Cycle 1	Cycle 2 to Progression
Dose Level 5		
Carfilzomib	20 mg/m^2 IV D 1, 2 / 56 mg/m^2 IV D 8, 9, 15, 16	56 mg/m^2 IV D 1 ,2, 8 ,9, 15, 16
Panobinostat	30 mg D 1, 3, 5, 15, 17, 19	30 mg D 1, 3, 5, 15, 17, 19
Dose Level 6		
Carfilzomib	20 mg/m^2 IV D 1, 2 / 56 mg/m^2 IV D 8, 9, 15, 16	56 mg/m^2 IV D 1 ,2, 8 ,9, 15, 16
Panobinostat	20 mg D 1, 3, 5, 15, 17, 19	20 mg D 1, 3, 5, 15, 17, 19

A parallel Phase I study will occur to evaluate a minimum of 3 patients and a maximum of 6 patients following a standard dose escalation design at additional dose levels of the combination of carfilzomib and panobinostat.

Patients will enter in the dose level confirmed in their enrollment confirmation from SCRI Innovations.

5.2.1. Dose Escalation Phase I

The study will follow a standard dose-escalation design (see Table 2). For each cohort, the decision whether to dose-escalate will be made once all subjects have been

enrolled into the cohort and have received one full cycle (28 days) of study drug treatment. The following dose-escalation rules will be used:

- Initially, 3 subjects will be entered into a dose level.
- If 2 or more of the initial subjects experience dose-limiting toxicity (DLT) (see Section 5.2.2), then the MTD (see Section 5.2.3) has been exceeded.
- If none of the 3 subjects initially enrolled into this dose level cohort experiences DLT, then subsequent subjects will be enrolled in the next higher dose level.
- If 1 of the initial subjects experiences DLT, then 3 additional subjects (to a total of 6 subjects) will be enrolled in the dose level.
- If it is found that 1 of the 6 subjects in the dose level encounters DLT, then subsequent subjects will be enrolled into the next higher dose level cohort.
- If it is found that 2 or more of the 6 subjects in a dose level encounter DLT, then the MTD has been exceeded. If ≥2 of 6 patients have DLT on the first dose level tested (Dose Level 1, Table 2), dose level -1 will be evaluated. If dose level -1 is too toxic (≥2 of 6 patients with DLT), the study will continue only after discussion by the study chair and the sponsors.

No intra-patient dose escalation is permitted.

When the MTD has been exceeded:

When the MTD has been exceeded, the next lower dose previously studied will be evaluated for the MTD criteria. If only 3 subjects have been treated at this dose level, 3 additional subjects will be entered into this dose level until 6 subjects total have been treated.

- Once 6 subjects have been enrolled and evaluated at this dose level, if there was ≤1 DLT, this dose level will be declared the MTD.
- If >1 DLT occurred, then the MTD has been exceeded, and the next lower dose level will be similarly evaluated.
- Dose level -1 will only be tested if dose level 1 exceeds MTD.

5.2.2. Definitions of Dose-Limiting Toxicity (DLT)

For the purpose of determining the MTD (see Section 5.2.3), DLT is defined as any of the following that are determined to be related to study treatment during **Cycle 1**:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/μL) for >7 days.
- Febrile neutropenia (ANC <1000/ μL with fever >101°F [38.5°C]).
- Grade 3 thrombocytopenia with ≥ Grade 2 bleeding.
- Grade 4 thrombocytopenia (platelets <25,000/μL) > 7 days (patients may receive platelet support/transfusion).
- ≥ Grade 2 neuropathy with uncontrolled pain
- ≥ Grade 3 non-hematologic drug-related toxicity (excluding alopecia) despite optimal supportive care lasting >72 hours or requiring a dose reduction in the first cycle.
- Patients who are unable to receive 75% of the required doses of both agents secondary to toxicity.

Adverse events will be graded using the National Cancer Institute (NCI) Common Toxicity Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0).

Dose modifications are not permitted during Cycle 1 in any cohort unless the subject experiences a DLT. Subjects in dose level -1 (see Table 2) who develop a DLT during Cycle 1 will be discontinued from the study. Subjects in dose level 1 or higher who experience a DLT during Cycle 1 will have treatment held. The DLT will be counted toward the assessment of the MTD for the given cohort; however, the subject may continue on therapy if the toxicity resolves and dose modifications can be implemented according to the dose modification guidelines in Section 6.0.

Patients who withdraw from the study before receiving 75% of their scheduled Cycle 1 doses due a non-drug related AE (i.e., tumor progression) will be considered inevaluable and will be replaced.

Patients without clinical evidence of progressive disease at the end of the first cycle of study therapy will continue treatment. Patients will be reevaluated for response after completing 2 cycles (8 weeks) of treatment. Patients with objective response or stable disease according the International Myeloma Working Group Uniform Response Criteria (see Appendix C) will continue treatment, with reevaluations until disease progression occurs, unacceptable toxicity develops, or the subject chooses to discontinue study treatment.

5.2.3. Definition of Maximum Tolerated Dose (MTD)

The MTD of carfilzomib and panobinostat when given as a combination therapy will be defined as the highest dose level at which ≤1 of 6 subjects experiences dose-limiting toxicity (DLT).

When the MTD has been determined:

When the MTD has been determined, the trial will continue to enroll patients with relapsed/refractory multiple myeloma at the established MTD established during the Phase I portion.

5.3. Phase II

If a dose level in the parallel Phase I study is found to be tolerable, then additional patients will be recruited into an expansion cohort of 30 patients for Phase II for a total of 60 Phase II patients (including 30 patients for dose level 4).. A maximum of up to 80 total patients may be enrolled in this study (including patients from the dose escalation Phase I studies).

5.4. Concomitant Medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the study physician. All medications taken within 30 days of screening should be noted. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Any medications which may cause QTc prolongation or induce Torsades de Pointes should not be used (see Appendix F). Dolasetron is contraindicated while on treatment with Panobinostat.
- Any medications that have the potential to alter serum electrolytes (e.g. diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QTc prolongation and vent.
- No other investigational therapy should be given to patients.
- Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the study physician's discretion. These patients 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.

- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g. G-CSF and GM-CSF) are not to be administered prophylactically but may be prescribed by the study physician for severe neutropenia if this is thought to be appropriate.
- Medications known to be substrates of the isoenzyme CYP2D6 should be avoided if possible, as panobinostat can inhibit isoenzyme CYP2D6 at low micromolar ranges (see Appendix G).
- Medications, food, and herbal preparations known to be strong inducers or inhibitors of CYP34A should be avoided if possible (see Appendix G).

6. DOSE MODIFICATIONS

The criteria for interruption and resumption of treatment due to toxicity are outlined in the following tables. Dose re-escalation will not be allowed in any patient. All toxicities will be graded utilizing the NCI CTCAE v4.0. If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. If one drug is held, treatment may continue with the other study drug as appropriate. If study medication is held for over 3 weeks due to toxicity, that study medication will be discontinued. Treatment medications will be adjusted with a one level dose-reduction. The dose level criteria in Table 3 should be used to adjust the panobinostat or carfilzomib dose in the event of toxicity. If patients who are on the lowest allowable dose have a toxicity requiring dose reduction, the offending agent should be discontinued. Either or both drugs may be adjusted according to the dose modification tables below.

Table 4. Panobinostat and Carfilzomib Dose Level Modifications

Panobinostat PO	Carfilzomib IV
15 mg	15 mg/m^2
20 mg	20 mg/m^2
30 mg	27 mg/m^2
	36 mg/m^2
	45 mg/m^2
	56 mg/m^2

6.1. Dose Modifications for Hematologic Toxicity

Panobinostat and carfilzomib have been associated with hematologic toxicity. Blood counts will be measured on Days 1, 8, and 15 of each cycle, and dose modifications will be based on these blood counts. Dose reductions, when necessary, are outlined in Table 5. If toxicity occurs when the patient is already on the lowest acceptable dose, the drug should be discontinued.

