PROTOCOL INFORMATION

Study Title: PHASE I/IIA STUDY CARFILZOMIB + HIGH DOSE MELPHALAN AS PREPARATIVE REGIMEN FOR AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA

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Amendment #6 dated November 21, 2014

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Amendment #5 dated May 22, 2014
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PROTOCOL SYNOPSIS

TITLE: Phase I/IIa Study of Carfilzomib + High Dose Melphalan as Preparative Regimen for Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma

OBJECTIVES:

PRIMARY OBJECTIVE

Phase I: To determine the MTD of carfilzomib when added to standard melphalan conditioning for AHSCT in relapsed MM.

Phase IIa: To evaluate the anti-myeloma activity and the toxicity of carfilzomib + high dose melphalan conditioning in relapsed MM.

SECONDARY OBJECTIVES

To describe the pharmacodynamic effects of carfilzomib + high dose melphalan in terms of changes in expression of fanconi anemia/BRCA DNA repair genes and DNA fragmentation.
To provide preliminary pharmacodynamic, safety and patient preference data on two schedules of carfilzomib maintenance therapy after AHSCT.

STUDY DESIGN: The study has a phase I/IIa design. Phase I will be a standard 3+3 dose escalation. The phase IIa portion of the study will expand the MTD cohort, (or cohort 4 if no MTD is identified), to enroll a total of 28 patients using a single stage design. This expansion phase will also include evaluation of two single agent carfilzomib

	maintenance therapy regimens for patients without disease progression at day 100. See section 3 Experimental Plan for more detail.
STUDY POPULATION:	Patients with relapsed MM and indication for autologous HSCT.
INCLUSION CRITERIA:	1. Age ≥ 18 years (or age of majority at participating site, whichever is greater) and ≤ 70 years. 2. Life expectancy ≥ 12 months. 3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2. 4. Diagnosis of symptomatic multiple myeloma, relapsed after initial therapy. 5. At least minimal response (defined as 25% decrease in the M protein in serum or urine) to the most recent treatment regimen. 6. Evaluable disease prior to the most recent reinduction regimen as defined by at least one of the following: -Serum monoclonal (M) protein ≥0.5 g/dl by protein electrophoresis ->200 mg of M protein in the urine on 24 hour electrophoresis - Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio - Monoclonal bone marrow plasmacytosis ≥30% 7. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 14 days prior to registration. 8. Hemoglobin ≥ 8 g/dL (80 g/L) within 14 days prior to start of therapy (subjects may be receiving red blood cell [RBC] transfusions in accordance with institutional guidelines). 9. Creatinine clearance (CrCl) ≥ 40 mL/minute within 14 days prior to start of therapy, either measured or calculated using a standard formula (eg, Cockcroft and Gault). 10. Prior storage of at least 2 x 10^6 CD34+ cells/kg available for autologous transplantation. During the phase I component of

the study, at least the same amount of cells is required as "back up" in the unlikely event of non-engraftment.

11. Subjects may have had a prior AHSCT for the treatment of MM as long as it was performed greater than 12 months from study registration.
12. Subjects must meet institutional general eligibility criteria for autologous transplantation.
13. Written informed consent in accordance with federal, local, and institutional guidelines.
14. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception. Male subjects must agree to practice contraception.

EXCLUSION CRITERIA:

1. Pregnant or lactating females.
2. Major surgery within 30 days prior to start of treatment.
3. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to registration.
4. Known human immunodeficiency virus infection.
5. Active hepatitis B or C infection.
6. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
7. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration.
8. Nonhematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.

9. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to registration.
10. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
11. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration.
12. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

STUDY PROCEDURES:

Patients enrolled during the Phase I portion of the study will only follow procedures related to conditioning therapy and autologous HSCT (day -30 screening through day 100 disease assessment).

Patients enrolled during the Phase IIa portion of the study will follow procedures related to conditioning therapy at the MTD and autologous HSCT (day -30 screening through day 100 disease assessment). In addition, for eligible patients, single agent carfilzomib maintenance therapy will be administered for a maximum of 12 cycles (one cycle equals 28 days).

CONDITIONING THERAPY AND AUTOLOGOUS HSCT
(day -30 screening through day 100 disease assessment)
Applicable during Phase I and Phase IIa study activity

Screening – Subjects likely to meet eligibility criteria will be offered participation in the study after the investigator verifies UAB CTNMO registration. During the phase I portion, investigators should have confirmed with MUSC availability of a cohort slot prior to offering study participation. Subjects will sign informed consent prior to any protocol associated procedure. Screening procedures are outlined in Table 7 and will 1) ensure that subject meets all the eligibility criteria, 2) obtain disease

assessment to allow efficacy measurements, 3) assess baseline toxicity, and 4) provide initial biological samples for pharmacodynamic and correlative studies.