Table 5. Panobinostat and Carfilzomib Dose Adjustments for Hematologic Toxicities

AE Term and Description	**Dose Modification**	
	Panobinostat	**Carfilzomib**
THROMBOCYTOPENIA		
Grade 1 or 2	Maintain dosing; monitor as clinically indicated.	Maintain dosing; monitor as clinically indicated.
Grade 3 (25 - <50 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction (Table 3).	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. If improves in ≤ 7 days, maintain same dose, if > 7 days reduce dose 1 level.
Grade 4 (<25 x 10^9/L)	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After *Initial Dose Reduction*	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a second 1 level dose-reduction.	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Grade 3/4 Event After 2 Dose Reductions	***Discontinue***	***Discontinue***

Table 5. Panobinostat and Carfilzomib Dose Adjustments for Hematologic Toxicities (continuation)

AE Term and Description	Dose Modification	
	Panobinostat	**Carfilzomib**
NEUTROPENIA		
Grade 1 or 2	Maintain dosing; monitor as clinically indicated.	Maintain dosing; monitor as clinically indicated.
Grade 3 (0.5×10^9/L ≤ ANC $<1.0 \times 10^9$/L)	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction (Table 3).	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. If improves in ≤ 7 days, maintain same dose, if >7 days reduce dose 1 level.
Grade 4 (ANC $<0.5 \times 10^9$/L)	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After *Initial Dose Reduction*	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.	1. Interrupt study treatment until toxicity reduced to ≤ grade 2[a]. 2. Restart treatment with a 1 level dose-reduction.
Recurrent Grade 3/4 Event After 2 Dose Reductions	***Discontinue***	Interrupt until toxicity ≤ grade [2a] and restart treatment with a 1 level dose-reduction if possible, or discontinue.
FEBRILE NEUTROPENIA		
Grade 3 ANC $<1.0 \times 10^9$/L, fever ≥38.5°C	1. Interrupt study treatment until ANC recovery to ≤ grade 2[a] (ANC ≥ 1.0×10^9/L) and resolution of fever <38.5°C. 2. Restart treatment with a 1 level dose-reduction.	1. Interrupt study treatment until ANC recovery to ≤ grade 2[a] (ANC ≥ 1.0×10^9/L) and resolution of fever <38.5°C. 2. Restart treatment with a 1 level dose-reduction.
Grade 4 ANC $<1.0 \times 10^9$/L, fever ≥38.5°C and life-threatening consequences	***Discontinue***	1. Interrupt study treatment until ANC recovery to ≤ grade 2[a] (ANC ≥ 1.0×10^9/L) and resolution of fever <38.5°C and any complications. 2. Restart treatment with a 1 level dose-reduction.

[a] Repeat labs weekly until recovery.

The criteria for adjusting the dose of panobinostat in the event of non-hematologic toxicities are detailed in Table 6.

Table 6. Panobinostat Dose Adjustments for Non-Hematologic Toxicities

AE Term and Description	Panobinostat Dose Modification
RENAL	
Serum Creatinine	
Serum creatinine < 2 x ULN	Maintain dosing.
Serum creatinine 2-3 X ULN	1. Interrupt panobinostat until toxicity resolved to ≤ 1.5 X ULN. 2. Restart treatment with a 1 level dose-reduction (Table 3).
Serum creatinine (>3 X ULN) Grade 3 or 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity ≤ 1.5 X ULN. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***
HEPATIC	
Total Bilirubin	
Total bilirubin < 2 x ULN	Maintain dosing.
Total bilirubin 2-3 X ULN	1. Interrupt panobinostat until toxicity resolved to ≤ 1.5 X ULN. 2. Restart treatment with a 1 level dose-reduction (Table 3).
Total bilirubin (>3 X ULN) Grade 3 or 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity ≤ 1.5 X ULN. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***
AST/SGOT, ALT/SGPT	
AST/SGOT, ALT/SGPT ≤5 x ULN (Grade 1 or 2)	Maintain dosing.
AST/SGOT, ALT/SGPT >5 - 10 x ULN	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1 (or baseline). 2. Restart treatment with a 1 level dose-reduction (Table 3).
Total bilirubin (>3 X ULN) Grade 3 or 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1 (or baseline). 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***

Table 6. Panobinostat Dose Adjustments for Non-Hematologic Toxicites (continuation)

AE Term and Description	Panobinostat Dose Modification
GASTROINTESTINAL	
Diarrhea[1]	
Grade 1	Maintain dosing.
Grade 2 or Grade 3[2] (Despite anti-diarrheal therapy)	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1. 2. Restart treatment with a 1 level dose-reduction (Table 3).
Grade 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***
Vomiting	
Grade 1	Maintain dosing.
Grade 2 or Grade 3[2] (Despite anti-nausea therapy)	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1. 2. Restart treatment with a 1 level dose-reduction (Table 3).
Grade 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***
Fatigue	
Grade 4	1. Interrupt panobinostat until toxicity resolved to ≤ grade 2 or baseline. 2. If resolved in 7 days after interruption of panobinostat, then restart panobinostat at an unchanged dose level. 3. If resolved in more than 7 days after interruption of panobinostat, then restart panobinostat with a 1 level dose-reduction.
Other Non-Hematologic Toxicity	
Grade 3	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1 or baseline. 2. Restart treatment with a 1 level dose-reduction (Table 3).
Grade 4	***Discontinue panobinostat***
Recurrent Event After *Initial Dose Reduction*	1. Interrupt panobinostat until toxicity resolved to ≤ grade 1. 2. Restart treatment with a second 1 level dose-reduction.
Recurrent Event After 2 Dose Reductions	***Discontinue panobinostat***

Table 6. Panobinostat Dose Adjustments for Non-Hematologic Toxicites (continuation)

Each patient is allowed a maximum of 2 dose reductions (Table 3). No patient will receive less than 15 mg three times weekly. If toxicity recurs at this dose level, panobinostat will be discontinued.
Patients with grade 4 adverse event should be discontinued from further treatment with study drug.
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)
[1] Patients should be instructed to contact their physician at the onset of diarrhea. Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours not to exceed a total of 16 mg in 24 hours. Patients with diarrhea grade 2 despite this loperamide regimen should interrupt treatment with panobinostat as described in the table. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use. Patients should be instructed to contact their physician at the onset of diarrhea. If severe diarrhea (grade 3 and 4) happens, patient should be admitted into the hospital. Replace IV fluids and electrolytes as appropriate. Treatment should follow institutional standard of care or local guidelines. [2]If patient has two grade 3 diarrhea events or vomiting episodes with or without prophylaxis medications, the patient may be discontinued from study drug rather than attempting dose reductions at the discretion of the investigator.

6.2. Panobinostat Dose Modifications for Prolonged QTc Interval

All cardiac events should be treated according to institutional standards and referred to a specialist if clinically indicated. Treatment decisions at the sites will be based on QTc as determined by the automated machine reading (or as measured and calculated by trained personnel at the site). If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient should be discontinued from study.

Table 7: Criteria for Dose Reductions, Delays and/or Re-Institution Due to Drug-Related QTcF Abnormalities

ECG TIME POINT	ABNORMALITY	DOSE MODIFICATION GUIDELINE
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
Cycle 1 Dose Modification Criteria:		
Cycle 1 PRE-DOSE **Days 1 and 5** **<u>Triplicate ECGs</u>**	**Day 1:** **Average QTcF:** **>450 msec**	**Check and correct** the patient's serum potassium, magnesium, calcium, phosphorus immediately, as well as evaluate concomitant medications. If abnormality noted on Cycle 1 Day 1: Repeat 3 pre-dose ECGs. If the 3 pre-ECGs: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer panobinostat.
	Day 5: **Average QTcF:** **≥480 msec to <500 msec** **Or** **>60 msec increase from baseline average**	If abnormality noted on Cycle 1 Day 5: Delay dose at least 3 days and repeat 3 pre-dose ECGs. If the repeat 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria again, discontinue panobinostat. **Do meet** pre-dose ECG criteria for dosing and QTc prolongation determined to be related to panobinostat, resume panobinostat treatment with a 1-level dose reduction. If however, it was determined that the QTc prolongation was secondary to electrolyte abnormalities or concomitant medications, continue at the same dose level. Repeat ECGs – pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.
	Average QTcF: **≥500 msec**	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. **Discontinue** patient from panobinostat. If however, it was determined that the QTc prolongation was secondary to electrolyte abnormalities or concomitant medications: **Omit dose.** On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

Table 7.Criteria for Dose Reductions, Delays, Re-Institution Due to Drug Related QTcF Abnormalities (continuation)

ECG TIME POINT	ABNORMALITY	DOSE MODIFICATION GUIDELINE
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
Cycle 1 Dose Modification Criteria:		
Cycle 1 POST-DOSE **Days 1 and 5** **<u>Triplicate ECGs</u>**	**Average QTcF:** **≥480 msec to <500 msec** **Or** **>60 msec increase from baseline average**	**Check and correct** the patient's serum potassium, magnesium, calcium, phosphorus immediately, as well as evaluate concomitant medications. **Monitor ECG hourly** or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose are <480. Next scheduled dosing day: repeat 3 pre-dose ECGs. If these 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria for dosing (average QTcF ≥480 msec), discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing (average QTcF <480 msec) and QTc prolongation determined to be related to panobinostat, resume panobinostat treatment with a 1-level dose reduction. If however, it was determined that the QTc prolongation was secondary to electrolyte abnormalities or concomitant medications, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3) on the next scheduled dosing day.
	Average QTcF: ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. **Discontinue** patient from panobinostat. If however, it was determined that the QTc prolongation was secondary to electrolyte abnormalities or concomitant medications: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

6.2.1. General Monitoring Principles

6.2.1. General Monitoring Principles

The following cardiac monitoring guidelines are required for this study:

1. Patients in screening will have a baseline ECG performed to determine eligibility.
2. Enrolled patients will have ECGs collected as defined in Table 1.
3. On treatment days when ECGs are to be obtained, the patient will take their medication in the clinic. Prior to the first dose of panobinostat (Cycle 1, Day 1), the QTcF interval from each of the 3 ECGs must be ≤450 msec and the average of the pretreatment QTc intervals must be ≤450 msec before the patient is dosed. This real-time assessment will be based on the QTc intervals as determined at the clinical center.
4. If the patient does not meet the QTc criteria for dosing, the patient's serum potassium, magnesium, calcium and phosphorus must be measured immediately, and the patient must receive supplements to correct any low values.
5. If the patient experiences a QTcF >480 msec in Cycle 1 or in any subsequent cycle, the Cycle 1 ECG monitoring schedule will be repeated until they have a treatment cycle with no QT prolongation.
6. At any time, if any ECGs (baseline or post-dose) demonstrate a QTc value ≥ 480 msec the Investigator must notify the Sponsor immediately. In addition, the patient's serum potassium, magnesium, calcium and phosphorus must be measured immediately, and the patient must receive supplements to correct any low values.
7. All ECGs will be reviewed by the treating physician prior to administering the dose of panobinostat.
8. In general, panobinostat dose reductions or discontinuations will occur in the following circumstances:
    - Repeat dosing delays due to prolonged QTc intervals
    - QTc ≥ 480 msec but < 500 msec (in absence of electrolyte abnormalities).
    - Any QTc ≥ 500 msec (discontinuation).

    For patients requiring a dose reduction, 3 pre-dose ECG's will be done on the first day of the new lower dose, and 3-hours post-dose (x 3).

    If however, it was determined that the QTc prolongation was secondary to electrolyte abnormalities or concomitant medications, panobinostat may be continue at the same dose level. ECGs will be repeated - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.
9. Any QTc ≥ 500 msec will lead to discontinuation of the panobinostat.
10. All other cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator (if clinically indicated).

11. If no significant QTcF prolongation is noted during the first 8 cycles, the QT monitoring is no longer required and may be performed at the Investigator's discretion.

Any patient who has an ECG with a QTc ≥ 500 msec must be monitored very closely. Check and correct the patient's serum potassium, magnesium, calcium, and phosphorus immediately.

If any QTc interval is ≥500 msec, the patient must have at a minimum, hourly ECG monitoring until the QTc is <480 msec. In addition to the minimum hourly ECG monitoring, telemetry monitoring is strongly recommended. Prior to a patient with a QTc interval >500 msec being discharged to home, that patient must have at least 2 consecutive, hourly ECGs obtained at least 6 hours after dosing that demonstrate a QTc interval of ≤480 msec.

If any patient has a QTc interval ≥500 msec, the Investigator must notify the Sponsor immediately. The patient must not receive any further doses of panobinostat and must be discontinued from the study.

6.3. Carfilzomib Dose Modifications for Non-Hematologic Toxicities

Treatment with carfilzomib and panobinostat should be held for ≥ grade 3 events until resolved to ≤ grade 1 or return to baseline. If the adverse event was not treatment-related, or was attributable to panobinostat, subsequent treatment with carfilzomib may be resumed at full dose after resolution to ≤ grade 1 or return to baseline.

If the event was carfilzomib-related, subsequent treatment with carfilzomib will resume at one level dose reduction (see Table 3). If toxicity continues or recurs, a 2nd carfilzomib dose reduction is permitted unless the patient is already receiving the lowest dose level shown in Table 3. If toxicity continues, the patient should be discontinued from treatment.

If there is no resolution of carfilzomib-related toxicity after 2 weeks of withholding carfilzomib (up to 3 weeks for infection treatment), carfilzomib will be discontinued.

Specific carfilzomib-associated non-hematologic toxicities are addressed in Table 7.

Table 8. Carfilzomib Dose Modifications for Non-Hematologic Toxicity

Event	Action to be Taken
Allergic reaction/hypersensitivity	
Grade 2 – 3	Hold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue
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 abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection	Hold carfilzomib (no more than 3 weeks) until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions (Table 4).
Grade 3 or 4	
Herpes zoster or simplex of any grade	Hold carfilzomib until lesions are dry. Reinstitute at full dose.
Neuropathy	
Grade 2 treatment emergent neuropathy with pain or Grade 3 neuropathy	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement
Grade 4 neuropathy	Discontinue carfilzomib
Renal Dysfunction	
CrCl ≤ 30 mL/min	Hold until CrCl > 30 mL/minute; restart at 1 dose decrement
Congestive heart failure	Any subject with symptomatic 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.
Hypertension	All patients should be evaluated for hypertension and treated as needed. If hypertension cannot be controlled, reduce carfilzomib.

Table 8 Carfilzomib Dose Modifications for Non-Hematologic Toxicity

Event	Action to be Taken
Hypertensive crisis, **or Pulmonary hypertension,** **or Pulmonary toxicity**	Stop carfilzomib until resolved or returned to baseline. Consider whether to restart carfilzomib based on a benefit/risk assessment.
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

6.4. Management of Carfilzomib-Related Events

6.4.1. Cardiopulmonary Disorders

New or worsening cardiac failure (e.g., congestive cardiac heart failure, pulmonary edema, and decreased ejection fraction), myocardial ischemia, and myocardial infarction have occurred following administration of carfilzomib. Death due to cardiac arrest has occurred within a day of carfilzomib administration, and fatal outcomes have been reported with cardiac failure and myocardial infarction.

While adequate hydration is required prior to dosing in Cycle 1, all subjects should be monitored for evidence of volume overload, especially subjects at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at high risk for cardiac failure.

Withhold carfilzomib for Grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib at 1 dose level reduction based on a benefit/risk assessment.

6.4.2. Pulmonary Hypertension

In Phase 2 studies, pulmonary arterial hypertension was reported in 2% of subjects treated with carfilzomib and was Grade 3 or greater in less than 1% of subjects. In the pooled safety data from studies where carfilzomib was used in combination with lenalidomide-dexamethasone and in monotherapy studies (with or without dexamethasone) (N = 1581), events within the narrow pulmonary hypertension standardized Medical Dictionary for Regulatory Activities (MedDRA) query were reported in 1.1% of subjects. However, the incidence of pulmonary hypertension was similar across treatment groups in randomized, controlled studies where carfilzomib was used in combination with lenalidomide-dexamethasone and also in monotherapy studies (with or without dexamethasone). Therefore, a causal relationship with carfilzomib has not been demonstrated and pulmonary hypertension is considered an important potential risk.

Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were excluded from clinical studies with carfilzomib, as they may be at greater risk of cardiopulmonary complications.

Monitor subjects for signs and symptoms of pulmonary hypertension. Evaluate with cardiac imaging and/or other tests as indicated. Withhold carfilzomib until resolved or returned to baseline and consider whether to restart carfilzomib based on a risk/benefit assessment.

6.4.3. Acute Renal Disorder

Cases of acute renal failure have been reported in subjects who received carfilzomib. Acute renal failure was reported more frequently in subjects with advanced relapsed and refractory multiple myeloma who received carfilzomib monotherapy. This risk was increased in subjects with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving carfilzomib. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

6.4.4. Tumor Lysis Syndrome

Cases of TLS, including fatal outcome, have been reported in subjects who received carfilzomib. Subjects with a high tumor burden should be considered to be at greater risk for TLS. Ensure that subjects are well hydrated before administration of carfilzomib in Cycle 1 and in subsequent cycles as needed. Uric acid-lowering drugs should be considered in subjects at high risk for TLS. Monitor for evidence of TLS during treatment, including regular measurement of serum electrolytes, and manage promptly. Interrupt carfilzomib until TLS is resolved.

6.4.5. Infusion Reactions

Infusion reactions, including life-threatening reactions, have been reported in subjects who received carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, and weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Administer dexamethasone prior to carfilzomib either as premedication or as part of combination therapy to reduce the incidence and severity of reactions.

6.4.6. Thrombocytopenia

Carfilzomib causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle with recovery to baseline platelet count by the start of the next cycle. Monitor platelet counts frequently during treatment with carfilzomib. Reduce or withhold dose as appropriate.

6.4.7. Hepatic Toxicity

Cases of hepatic failure, including fatal cases, have been reported. Carfilzomib can cause elevations of serum transaminases. Monitor liver enzymes regularly. Reduce or withhold dose as appropriate.