Conditioning Treatment- Subjects will receive the appropriate dose of carfilzomib on days -3 and -2. The Phase I portion of the study was completed and data was reviewed on October 28, 2013. There were no DLT even at the highest dose cohort and the MTD was not identified. Therefore, phase II enrollment is ongoing at the maximum tested dose of 27 mg/m^2 on day -3 and 56 mg/m^2 on day -2. Carfilzomib will be infused over 30 minutes (±10 minutes) as described in section 6.1.1. On day -2, with 60 to 120 minutes of the end of infusion of carfilzomib, subjects will receive 200 mg/m2 of intravenous melphalan as an intravenous push or a fast infusion, according to institutional standard operating procedure (SOP) (also see section 6.1.2). Prophylaxis of chemotherapy induced nausea and vomiting will follow institutional guidelines and SOPs.

Infusion of autologous cells- Infusion of autologous hematopoietic stem cells will occur on day 0 and follow institutional SOP.

Post AHSCT Follow-up phase – On day 1 following AHSCT, patients will receive pegfilgrastim 6 mg subcutaneously (single dose) or start filgrastim 5 mcg/kg/day subcutaneously that will continue daily at least until absolute neutrophil count > 500/mm^3 for 2 consecutive days as per institutional standard of care aiming at faster engraftment. The post AHSCT follow-up phase will last 100 days (+/- 7 days) and will consist of standard post transplantation supportive care and monitoring of AEs. For the phase I component of the study, dose-limiting toxicities will be captured during the first 30 days after transplantation (DLT period).

Post AHSCT Disease assessment- Disease assessment will occur at day 100 (+/- 7 days) and will consist of interim medical history and physical exam assessment, serum protein electrophoresis, serum and urine immunofixation, 24h urine protein electrophoresis, serum free light chains, bone marrow aspiration and biopsy, complete blood counts and metabolic panel including uric acid and phosphorus. Disease response will be categorized according to appendix B. Patients enrolled to the Phase I portion of the study will only be followed until the disease assessment visit at day 100 (+/- 7 days) and resolution of any treatment related toxicities to baseline or until toxicities have been deemed irreversible by the investigator.

MAINTENANCE THERAPY

(post day 100 disease assessment through a maximum of twelve 28 day maintenance cycles)

Applicable only to phase IIa study activity

Screening for Maintenance Therapy- Patients must undergo Day 100 disease assessment and be without disease progression in order to continue with maintenance therapy. Patients must be registered by UAB CTNMO prior to starting any maintenance therapy. Maintenance registration forms are included in the UAB CTNMO case report form packet. Registration can occur any time after day 100 assessments are completed, but subjects must start maintenance therapy by day 120 after transplantation. At the time of registration, patients will be randomized to Arm 1 or Arm 2.

Maintenance therapy – Maintenance regimen A will consist of carfilzomib 36 mg/m2 infused over 30 minutes (±10 minutes) on days 1,8,15. Maintenance regimen B will consist of carfilzomib 36mg/m2 infused over 30 minutes (±10 minutes) on days 1, 2, 15 and 16. Each cycle will have 4 week duration. The first four maintenance therapy cycles will be dictated by a randomized assignment at time of study registration to maintenance therapy. Patients will either be randomized in blocks of two to either maintenance therapy **Arm 1**= AABB (two cycles of A followed by two cycles of B), or maintenance therapy **Arm 2=** BBAA (two cycles of B followed by two cycles of A). For both maintenance therapy arms, a patient preference questionnaire will be administered to the patient upon completion of the 4^{th} cycle. The remaining 8 cycles (cycles 5-12) will be administered according to the regimen schedule preferred by the patient as documented on the patient preference questionnaire.

Maintenance Therapy Disease Assessment- During maintenance therapy, disease assessments will occur at the end of each even cycle and consist of medical history and physical exam assessment, serum protein electrophoresis, serum and urine immunofixation, 24h urine protein electrophoresis, serum free light chains, complete blood counts and metabolic panel including uric acid and phosphorus. Bone marrow aspiration and biopsy will only be performed if needed to confirm complete response. Patients will complete Quality of Life assessments at the end of each even cycle.