6.4.8. Thrombocytopenic Thrombotic Purpura/Hemolytic Uremic Syndrome

Cases of thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS) including those with fatal outcome have been reported in subjects who received carfilzomib. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If the diagnosis of TTP/HUS is excluded, carfilzomib can be restarted. The safety of reinitiating carfilzomib therapy in subjects previously experiencing TTP/HUS is not known.

6.4.9. Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension.

The diagnosis is confirmed by neuro-radiological imaging. If diagnosed early and treated, the symptoms of PRES may be reversed. Cases of PRES have been reported in subjects receiving carfilzomib. Discontinue carfilzomib if PRES is suspected. The safety of reinitiating carfilzomib therapy in subjects previously experiencing PRES is not known.

7. STUDY ASSESSMENTS AND EVALUATIONS

All patients should visit the study center on the days specified within this protocol. The Schedule of Assessments for this trial is shown in Appendix E.

7.1. Comprehensive Metabolic Profile (CMP)

The following laboratory tests should be performed for each patient for assessment of CMP:

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium

- carbon dioxide (CO_2)
- alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- total bilirubin
- total protein
- albumin

plus

- magnesium
- phosphorus

7.2. Baseline Assessment

All patients must have the following assessments performed before receiving their first dose of protocol therapy (labs may be obtained up to 72 hours prior to treatment):

- Obtain Signed Consent Form
- Medical history
- Physical examination, including measurement of vital signs (blood pressure, height, pulse, and respiratory rate) and weight [BSA]. Height will be obtained only at baseline.
- ECOG PS (Appendix A)
- Complete blood count (CBC)3-part differential and platelets
- CMP (see Section 7.1.) plus magnesium and phosphorus
- Uric acid
- LDH
- PT/PTT/INR
- Chest X-ray (repeat if/when clinically indicated)
- 12- lead ECG
- MUGA or ECHO with calculated left ventricular ejection fraction (LVEF) (repeat if/when clinically indicated)
- Serum or urine pregnancy test (for women of childbearing potential)
- Bone marrow biopsy/aspiration (including flow cytometry, cytogenetics and FISH for the following chromosomal abnormalities: 1q amplification, 1p del, t(4;14), t(11;14), t(14,16) or 17p del
- Skeletal survey
- Serum free light chain
- Serum immunoglobulin G, A, M
- Serum ß-2 microglobulin
- SPEP and immunofixation
- UPEP and immunofixation requiring a 24-hour urine sample collection
- Record concomitant medications

The baseline assessments described in Appendix E will be collected prior to the initiation of treatment. The physical examination, ECOG PS, CBC, CMP, uric acid and pregnancy test should be done <7 days prior to initiation of treatment. All other assessments should be performed ≤4 weeks prior to initiation of treatment.

7.3. Study Treatment Period

7.3.1. Cycle 1 Day 1, 2, 5, 8, 9, 15, 16

- Vital signs (blood pressure, weight, pulse, and respiratory rate) at each treatment visit.
- Adverse event evaluation

7.3.2. Cycle 1 Day 1

- Physical examination, including measurement of vital signs (blood pressure, pulse, and respiratory rate) and weight.
- ECOG PS (Appendix A)
- 12- lead ECGs - three ECGs will be obtained 5-10 minutes apart before the patient takes panobinostat and repeated three hours later (x 3) 5-10 minutes apart.
- CBC, 3-part differential and platelets (-3 to Day 1 window allowed)
- CMP (see Section 7.1.) plus magnesium and phosphorus (-3 to Day 1 window allowed)
- Uric acid (-3 to Day 1 window allowed)
- LDH
- PT/PTT/INR (if medically indicated or if patient is receiving warfarin or other anti-coagulant)
- Adverse event evaluation
- Record concomitant medications

7.3.3. Cycle 1 Day 5

- 12- lead ECGs – three will be obtained 5-10 minutes apart before the patient takes panobinostat and repeated three hours later (x 3) 5-10 minutes apart.
- Vital signs (blood pressure, weight, pulse, and respiratory rate)

7.3.4. Cycle 1 Day 8 and 15

- Medical history (Day 15 only)
- Physical examination (Day 15 only)
- ECOG PS (Appendix A)

- Vital signs (blood pressure, weight, pulse, and respiratory rate)
- CBC, 3-part differential and platelets (-3 to Day 1 window allowed)
- CMP (see Section 7.1.) plus magnesium and phosphorus (-3 to Day 1 window allowed)
- Uric acid (-3 to Day 1 window allowed)
- LDH
- PT/PTT/INR (if medically indicated or if patient is receiving warfarin or other anti-coagulant)
- Adverse events assessment
- Record concomitant medication

7.3.5. Cycle 2 and Beyond - Day 1, 8 and 15

- Medical history (Day 1 only)
- Physical examination (Day 1 only)
- Measurement of vital signs (blood pressure, pulse, and respiratory rate and weight)
- ECOG PS (Day 1 only) (Appendix A)
- CBC, 3-part differential and platelets (-3 to Day 1 window allowed)
- CMP (see Section 7.1.) plus magnesium and phosphorus (Day 1 only) (-3 to Day 1 window allowed)
- Uric acid (if clinically indicated) (-3 to Day 1 window allowed)
- LDH (if clinically indicated)
- PT/PTT/INR (Day 1 only; if medically indicated or if patient is receiving warfarin or other anti-coagulant)
- 12- lead ECG (Day 1 only if no previous problems with QTc prolongation)
- Adverse event evaluation
- Record concomitant medications

7.4. Re-Staging – 4 Weeks (-7 to Day 1 window allowed)

- Bone marrow biopsy/aspiration (including cytogenetics and FISH for the following chromosomal abnormalities: 1q amplification, 1p del, t(4;14), t(11;14), t(14,16) or 17p del) (REQUIRED ONLY TO DOCUMENT A CR)
- Serum free light chain
- Serum immunoglobulin G, A, M
- SPEP and immunofixation
- UPEP and immunofixation requiring a 24-hour urine sample collection

At any point in this treatment, patients suspected of PD will have response assessed again to confirm disease progression (i.e. 2 sets of response assessments at least 1

week apart). The outcomes will be reviewed by the study chair before the patient is removed from the study. After the second set of response assessments, if disease progression is confirmed, the date of the first set of response assessments should be recorded as the progression date.

7.5. End of Study Treatment

The following assessments will be performed for each patient within 30 days after treatment ends according to protocol guidelines.

- Physical examination, including measurement of vital signs
- Update Medical history
- ECOG Performance Status
- CBC, 3-part differential and platelets
- CMP (see Section 7.1.) plus magnesium and phosphorus
- Uric acid (if clinically indicated)
- LDH (if clinically indicated)
- 12-lead ECG
- Serum free light chain
- Serum immunoglobulin G, A, M
- SPEP and immunofixation
- UPEP and immunofixation requiring a 24-hour urine sample collection
- Adverse event assessment
- Concomitant medication review

Patients who discontinue treatment prior to disease progression will have the study assessments performed as described in Appendix E.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End of Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for adverse events for 30 calendar days after the last dose of study drug.

7.6. Follow-Up

7.6.1. Follow-Up for Patients who Discontinue Treatment Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months from date of last dose of study drug during years 1 and 2, every 6 months during years 3-5, and annually thereafter for toxicity, disease progression, and survival. Appropriate disease assessments will be performed every 3 months during years 1 and 2 after study discontinuation, and every 6 months during

years 3, 4, and 5. After disease progression is documented, patients will be followed every 3 months as specified in Section 7.5.2. Assessments at these visits will be performed as described in Appendix E.

7.6.2. Follow-Up After Disease Progression

After disease progression is documented, patients will be followed every 3 months. Assessments during this time will be performed as described in Appendix E.

7.6.2.1. Pregnancy test

All females of childbearing potential should complete a serum or urine pregnancy test within 7 days prior to the administration of trial drug on day 1 of cycle 1. Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered “of non-childbearing potential”.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1. Panobinostat

8.1.1. Panobinostat Formulation

Panobinostat (also known as LBH589) will be provided by Novartis. Oral panobinostat will be supplied as 5-mg, 15-mg, or 20-mg pink/opaque-colored, hard gelatin capsules.

8.1.2. Panobinostat Drug Supply

Panobinostat for use in this study will be supplied to the Sponsor, SCRI Development Innovations, LLC (SCRI Innovations), by Novartis. Study sites will obtain panobinostat from Sponsor designee(s) at SCRI Innovations per instructions provided to participating study sites.

Accountability for the drug at all study sites is the responsibility of the principal investigator at each study site. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug’s delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to SCRI Innovations or disposal of the drug (if applicable and if approved by SCRI Innovations) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. Once panobinostat is shipped to a site, it may not be shipped or shared with another site or patient.