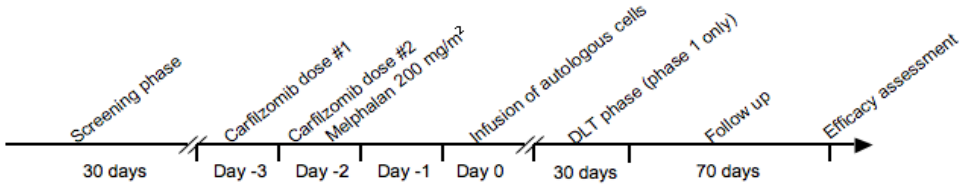
Maintenance Therapy Follow-Up- For the phase IIa portion of the study, patients will be followed until the completion of the last 4-week cycle of maintenance carfilzomib therapy (up to a maximum of twelve cycles) and resolution of all treatment

	associated toxicity to baseline or until the toxicity is deemed irreversible by the investigator.
PRIMARY ENDPOINT:	Phase I – The primary endpoint in phase I is the occurrence of a dose-limiting toxicity as defined in section 3.1.1.1. Phase IIa – Rate of very good partial response (VGPR) + complete response (CR) in patients with relapsed MM treated with the melphalan + MTD of Carfilzomib (or maximum tested dose if MTD is not reached) as determined in the phase 1 component of the study.
SECONDARY ENDPOINTS:	Phase I and IIa – Pharmacodynamic effects of this combination at the proposed doses and schedule: changes in expression of Fanconi anemia/BRCA DNA repair genes and DNA fragmentation. Phase IIa – Rate of overall response, defined as CR+VGPR+PR (Appendix B). Rate of PFS 12 months after AHSCT in the setting of carfilzomib + melphalan conditioning and carfilzomib maintenance therapy. Pharmacodynamic effect of maintenance regimens A and B assessed by proteasome inhibition in peripheral blood mononuclear cells. Subject's preference for maintenance regimens A and B.
STATISTICAL METHODS:	Phase I will be a standard 3+3 dose escalation study to include between 9 and 30 patients. However, it is highly unlikely that 30 patients will be enrolled (this would occur if dose expansion to 6 patients per level occurred at all dose levels 0 through 4) and expected enrollment is 18 or fewer. The phase IIa portion of the study will expand the MTD cohort, (or cohort 4 if no MTD is not reached), to enroll a total of 28 patients using a single stage design. More specifically, N=28 provides a halfwidth of <0.20 for the 95%

confidence interval for any response rate. This precision will provide sufficient information to determine if the regimen is sufficiently promising, in conjunction with the safety information learned in the phase IIa portion. Due to the 100 day lag between treatment and evaluation, an interim analysis for the primary endpoint is not feasible. PFS will be graphically displayed using Kaplan-Meier curves and 12 month PFS will be estimated with its 95% confidence interval. For those patients in the maintenance phase of the phase IIa portion of the study, proteasome inhibition will be treated as a continuous variable and summarized by treatment arm using graphical displays and summary statistics. Preference for A vs. B and completion rates will be estimated by proportions with exact 95% confidence intervals. Given that the number of patients in the maintenance portion of the study is expected to be small (20-22), hypothesis testing will not be performed to compare patients who receive A first versus those who receive B first.

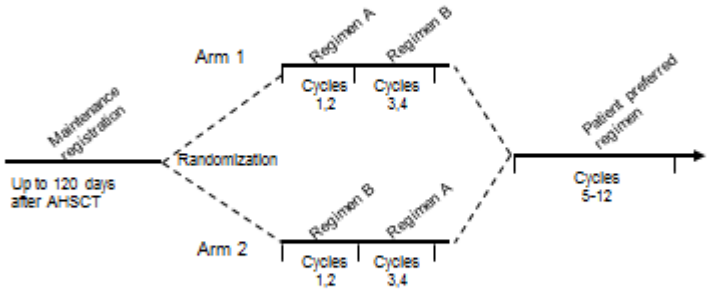
SCHEMA

Phases I and II transplant schema



	Carfilzomib dose #1	Carfilzomib dose #2
Cohort -1	20 mg/m²	20 mg/m²
Cohort 0	20 mg/m²	27 mg/m²
Cohort 1	27 mg/m²	27 mg/m²
Cohort 2	27 mg/m²	36 mg/m²
Cohort 3	27 mg/m²	45 mg/m²
Cohort 4	27 mg/m²	56 mg/m²

Phase II maintenance schema



	Carfilzomib dose	Treatment days
Regimen A	36 mg/m² over 30 minutes	1, 8, 15
Regimen B	36 mg/m² over 30 minutes	1, 2, 15, 16

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degrees Centigrade
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (also PTT)
AST	aspartate aminotransferase
bid	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CR	complete response
CrCl	Creatinine Clearance
CRF	case report form(s)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	deciliter
DLT	dose-limiting toxicity
DVT	deep venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram(s)
LDH	lactate dehydrogenase
mg	milligram(s)
min	minute(s)
mIU	Milli International Units
mL	milliliter(s)
MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
MR	minimal response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose in 10% of animals
TLS	Tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis

VGPR	very good partial response
WBC	white blood count

1 INTRODUCTION

1.1 DISEASE SPECIFIC BACKGROUND

Multiple Myeloma (MM) is a malignant plasma cell disorder with no standard curative therapy.[1] Symptomatic MM is characterized by a clonal proliferation of plasma cells preceding clinical findings that include bone lesions, fractures, anemia, renal failure and hypercalcemia.[2] MM affects 4.3 per 100,000 individuals yearly[3] and accounts for about 1% of all cancers and 10% of all hematological malignancies in the United States.[2]

For decades, low doses of melphalan and prednisone was the cornerstone of MM treatment. However, complete responses under this regimen are rare, and the median time for progression is not higher than 15 months[4,5]. A first significant advance in the management of MM was the upfront use of high doses of melphalan with autologous hematopoietic stem cell transplantation (AHSCT). Such treatment has allowed for improved response rates, progression free survival and, in some trials, prolonged survival in MM[6-9]. High dose melphalan with AHSCT is considered a fundamental therapeutic modality to be explored by younger patients upfront (after response to conventional induction therapy) and/or at the time of disease progression.

The advent of new "biological" agents in treatment regimens for MM has led to marked improvement in the depth and duration of the responses obtained. The immunomodulatory drugs thalidomide and lenalidomide, along with the first proteasome inhibitor, bortezomib, have shown efficacy in the management of both newly diagnosed as well as relapsed and refractory MM patients [1,10-12]. Treatment of MM patients with combination regimens, containing one or more biological agents, followed by autologous HSC transplantation consolidation have resulted in the highest response rates ever reported in the management of newly diagnosed MM patients[13-18].

1.2 PROTEASOME BACKGROUND

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

1.3 CARFILZOMIB BACKGROUND

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[19,20].

1.3.1 CARFILZOMIB TOXICOLOGY STUDIES

In the initial Good Laboratory Practice (GLP)-compliant toxicity studies done by the drug maker, Onyx, carfilzomib was administered to rats and monkeys as two complete two-week cycles of QDx5 for five days with nine days rest[21]. Administration to rats at 12 mg/m^2, the severely toxic dose in 10% of animals (STD_{10}) caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomib. Daily administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The dose-limiting toxicities (DLTs) of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or

histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In 6-month rat and 9-month chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the active anti-tumor regimen being used in ongoing Phase II studies in myeloma and solid tumors[21]. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity, including neuropathology, observed, even at high doses. This is in stark contrast to that observed with bortezomib[14,22]. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to be related to Cmax effects. Of note, neutropenia was not observed; rather, transient neutrophilia was seen following acute dosing. Renal, cardiovascular and gastrointestinal toxicities were similar to those observed with bortezomib. Finally, cyclical thrombocytopenia, likely due to inhibition of platelet budding from megakaryocytes, was similar to that seen with bortezomib. Proteasome inhibition in the blood in excess of 90% was achievable at well-tolerated doses, which contrasts with the ~70% proteasome inhibition achieveable with bortezomib at its maximum tolerated dose (MTD). In summary, these animal toxicity studies support the tolerability of carfilzomib in clinical studies, even on intensive dosing schedules and at doses achieving proteasome inhibition in excess of what can be achieved with bortezomib at its MTD on a less intensive schedule.

1.3.2 CARFILZOMIB PRECLINICAL ANTITUMOR ACTIVITY

Based upon the results of *in vitro* and *in vivo* studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti-tumor activity relative to bortezomib. Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture[12,19]. Incubation of hematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines[12,19].

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant

reduction in tumor size and was superior to a twice-weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level. Bortezomib at its MTD has no activity in this xenograft model using the standard Day 1, Day 4 schedule[19].