All material containing panobinostat will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.1.3. Storage and Stability

The storage conditions for study drug will be described on the medication label.

8.1.4. Administration

Oral panobinostat capsules should be administered as follows:

- Patients should be instructed to take their three times a week oral dose of panobinostat at the same time on each dosing day (e.g. day 1, 3, and 5). Doses should be separated by a minimum of 30 hours.
- Dose may be taken with or without food.
    - In the event that the patient does not take the daily dose at the specified routine time, unrelated to toxicity (for example, the patient forgets), but the dose can be taken within 12 hours of the specified time, then s/he may take the daily dose at that time. If more than 12 hours have passed, that day's dose should be withheld, and the patient should wait to take panobinostat until the next scheduled treatment day. The patient should then continue treatment with the original dosing schedule. This should be clearly documented on the Dosage Administration Record CRF by a member of the research team.
    - Each dose of panobinostat should be taken with a glass (approximately 240 mL) of water. Patients should be instructed to swallow the capsules whole and not chew them.
    - If vomiting occurs during the course of treatment, then no re-dosing of the patient is allowed before the next scheduled dose.
    - Patients must avoid grapefruits, grapefruit juice, Seville (sour) oranges and Seville orange juice during the entire study period.

Note: Food influence on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive 1 of 6 treatment sequences where PK was evaluated weekly under fasting, high fat, and normal breakfast conditions CLBH589B2111. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas C_{max} was transiently reduced (<45%) by food (i.e., both normal and high fat breakfast). Since the overall extent of absorption was not altered by food, food is unlikely to significantly impact panobinostat systemic exposure in cancer patients.

8.1.5. Panobinostat Toxicities

Most frequently reported adverse events (occurred in at least 30% of patients):

1. Fatigue and weakness
2. Decreased appetite, anorexia or altered taste
3. Diarrhea which can lead to dehydration, loose stools, abdominal cramping
4. Nausea and vomiting

5. Thrombocytopenia
6. Leukopenia
7. Anemia

Additional side effects that have been observed in ongoing clinical trials:

1. Weight loss
2. QTc prolongation, atrial fibrillation
3. Changes in thyroid function
4. Changes in blood electrolytes and glucose
5. Increase in creatinine levels
6. Other side effects reported include: back, extremity, muscle, joint and bone pain, headache, coughing, breathing problems including shortness of breath, anxiety, depression, dizziness, constipation, fever, abdominal pain, swelling in the legs or eye, itchiness, peripheral ischemia, chest pain, loss of feeling or tingling in the arms and legs, inflammation of nose, throat and lining of the mouth.

8.1.6. Panobinostat Precautions and Risks

Patients must avoid grapefruit or grapefruit juice and Seville (sour) oranges or juice during the entire study.

Medications known to be substrates of the isoenzyme CYP2D6 should be avoided if possible, since panobinostat can inhibit isoenzyme CYP2D6 at low micromolar ranges.

<u>Drugs that can inhibit/induce CYP3A4/5</u>

Drugs that can inhibit CYP3A4/5

Panobinostat is metabolized *in vitro* by CYP3A4/5. A clinical drug-drug interaction study with ketoconazole and panobinostat has recently been completed. The less than 2-fold increase in panobinostat AUC upon co-administration with ketoconazole suggests that CYP3A contribution to the total clearance of panobinostat is low. The observed interaction is not considered clinically relevant, as panobinostat doses at least 2-fold greater than 20 mg (40 and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of panobinostat and may be co-administered when medically necessary.

Drugs that are potent CYP3A4/5 inducers

As it is with other medications that are metabolized by CYP3A4, clinical judgment is to be exercised when potent CYP3A4 inducers are concomitantly taken with panobinostat.

Serum Electrolytes

Any patients who are taking medications that have the potential to alter serum electrolytes (e.g. diuretics) should be monitored closely for electrolyte abnormalities as these can contribute to the risk of QTc prolongation and ventricular arrhythmias.

Anti-Coagulant Therapy

Panobinostat therapy is commonly associated with mild to moderate degree thrombocytopenia, which may increase the risk of bleeding with concomitant sodium warfarin (Coumadin). It is recommended that patients who require anticoagulation therapy while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, patients on sodium warfarin may continue such therapy while on panobinostat but for such patients, PT/INR should be closely monitored and maintained within a therapeutic range. The dose of sodium warfarin may be adjusted as needed while on panobinostat. If the patient's platelets drop below 50,000 consideration should be given to suspending treatment with anticoagulation.

8.2. Carfilzomib

8.2.1. Carfilzomib Formulation

Carfilzomib for injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib free base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

8.2.2. Drug Supply of Carfilzomib

Carfilzomib for use in this study will be supplied to the Sponsor, SCRI Innovations by Onyx. Study sites will obtain carfilzomib from Sponsor designee(s) at SCRI Innovations per instructions provided to participating study sites.

Accountability for the drug at all study sites is the responsibility of the principal investigator at each study site. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to SCRI Innovations or disposal of the drug (if applicable and if approved by SCRI Innovations) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. Once carfilzomib is shipped to a site, it may not be shipped or shared with another site or patient.

All material containing carfilzomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.2.3. Storage and Stability

Lyophilized carfilzomib for injection must be stored at 2–8ºC, in a securely locked area to which access is limited to appropriate study personnel.

8.2.4. 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.

At least 48 hours before Cycle 1 Day 1, **oral hydration** should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. In subjects considered at risk for TLS, oral hydration should be continued in Cycle 2 and beyond as required by the subject's medical condition and at the Investigator's discretion.

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 (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

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.

Carfilzomib will be given as an IV infusion over approximately 10 minutes. For doses > 27 mg/m2, carfilzomib should be infused over 30 minutes. 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) will be given. Subjects should be monitored periodically during this period for evidence of fluid overload.

8.2.5. Carfilzomib Toxicities

Most frequently reported adverse events are reported in the current carfilzomib Investigator's Brouchure (IB)**.**

8.2.6. Carfilzomib Precautions and Risks

The precautions and risks that are related to carfilzomib are pulmonary hypertension, cardiopulmonary disorders, acute renal failure, tumor lysis syndrome, infusion reactions,

thrombocytopenia, hepatic toxicity, thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS), and posterior reversible encephalopathy syndrome (PRES). Management of carfilzomib-related toxicities is addressed in Section 6.3 and 6.4 and in the current carfilzomib IB.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response to treatment and disease progression will be evaluated using the International Myeloma Working group Uniform Response Criteria: Disease Progression and Relapse (see Appendix C).

CR	Complete Response
sCR	*subcategory: stringent complete response*
VGPR	Very good partial response
PR	Partial response
SD	Stable disease
PD	Progressive disease

All response categories (CR, sCR, VGPR, PR, PD) require two consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

Complete Response should be confirmed with a bone marrow biopsy for morphology and a bone marrow aspiration for flow cytometry, FISH and cytogenetics performed locally. Additional confirmatory studies include SPEP, UPEP, immunofixation of blood and urine and serum free light chains (see Appendix E).

MR	Minimal Response

Minimal Response (MR) should be reported for patients with relapsed refractory myeloma. When reported, the specific rate of MR should be distinguished from PR or better.

10. STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

10.1. Determination of Sample Size

MM 27 is a Phase I/Phase II study of carfilzomib in combination with panobinostat in the treatment of relapsed/refractory multiple myeloma. The total number of patients expected to be accrued is up to 80.

The Phase I efficacy objective is to establish the optimal dose of carfilzomib with panobinostat that can be administered to patients with relapsed/refractory multiple myeloma. In this part of the trial, the optimal dose combination to be administered will be determined as described in Section 5.2. Since 3-6 patients will be treated in each cohort, the maximum number of patients treated in this phase will be 24.

The Phase II efficacy objective is to evaluate the overall response in patients with relapsed/refractory multiple myeloma treated at the optimal dose level in the first 4 dose levels established during the Phase I portion. In addition, the overall response in patients at any additional dose levels will be evaluated. The response rates in the two dose levels will be evaluated separately. When used in the treatment of patients with relapsed/refractory multiple myeloma, the historical carfilzomib overall response rate is approximately 18%. It is hypothesized that the overall response rate for the treatment regimen of carfilzomib plus panobinostat is greater than that for patients treated with carfilzomib alone. A sample size of 27 achieves 80% power to detect an increase in the overall response rate to 36% (representing a 100% relative improvement) based on a one-sided test of proportion at an alpha level of 0.10. The sample size will be increased by 10% to account for potential non-evaluable patients and adjusted relative to the actual number of patients in the Phase I portion who are treated at the optimal dose level.