1.3.3 PHASE 1 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

A Phase 1 clinical trial, PX-171-002, testing carfilzomib in subjects with relapsed/refractory hematologic malignancies, is being completed[23]. During the dose escalation portion of the trial, 36 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

No dose limiting toxicities (DLTs) were observed in the initial seven cohorts (doses ranged from 1.2 to 15 mg/m^2) of three subjects each. At the 20 mg/m^2 dose level, one of eight patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m^2 dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m^2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were rechallenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M-protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels although some increases in LDH and other markers of tumor lysis were noted. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies and have

essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects.

Hematologic toxicities were primarily mild or moderate. The thrombocytopenia reported with carfilzomib is cyclical and similar to that reported with bortezomib. The cause and kinetics of the thrombocytopenia following treatment are different from those of standard cytotoxic agents. To maximize the likely benefit of carfilzomib, subjects with thrombocytopenia should be supported as clinically indicated rather than having treatment reduced due to thrombocytopenia.

Of the 36 evaluable patients enrolled in PX-171-002, 20 had MM[7]. Four MM patients achieved a partial response (PR), one of two at the 15 mg/m^2 dose, one of six at the 20 mg/m^2 dose, and two of five at the 27 mg/m^2 dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m^2 wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. These results led to the initiation of two Phase 2 studies.

1.3.4 PHASE 2 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

Two Phase 2 clinical studies are ongoing with carfilzomib in 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 dosed with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional patients with relapsed or refractory MM treated in ongoing Phase II studies. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased serum creatinine that were primarily

< Grade 2 and were transient, rapidly reversible, and non-cumulative. 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[24].

The response rate in PX-171-003-A0 was 18% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time to progression on the PX-171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months)[24].

A "stepped up" dosing schedule, referred to as 20/27 mg/m^2, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) 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. To date, this dosing schedule has been well tolerated[7]. 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% in A1 (from 15% in A0), most likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. 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-A1[24]. 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[24].

In PX-171-004, a first cohort of patients received 20 mg/m^2. The subset of patients (N=54) that had not seen bortezomib had an 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)[25,26]. The median TTP was 7.6 and 5.3 months in these two groups, respectively. Thus, carfilzomib

can induce very high levels of response in patients who have not previously been treated with bortezomib and, even in bortezomib-treated patients, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicities (e.g., bone marrow, severe fatigue, or neuropathy) have been observed. The protocol was amended to allow patients to increase to 27 mg/m^2 in Cycle 2 or later based on tolerability, similar to that used in PX-171-003 – A1.

Based on its single agent activity, carfilzomib received FDA accelerated approval on July 20, 2012 for "the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy".

1.3.5 EXPERIENCE WITH CARFILZOMIB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE

PX-171-006 is an ongoing Phase 1b study in patients with relapsed multiple myeloma in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and dexamethasone. "Low-dose" dexamethasone 40 mg/day is given on Days 1, 8, 15, and 22 in all cases. Carfilzomib is administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide is administered PO on Days 1 through 21.

Enrollment has closed in this study, and no MTD was reached. The maximum per protocol doses of carfilzomib (27 mg/m^2) with lenalidomide 25 mg and low dose dexamethasone are being used[27]. After 8 patients tolerated these doses well, an additional 44 patients were enrolled in an "expansion" cohort at this level, and this regimen is being taken into Phase III in study PX-171-009.

To date, 40 patients were treated in cohorts 1-6 and 44 in the cohort 6 expansion. 27/32 patients in cohorts 1–5 are evaluable for safety and 29/32 for response. Patients were heavily pre-treated; 72% received prior BTZ and 87.5% received prior LEN or thalidomide (Thal). 47% of patients were refractory to their last therapy (typically lenalidomide + high dose dexamethasone; > 84% of patients had a history of neuropathy with 67% BTZ- or Thal-related. No treatment emergent

fatigue, neuropathy, or thrombotic events ≥ Grade (G) 3 were observed. Hematological AEs ≥ G3 (thrombocytopenia [n=6], anemia [n=4], and neutropenia [n=6]) were reversible. Four patients had drug-related SAEs as follows: transient G3 sinus bradycardia, G3 upper respiratory tract infection, febrile neutropenia, and G3 diarrhea + G3 urinary infection. ORR and CBR for the 29 evaluable patients are 59% and 72%, respectively. Response data is shown in the table below. Initial responses improved with continued therapy (up to 18 cycles). Median duration of response has not been reached (median follow-up 5.2 months). No dose-limiting toxicities or deaths attributed to study treatment have been observed. Several patients have completed the study (in the lower dose cohorts) after 18 cycles and are continuing in an extension study. Updated efficacy data are presented in the following table:

Table 1

	CRd: Cohorts 1–5 (CFZ: 15 to 20 mg/m2; LEN: 10 to 25 mg)		
Response	**Relapsed (n=16)**	**Refractory (n=13)**	**Overall (n=29)**
≥ CR/nCR	5 (31)	1 (8)	6 (21)
≥ VGPR	7 (44)	4 (31)	11 (38)
≥ PR	9 (56)	8 (62)	17 (59)
≥ MR	11 (67)	10 (77)	21 (72)

Together, these results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in combination are active and well tolerated and that there are no significant overlapping toxicities (in the dose ranges tested). Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with carfilzomib, even up to 27 mg/m^2, suggesting that carfilzomib will combine well with other anti-cancer agents.

1.4 DOSE RATIONALE

Preliminary data suggest that carfilzomib, as a single agent, can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m^2. Maximum proteasome inhibition was seen at doses 11 mg/m^2 and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination

half life of < 60 minutes at the 20 mg/m^2 dose. Large, single arm studies of the 27 mg/m^2 dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

By the end of 2009, 269 patients with relapsed and refractory multiple myeloma have been enrolled in the PX-171-003-A1 study. The goal of dose escalating to 27 mg/m^2 beginning with Cycle 2 is to improve ORR, DOR, and TTP.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 minute infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of carfilzomib *above the MTD* at a dose of 48 mg/m^2 include evidence of prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m^2 when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m^2) as a 30 minute continuous infusion was well tolerated, with no changes in BUN and creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of carfilzomib for 30 minute was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced C_{max} of carfilzomib versus that with bolus dosing. Inhibition of the pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD of carfilzomib has not been reached in the multiple myeloma (MM) setting, particularly when administered as a 30 minute infusion. 27 mg/m^2 of carfilzomib (bolus administration over 2-10 minutes) is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities.

A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib administered is ongoing and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m^2 (bolus administration over 2-10 minutes). 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 27 mg/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 of carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

More recently in the PX-171-007 trial, patients have been treated with carfilzomib given as a 30-minute infusion in order to potentially minimize Cmax-related infusion events. The protocol was amended and doses 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/m2 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 with the lower doses being 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 20/56 mg/m^2, dexamethasone was increased from 4 mg/dose to 8mg with the 56mg/m^2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients had received 20/56 mg/m^2 and were tolerating it. Patients with advanced, refractory MM being treated at 36 mg/m^2 and 45 mg/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. All protocols using ≥ 36 mg/m^2 carfilzomib are now administering the drug as a 30-minute infusion.

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[28]. 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.

As part of recent continuous evaluations of product safety information performed by Onyx, 4 case reports consistent with Posterior Reversible Encephalopathy Syndrome (PRES) have been associated with the use of carfilzomib. PRES is a rare, potentially fatal neurological disorder, which can present with headaches, altered mental status, seizures, visual disturbances, and hypertension. If diagnosed early, the symptoms of PRES may be reversible. One case was reported from a company-sponsored clinical trial (of the approximately 2,621 subjects treated in company sponsored trials), one case was reported from an investigator-sponsored trial (of the approximately 1,719 subjects treated in IST studies), and the remaining two cases were reported in the post-marketing setting (of the approximately 16,500 patients treated). Also noted is that 2 of the events of PRES occurred during the use a high dose (36 and 56 mg/m^2) carfilzomib. In this study patients will be informed about the risk of PRES and instructed to contact the investigator immediately if seizures, confusion, severe headaches, fainting, blurred vision or blindness develops

1.5 STUDY RATIONALE

Proteasome inhibitors (PI) have been shown in vitro to impair the fanconi/BRCA pathway of DNA repair and increase DNA fragmentation and apoptosis induced by alkylating agents in MM cells[29]. Clinically, regimens combining alkylating agents with the PI bortezomib have resulted in high rates of overall response and responses ≥ VGPR, particularly in untreated, newly diagnosed patients[14,30,31].

The alkylating agent melphalan, given in high (myeloablative) doses preceding AHSCT is part of the upfront management of younger patients with MM[6-8]. AHSCT has also been utilized in the salvage setting[32,33] (late transplantation) and can be repeated (retransplantation) in patients deriving meaningful benefit from the first transplantation procedure[34]. Melphalan at the dose of 200 mg/m^2 is the most frequently utilized conditioning regimen for autologous transplantation in MM. The proteasome inhibitor bortezomib has been successfully combined with high-dose melphalan leading to apparently greater reduction in disease burden without significant enhancement of the post transplantation toxicity[35]. As a proteasome inhibitor, carfilzomib may intensify the anti-myeloma effect of melphalan and be potentially more synergistic than bortezomib in combination with high dose melphalan due to the irreversible nature of proteasome inhibition. Also, contrary to bortezomib, carfilzomib has minimal neurologic

toxicity. We intend to find the maximal tolerated dose (MTD) of carfilzomib that can be safely combined with standard high-dose (200 mg/m^2) melphalan as preparative regimen prior to AHSCT for MM and obtain additional data on the efficacy and safety of this combination. Patients who undergo autologous transplantation for mm in the relapse setting will often have short duration of remission and post-transplant therapy, either as maintenance or consolidation. Due to its favorable efficacy and side effect profile, carfilzomib is a suitable drug for maintenance therapy. An ideal regimen for carfilzomib maintenance therapy would combine minimal toxicity, adequate drug exposure and convenience. Currently, there is not a "standard" regimen for carfilzomib maintenance therapy. Therefore, the phase iia of the present study will assess the toxicity, pharmacodynamics and convenience of two schedules in individuals who have not progressed on day 100 assessment. The intercalation of regimens within the same subject will minimize inter-patient variability and better characterize the tolerance, pharmacodynamics and convenience of the two regimens.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

Phase I: To determine the MTD of carfilzomib when added to standard melphalan conditioning for AHSCT in relapsed MM.

Phase IIa: To evaluate the anti-myeloma activity and the toxicity of carfilzomib + high dose melphalan conditioning in relapsed MM.

2.2 SECONDARY OBJECTIVES

To describe the pharmacodynamic effects of carfilzomib + high dose melphalan in terms of changes in expression of fanconi anemia/BRCA DNA repair genes and DNA fragmentation.
To provide preliminary pharmacodynamic, safety and patient preference data on two schedules of carfilzomib maintenance therapy after AHSCT.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a phase I/IIa trial. Since this is an AHSCT conditioning regimen trial, only one cycle of therapy will be administered for each subject during the phase 1. During the phase IIa subjects will undergo 12 cycles of maintenance therapy with carfilzomib..

3.1.1 PHASE 1

The phase I component has a typical 3+3 design[36].

-Initially up to three subjects will be enrolled in each cohort starting at cohort 0 in the table below.

-If no dose limiting toxicity (DLT) is noted among the 3 initial subjects, 3 additional patients will be accrued at the subsequent cohort.

-If 1/3 subjects experience DLT, 3 additional subjects will be accrued at the cohort. If no additional DLT occur, accrual will continue at the subsequent cohort.

-If 2 or more subjects experience DLT in a given cohort, the dose will be considered higher than the maximum tolerated dose (MTD) and the immediately lower dose will be considered the MTD.

-If accrual is completed in cohort 4 with 0/3 or 1/6 DLT, the MTD will be considered "not reached" and cohort 4 will be expanded into the phase II portion of the trial.

-If 2 subjects experience DLTs in cohort 0, patients will be accrued in cohort -1, one subject at a time, with the subsequent subject only being accrued once the current subject has completed the DLT period (transplant day 30). The doses in cohort -1 will be considered the MTD if 0/3 or 1/6 subjects experience DLT.

-If $\geq$ 2 subjects experience DLT in cohort -1 the study will be interrupted without proceeding to phase IIa and the combination of carfilzomib and high dose melphalan will be considered too toxic.

Table 2

	Carfilzomib dose			
	Day -3	**Day -2**	**Day -2, after CFZ administration**	**Day 0**
Cohort -1	20 mg/m^2	20 mg/m^2	Mel 200 mg/m^2	Autologous Cells
Cohort 0	20 mg/m^2	27 mg/m^2	Mel 200 mg/m^2	Autologous Cells
Cohort 1	27 mg/m^2	27 mg/m^2	Mel 200 mg/m^2	Autologous Cells
Cohort 2	27 mg/m^2	36 mg/m^2	Mel 200 mg/m^2	Autologous Cells
Cohort 3	27 mg/m^2	45 mg/m^2	Mel 200 mg/m^2	Autologous Cells
Cohort 4	27 mg/m^2	56 mg/m^2	Mel 200 mg/m^2	Autologous Cells

3.1.1.1 Definition of DLT

During phase I of the study, the occurrence of any of the below toxicities during the first 30 days after transplantation will be considered dose-limiting toxicities:

1) Delayed engraftment- Neutrophil engraftment will be defined as the first of three consecutive days with absolute neutrophil count >500/mm^3. Platelet engraftment will be defined as the first of 3 consecutive days of platelets > 20,000/mm^3 without platelet transfusion in the prior 7 days. Engraftment will be considered delayed (and therefore DLT) if the subject has not met criteria for both neutrophil and platelet engraftment by day 30 after AHSCT.