10.2. Statistical Analyses

10.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

10.4. Efficacy Analyses

Efficacy will be evaluated for patients treated at the optimal dose level from the first 4 dose levels during Phase I together with those entered in the Phase II dose expansion portion of the study, and at any additional dose levels (if found to be tolerable and patients are recruited into the expansion cohort). The data from the two dose levels will be evaluated separately, and no formal statistical comparisons will be made between the two dose levels.

The efficacy endpoints are overall response rate (primary endpoint), time-to-progression, progression-free survival, and overall survival.

10.4.1. Primary Efficacy Endpoint(s)

The overall response rate (CR, VGPR, or PR) will be presented along with 95% confidence intervals calculated using both asymptotic normal approximation and exact binomial methods.

10.4.2. Secondary Efficacy Endpoint(s)

Time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS) will be analyzed using Kaplan-Meier methods. Time-to-progression will be measured from the date of first protocol treatment until the date of tumor progression is documented (event), or date of last adequate tumor assessment (censored). Progression-free survival will be measured from the date of first protocol treatment until the date of tumor progression is documented or death occurs (event), or date of last adequate tumor assessment (censored). Overall survival will be measured as the interval from first study treatment until date of death (event), or date last known alive (censored). Median progression-free survival and median overall survival will be reported using the respective point estimate and 95% confidence intervals.

10.5. Safety Analyses

Safety will be evaluated for patients entered in the Phase I and Phase II portions of the study. The primary safety endpoint is tolerability of combination panobinostat and carfilzomib.

The analyses of safety will be based on the frequency of adverse events and their severity for patients in each cohort who received at least one dose of study treatment. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v4.0.

11. SAFETY REPORTING AND ANALYSES

11.1. Safety Analyses

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug.

11.2. Adverse Events

The PI is responsible for recognizing and reporting adverse events to the Sponsor. If not delegated it is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory body.

11.2.1. Definitions of Adverse Events

An adverse event is the development of an undesirable medical condition, or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

11.2.2. Recording of Adverse Events

All adverse events of any patient during the course of the trial will be reported in the case report form, and the investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious, it should be reported immediately to the sponsor or designee. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs (i.e., AEs that occur prior to assignment of trial treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

All AEs regardless of seriousness or relationship to trial drug(s), spanning from the start of trial treatment, until 30 calendar days after discontinuation of protocol-specific treatment as defined by the protocol for that patient, are to be recorded on the corresponding case report form (CRF).

11.2.3. Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the patient to discontinue trial treatment, or the investigator insists that the abnormality should be reported as an AE. Any grade 3 or 4 laboratory abnormalities or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF.

11.2.4. Handling of Adverse Events

All adverse events resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after discontinuation of protocol-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the CRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.3. Serious Adverse Events

11.3.1. Definitions of Serious Adverse Events

The definitions of serious adverse events (SAEs) are given below. The principal investigator is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Death due to disease progression will be recorded on the CRF and as an SAE up to 30 days post the last dose of trial drug.

Treatment within or admission to the following facilities is not considered to meet the criteria of “in-patient hospitalization” (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a serious adverse event to the Sponsor.

11.3.2. Serious Adverse Event Reporting by Investigators

It is important to distinguish between “serious” and “severe” adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the start of trial treatment through the 30-day follow-up period after the last trial treatment. The sponsor must be notified of all SAEs, regardless of causality, within one business day of the first knowledge of the event by the treating physician or research personnel.

To report a SAE, the appropriate CRF pages should be completed with the necessary information. The CRF pages required for SAE reporting include:

- Adverse Event and Safety Complementary pages
- Trial drug dosing
- Concomitant Medications
- Demographics
- Medical History

All SAEs and medically confirmed deaths (regardless of causality assessment) occurring on trial treatment or within 30 days of last trial treatment must be reported to the sponsor as SAEs within the CRF and followed until resolution (with autopsy report if applicable).

Deaths occurring 30 days after last trial treatment that are deemed 'possibly' or 'probably' related to trial drug must be reported as SAEs within the CRF (with an autopsy report if available).

Deaths occurring 30 after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

The investigator must review and sign off on the SAE data within the CRF. The SAE will be reported to the sponsor or designee as outlined in the Safety Monitoring Plan.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor or designee as soon as it is available; these reports should be submitted using the CRF. The detailed SAE reporting process will be provided to the sites in the Safety Monitoring Plan.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRBs)/Ethics Committee according to the policies of the responsible IRB/IEC.

Contact details for SCRI Innovations Sponsor Safety department are as follows:

Phone: 615-329-7941
Fax: 866-807-4325

11.3.3. Novartis Instructions for Rapid Notification of Serious Adverse Events

The Sponsor has the obligation to report all SAEs to Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E), and to report SAEs to the FDA and IRB as applicable. All events reported to the FDA are to be filed utilizing Form FDA 3500A (MedWatch Form), or other approved form.

All events must be reported by fax to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of its occurrence. This includes serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 1 business day of learning of its occurrence. Reports should be faxed to:

Novartis Pharmaceuticals
Clinical Safety and Epidemiology Dept.

Fax #: 888-299-4565

Any SAE occurring until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

11.3.4. Safety Reporting for Studies Done Under an IND

All written IND Safety Reports submitted to the FDA by the Sponsor must also be faxed to:

Novartis Pharmaceuticals
Clinical Safety and Epidemiology Dept.
Fax #: 888-299-4565

Onyx Drug Safety and Pharmacovigilance
Onyx Fax: (800) 783-7954

11.3.5. Onyx Instructions for Reporting Serious Adverse Events

All relevant SAEs will be reported to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements by the Sponsor.

All SAEs will be submitted to Onyx within 24 hours of learning of the events.

Onyx Drug Safety and Pharmacovigilance
Contact Information:

Onyx Fax: (800) 783-7954
SAE hotline: (510)-597-6501
E-mail: adverse.events@onyx-pharm.com

11.3.6. Sponsor SAE Reporting Requirements

The sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

The Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The sponsor will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use of the trial medications to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/IECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

11.4. Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in Section 11.3.2.

11.4.1. Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Coordinating Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

11.4.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE CRF.

11.4.3. Abnormal Laboratory Values

Any grade 3 or 4 laboratory abnormalities or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE CRF.

11.4.4. Deaths

For this protocol, progression-free survival is the primary efficacy endpoint; time to treatment-failure, overall survival, and response rate are secondary endpoints. Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the “Trial Discontinuation” CRF and reported as SAEs for up to 30 days post the last dose of trial drug. All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sponsor.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event page of the CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Death NOS” on the CRF Adverse Event page. During post-trial survival follow-up, deaths attributed to progression of disease will be recorded only on the “After Progressive Disease Follow-Up” CRF.

11.4.5. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE (refer to Section 11.3.1).

11.4.6. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.4.7. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 11.5 for specific instructions.

11.5. Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 11.2.1):

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form (a paper report form, not available within EDC system) should be completed and faxed to the sponsor. The sponsor should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.

Congenital anomalies/birth defects **always** meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

Trial Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the sponsor immediately (within one working day) using the corresponding screens in the CRF, and following the same process described for SAEs (see Section 11.3).

12. ETHICAL, FINANCIAL AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

12.1. IRB Approval

The trial protocol, investigators, informed consent form, IB, available safety information, patient documents (e.g., trial diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the trial start.

The Sponsor will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB trial review. The Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

12.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

Safety updates for panobinostat (Novartis) and carfilzomib (Onyx) will be prepared by the pharmaceutical company or its representative as required, for submission to the relevant regulatory authority.

12.3. Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

12.4. Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate

understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's consent to continue participation in the trial should be obtained.

12.5. Confidentiality

12.5.1. Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPPA) require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorised representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify patients on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or

database. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

12.5.2. Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.6. Financial Information

SCRI Innovations is sponsoring this study. The pharmaceutical company Novartis will provide funding to SCRI Innovations for this study, and will also provide the study drug panobinostat for all study participants. Onyx Pharmaceuticals provide funding to SCRI Innovations for this study, and will provide carfilzomib for all study patients. The physicians participating in this study will receive compensation from the SCRI Oncology Research Consortium.

13. RECORD RETENTION AND DOCUMENTATION OF THE STUDY

13.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of Novartis, Onyx, and the Principal Investigator supporting the trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to trial design, risk to patient, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by SCRI Innovations as applicable, after IRB approval and specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA approval include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase to dose or patient exposure to drug

- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

13.2. Documentation Required to Initiate the Trial

Before the study may begin, certain documentation required by FDA regulations must be provided by the Investigator. The required documentation should be submitted to:

SCRI Development Innovations, LLC
Regulatory Affairs
3322 West End Avenue, Suite 900
Nashville, Tennessee 37203
1-877-MY-1-SCRI
Fax #: (615) 297-2793

Documents at a minimum required to begin a trial in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract;
- A copy of the official IRB approval of the trial and the IRB members list;
- Current Curricula Vita for the principal investigator and any associate investigator(s) who will be involved in the trial;
- Indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB-approved consent form containing permission for audit by representatives of the Sponsor, SCRI Innovations, Novartis, Onyx, the IRB, and the FDA;
- Financial disclosure forms for all investigators listed on Form FDA 1572;
- GCP Certificate for trial training;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

13.3. Trial Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorised to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and trial staff are responsible for maintaining a comprehensive and centralised filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, PIs, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after

the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., CRFs and medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor will notify the investigator(s)/institutions(s) when the trial-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the trial, both the sponsor and its representative should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain the sponsor written permission before disposing of any records, even if retention requirements have been met. All trial files will be maintained by the Sponsor <or its representative> throughout the trial, and will be transferred to the Sponsor at the conclusion of the trial.

13.4. Data Collection

The trial CRF is the primary data collection instrument for the trial. CRFs will be completed using the English language and should be kept current to enable the monitor to review the patients' status throughout the course of the trial.

In order to maintain confidentiality, only trial number, patient number, initials and date of birth will identify the patient in the CRF. If the patient's name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

13.5. Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by the sponsor, government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial

monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, the sponsor or its representative(s).

At the Sponsor's discretion Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

13.6. Quality Assurance and Quality Control

Each trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7. Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

The financial disclosure information will be provided to the Sponsor prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

14. REFERENCES

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Wang L, Siegel D, Kaufman JL, Stewart AK, Jakubowiak AJ, Alsina M, Kukreti V, Bahlis NJ, McDonagh KT, Belch A, Sebag M, Gabrail N, Le MH, Bennett MK, Kunkel L, Kauffman M, Orlowski RZ, Vij R, and The multiple myeloma research consortium (MMRC). Updated results of bortezomib-naïve patients in PX-171-004, an ongoing open-label, phase II study of single-agent carfilzomib (CFZ) in patients with relapsed or Refractory myeloma (MM). Blood (ASH Annual Meeting Abstracts), Nov 2009; 114: 302.

15. APPENDICES

Appendix 1: ECOG Performance Status Criteria

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

Appendix 2: Diagnostic Criteria and Staging for Multiple Myeloma

International Myeloma Working Group Criteria for Diagnosis

The following criteria must be met except as noted:

- clonal bone marrow plasma cells ≥10%
- presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma*) and
- evidence of end-organ damage, which can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - hypercalcemia: serum calcium ≥11.5 mg/dL
    - renal insufficiency: serum creatinine >2 mg/dL
    - anemia: normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or, a hemoglobin value of <10 g/dL
    - bone lesions: lytic lesions, severe osteopenia or pathologic fractures

*More than 10% clonal plasma cells are required for the diagnosis of nonsecretory myeloma

Dimopoulos., et al., Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. 2011 Blood J 117: 4701-4705

A. Durie and Salmon Staging System

Stage I

All of the following:

- Hemoglobin >10 g/dL
- Serum calcium <12 mg/dL
- Normal bone structure or solitary plasmacytoma on radiographs
- Low M component
    - IgG <5 g/dL
    - IgA <3 g/dL
    - Urine light chains <4 g/24 hours

Stage II

Fitting neither Stage I nor Stage III

Stage III

One or more of the following:

- Hemoglobin < 8.5 g/dL
- Serum calcium >12 mg/dL
- Advanced lytic bone lesions
- Hyper M component
    - IgG > 7 g/dL
    - IgA > 5 g/dL
    - Urinary light-chain excretion > 12 g/24 hour

Subclassification

A: serum creatinine < 2.0 mg/dL

B: serum creatinine equal to or > 2.0 mg/dL

B. International Staging System (ISS) for Myeloma

Stage I	Serum $ß_2$-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
Stage II	Fitting neither Stage I nor III*
Stage III	Serum $ß_2$-microglobulin ≥ 5.5 mg/L

*There are two categories for stage II: serum $ß_2$-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum $ß_2$-microglobulin ≥ 3.5 mg/L and < 5.5 mg/L irrespective of the serum albumin level.

Greipp P., et al., International staging system for multiple myeloma. 2005. JCO 23:3412-3420

Appendix 3: International Myeloma Working Group Uniform Response Criteria[a]

Response Category	Definition
sCR **Stringent Complete Response**	CR criteria as defined below AND • Normal free light chain (FLC) ratio AND • Absence of clonal PCs by immunochistochemistry or 2-to 4-color flow cytometry
CR **Complete Response**	• Negative immunofixation on the serum and urine AND • Disappearance of any soft tissue plasmacytoma(s) AND • ≤ 5% plasma cells in bone marrow[b]. • In case the only measurable disease in a patient with CR at baseline is the serum FLC level, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR.
VGPR **Very Good Partial Response**	• Serum and urine M-protein detectable by immunofixation but not by electrophoresis (PEP) or ≥90% reduction from baseline serum) AND urine M-protein level <100 mg/ 24h AND • In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytomas In case the only measurable disease in a patient with VGPR at baseline is the serum FLC level (i.e. no measurable disease in serum and urine PEP), a decrease of > 90% in the difference between involved and uninvolved FLC levels from baseline is required.
PR **Partial Response**	≥50% reduction from baseline in serum M-protein AND ≥ 90% reduction from baseline in 24h urinary M-protein OR urine M-protein <200 mg/24h If serum and urine M-protein are non-measureable at baseline, a ≥ 50% reduction form baseline in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are non-measurable, and serum free light assay is also non-measurable, ≥50% reduction from baseline in percent plasma cells in bone marrow is required instead of M-protein measurement, provided baseline plasma cells in bone marrow was ≥ 30%. AND In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in the SPD by ≥50% is required.

Appendix C: International Myeloma Working Group Uniform Response Criteria: Complete Response and Other Response Categories (continuation)

SD	Not meeting criteria for sCR, CR, VGPR, PR or PD
PD[c] **Progressive Disease**	Increase of ≥ 25% from the nadir in at least one of the following criteria: • serum M-protein (absolute increase must be ≥0.5 g/dL) • urine M-protein (absolute increase must be ≥200 mg/24h) • only in patients with non-measurable serum and urine M-protein levels: difference in involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • only in patients with non-measurable serum and urine M-protein levels and non-measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥10%) OR • definite development of new lytic bone lesions or increase from baseline in size of lytic bone lesion(s) OR • development of new soft tissue plasmacytoma(s) or definite increase from nadir in existing soft tissue plasmacytomas OR • development of hypercalcemia (corrected serum calcium >11.5 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will only be assessed due to the hypercalcemia criterion in case the corrected serum calcium level was ≤11.5 mg/dL post-baseline and increased thereafter beyond 11.5 mg/dL.
Patients with relapsed refractory myeloma (adopted from the European Group for Blood and Marrow Transplantation [EBMT] criteria)	
MR **Minimal Response**	• ≥25% but ≤49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% AND • If present at baseline, 25-49% reduction in the size of sort tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response

[a]All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]At any point in this treatment, patients suspected of PD will have response assessed again to confirm disease progression (i.e. 2 sets of response assessments at least 1 week apart). The outcomes will be reviewed by the study chair before the patient is removed from the study

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

Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high dose therapy and haemopoietic stem cell transplantation:

Myeloma Subcommittee of the EBMT, European Group for Blood and Marrow Transplant. *Br J Haematol.* 1998;102(5):1115-1123.

Appendix 4: New York Heart Association (NYHA)

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in i*nab*ility to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 222

Appendix 5: Schedule of Assessments MM 27

Procedures	Pre-Treatment	Cycle 1 Cycle = 28 days							Cycle 2 and beyond			Restage Every Cycle (4 weeks)	End of Study Treatment [O]	Follow-up	
	Baseline[A]	Day[I,J]							Day[I,J]					Off Study Prior to Progression[P]	After Disease Progression [Q]
		1	2	5	8	9	15	16	1	8	15				
TESTS & OBSERVATIONS															
Medical history	X						X		X[D]				X	X	
Physical examination	X	X					X		X[D]				X	X	
Vital signs, height, weight [B]	X	X	X	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X							X				X	X	
12-lead ECG	X	X[G]		X[G]					X[H]				X	X	
Chest x-ray	X														
MUGA or ECHO	X[K]														
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X		X	X	
Concomitant medication review	X	X			X		X		X	X	X		X	X	
Survival Status															X
LABORATORY TESTS															
CBC, 3-part differential & platelets	X	X			X		X		X	X	X		X	X	
CMP[C] plus magnesium & phosphorus	X	X			X		X		X				X	X	
Uric acid & LDH[C]	X	X			X		X		X[S]				X[S]		
PT/INR[F]	X	X[F]			X[F]		X[F]		X[F]						
Serum or Urine β-HCG[E]	X														
DISEASE ASSESSMENTS[T]															
Bone Marrow Aspiration/Biopsy[L]	X											X[L]			
Skeletal Survey[N]	X														
Serum free light chain	X											X[M]	X[M]	X[M]	
Serum immunoglobulin G, A, M	X											X	X	X	
Serum β-2 microglobulin	X														
SPEP & immunofixation	X											X	X	X	
UPEP & immunofixation	X[R]											X[R]	X[R]	X[R]	

Appendix E: Schedule of Assessments for MM 27 Phase I Portion (continued)

A The physical examination, ECOG PS, CBC, CMP, PT/INR, urinalysis, and pregnancy test should be done <7 days prior to initiation of treatment. However, if these initial examinations are obtained ≤72 hours of Cycle Day1 they do not have to be repeated.

B Vital signs are defined as height, blood pressure, pulse, respirations, weight. Only at the baseline visit, height will be recorded.

C CMP includes the following laboratory tests: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, total protein, and albumin plus magnesium and phosphorus. Uric acid and LDH will also be collected during Cycle 1. Cycle 2 and beyond (and end of study) Uric acid and LDH will be obtained if clinically indicated. Labs may be obtained ≤72 hours of any or all assessments.

D Update of the medical history and physical examination should be obtained on D1 (+/- 72 hrs) of each cycle after Cycle 1 until progression.

E A serum pregnancy test will be performed **only** for women of childbearing potential (see Section 3.3.1).

F Evaluation should be performed at screening visit and repeated at investigator's discretion, if medically indicated. If patient is receiving warfarin or other anti-coagulant therapy, coagulation parameters should be monitored as indicated.

G On Cycle 1 Day 1, and Cycle 1 Day 5, three ECGs will be obtained 5-10 minutes apart before the patient takes panobinostat, and will be repeated (x 3, 5-10 minutes apart) approximately 3 hours after the panobinostat dose is taken orally.

H If no problems with QTc prolongation occur during Cycle 1, a single pre-dose ECG on Day 1 of each subsequent cycle is required.

I Oral hydration – (6-8 cups of liquid per day) starting 48 hours prior to the 1st dose of carfilzomib (i.e. Day -2 and Day -1, Cycle 1), and prior to all carfilzomib doses during Cycle 1. In patients considered at risk for TLS, oral hydration should be continued in Cycle 2 and beyond as required by the patient's medical condition and at the study doctor's discretion.

J IV hydration – 250-500 mL of NS (or other IV formulation) before and after each carfilzomib dose during Cycle 1 (Days 1, 2, 8, 9, 15 and 16). If LDH or uric acid is elevated at Cycle 2, Day 1, the recommended hydration should be repeated for Cycle 2.

K MUGA or ECHO must demonstrate LVEF> the lower limits of the institutional normal.

L Bone marrow should be sent for flow cytometry, cytogenetics and FISH for 1q amplification, 1p del, t(4;14), t(11;14), t(14;16) and 17p del). Repeat if clinically indicated or only to document a CR.

M Repeat if abnormal at baseline.

N Skeletal survey need only be repeated if clinically indicated (i.e. bone pain).

O After patients are discontinued from the study, they will visit the study center ≤30 days from the date of last dose of study drug for end-of treatment-assessments.

P Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months during years 1 and 2, every 6 months during years 3-5, and annually thereafter for toxicity, disease progression, and survival.

Q After disease progression is documented, patients will be followed every 3 months for survival assessment.

R UPEP requires the collection of a 24-hour urine sample.

S Evaluation should be performed at screening visit and C1 as indicated to monitor for TLS. If LDH and uric acid were normal during Cycle 1, repeat at study doctor's discretion, if clinically appropriate from C2 to progression (e.g. patients considered still at risk for TLS).

T Restaging must be done ≤ 7 days Day 1 of each cycle.

Appendix 6: Drugs That Prolong QT Interval and/or Induce Torsades De Pointes

Patients who are receiving treatment with any of the medications in the table below, and cannot either discontinue form this treatment or switch to a different medication prior to study enrollment, will be excluded from this study. Patients may not begin study treatment while receiving any of the medications identified below. If a patient must receive these drugs, the patient should be removed from study. Enrolling patients should be off study treatment at least 72 hours prior to taking the first dose of a medication listed below. This is not a comprehensive list. A complete list may be found and updated at the following web address: qtdrugs.org/medical-pros/drug-lists/drug-lists.htm.

Antiarrhythmics
Amiodarone (Cordarone®) (Pacerone®)
Disopyramide (Norpace®)
Dofetilide (Tikosyn®)
Ibutilide (Corvert®)
Procainamide (Pronestyl®) (Procan®)
Quinidine (Quinaglute®) (Cardioquin®)
Sotalol (Betapace®)

Antibiotics
Clarithromycin (Biaxin®)
Erythromycin (Erythrocin®) (E.E.S. ®)
Gatifloxacin
Moxifloxacin
Sparfloxacin (Zagam®)

Antipsychotics
Chlorpromazine (Thorazine®)
Haloperidol (Haldol®)
Mesoridazine (Serentil®)
Pimozide (Orap®)
Risperidone
Thioridazine (Mellaril®)
Ziprasidone

Appendix F: Drugs That Prolong QT Interval and/or Induce Torsades De Pointes (continuation)

Antidepressants
Amitriptyline
Desipramine
Doxepin
Imipramine
Maprotiline
Venlafaxine
Antifungals (azoles)*
Ketoconazole
Itraconazole
Antimalarials
Chloroquine (Arelan®)
Halofantrine (Halfan®)
Antiemetics
Dolasetron
Domperidone (Motilium®)
Droperidol (Inapsine®)
Ondansetron
Tropisetron
Miscellaneous
Arsenic trioxide (Trisenox®)
Bepridil (Vascor®)
Methadone (Methadose®)
Pentamidine (NebuPent®)
Cisapride (Propulsid®)
Tacrolimus

Appendix 7: Substrates, Inducers and Inhibitors of Isoenzyme CYP3A4 and CYP2D6 Substrates

CYP3A4 SUBSTRATES (*Competitive Inhibition*)		CYP3A4 INHIBITORS	CYP3A4 INDUCERS
Antibiotics: clarithromycin[a] erythromycin telithromycin[a] **Anti-Arrhythmics:** quinidine **Benzodiazepines:** alprazolam diazepam midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) **HIV Protease Inhibitors:** indinavir[a] ritonavir[a] saquinavir[a] **Prokinetic:** cisapride **Antihistamines:** astemizole chlorpheniramine	**Calcium Channel Blockers:** **amlodipine** **diltiazem** **felodipine** **nifedipine** **nisoldipine** **nitrendipine** **verapamil** **HMG CoA Reductase Inhibitors:** **atorvastatin** **cerivastatin** **lovastatin** **simvastatin** **Miscellaneous:** aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine	**Inhibitors:** Amiodarone Cimetidine Clarithromycin Delaviridine Diltiazem Erythromycin Fluvoxamine[a] Grapefruit juice Seville orange Indinavir Itraconazole[a] Ketoconazole[a] Voriconazole[a] Posaconazole[a] Mibefradil Nefazodone[a] Nelfinavir[a] Troleandomycin Verapamil	**Inducers:** Carbamazepine Phenobarbital Phenytoin[a] Rifabutin[a] Rifampin[a] St John's wort Troglitazone **Others:** barbiturates glucocorticoids modafinil pioglitazone

From: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and
[http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

[a] Strong inhibition/ induction ("strong inhibitor" implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates; moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values, or 50-80% decrease in clearance of sensitive CYP substrates. Distinction is not always categorical as interaction can vary according to conditions).

Drugs that are CYP2D6 substrates

If CYP2D6 substrates listed in Table 10 below are used concomitantly with panobinostat, patients should be carefully monitored and may require dose titration or dose reduction of the CYP2D6 substrate.

Beta blockers (listed below):	**Antipsychotics (listed below):**
carvedilol	aripiprazole
metoprolol	haloperidol
bufuralol	perphenazine
alprenolol	risperidone
nebivolol	thioridazine
propranolol	chlorpromazine
timolol	duloxetine
Antidepressants (listed below):	fluoxetine
amitriptyline	fluvoxamine
clomipramine	venlafaxine
desipramine	Antiarrhythmics (listed below):
imipramine	encainide
nortriptyline	flecainide
paroxetine	lidocaine
venlafaxine	mexiletine
Antiemetics (listed below):	propafenone
dolasetron	Others:
ondansetron	amphetamine
metoclopramide	atomoxetine
	codeine
	hydrocodone
	dextromethorphan
	promethazine
	tamoxifen
	tramadol

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/flockhart/clinlist.htm