2) Grade 4 toxicity, other than hematological toxicity.

3) Grade 3 toxicity, other than hematological toxicity, fever, chills, dyspnea, infection, rash, fatigue, abdominal pain, diarrhea, dysphagia, oral mucositis, oral pain, flu-like syndrome, pain, anorexia, dehydration, glucose intolerance, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, pain in extremity, headache,

insomnia, hypoxia, pneumonitis, dry skin, pruritus, hypertension, hypotension, increase in AST, ALT, bilirubin and alkaline phosphatase.

4) Acute toxicity of carfilzomib requiring omission of day -2 dose according to section 6.2.

5) Death from any cause.

3.1.1.2 Phase 1 findings

The phase I was completed and the safety and efficacy data analyzed in October 2013[37]. Fifteen subjects were enrolled in 5 cohorts. There was no DLT identified. The most common grade 3 toxicity was infection (8/15 subjects). Nine out of 14 subjects that were not in complete remission at the time of enrolment had improvement in the response category with protocol treatment. Since MTD was not reached, the decision was made to precede with phase 2 enrolling subjects in the expanded cohort 4 (highest dose cohort).

6)

3.1.2 PHASE IIa

Once the MTD for the combination of carfilzomib and high dose melphalan with AHSCT is found, there will be expansion of the MTD cohort, (or cohort 4 if no MTD is reached), so that 28 individuals will be treated at the MTD of carfilzomib and high dose melphalan.

3.1.2.1 Maintenance Therapy

Subjects enrolled in the phase IIa component of the study will receive maintenance therapy with single agent carfilzomib starting no sooner than day 100 and not later than day 120 after transplantation.

-Maintenance will consist of up to 12 cycles of 28 days. Therefore, a new cycle will start 28 (+/-2) days after initiation of prior cycle.

-Two regimens will be utilized during maintenance therapy. Regimen A will consist of carfilzomib 36 mg/m2 on days 1, 8, 15 and regimen B will consist of carfilzomib 36 mg/m2 on days 1, 2, 15, 16.

- Patients eligible for the maintenance therapy component will be registered to the maintenance therapy portion of the study and UAB will randomize the patient to Arm 1 or Arm 2 in blocks of two to ensure balance.

3.2 NUMBER OF CENTERS

During the Phase I portion of the study, there will be two centers involved in the study: Medical University of South Carolina (MUSC) and Memorial Sloan-Kettering Cancer Center (MSKCC). Additional sites will be added during the expansion Phase IIa phase. UAB (P.I. Dr. Luciano Costa) will be the coordinating center for the study upon approval of amendment 6. Medical College of Wisconsin (P.I. Dr. Parameswaran Hari) will be added as participating site after approval of amendment 6.

3.3 NUMBER OF SUBJECTS

A minimum of 6 and a maximum of 30 subjects will be accrued in the phase 1 portion of the study. Unless even dose in cohort -1 is considered too toxic and no MTD can be found, accrual will continue at the MTD (cohort expansion) to reach a total of 28 subjects treated at the MTD cohort.

3.4 ESTIMATED STUDY DURATION

The estimated duration of the phase I component of the study is 15 months. This includes 12 months for accrual and treatment and 3 months for monitoring of adverse events (AEs) and disease reassessments for the last subjects accrued.

The estimated duration of the phase IIa component of the study is 30 months, consisting of 18 months for accrual and transplant treatment of all subjects and 12 additional months to complete maintenance component for all subjects.

3.5 TREATMENT SCHEMA

Patient enrolled during the Phase I portion of the study will only follow procedures related to conditioning therapy and autologous HSCT (day -30 screening through day 100 disease assessment). Patients enrolled during the Phase IIa portion of the study will follow procedures related to conditioning therapy at the MTD, (or cohort 4 if no MTD is reached), and autologous

HSCT (day -30 screening through day 100 disease assessment. In addition, for eligible patients, single agent carfilzomib maintenance therapy will be administered for a maximum of 12 cycles (one cycle equals 28 days).

CONDITIONING THERAPY AND AHSCT

(day -30 screening through day 100 disease assessment)

Applicable during Phase I and Phase IIa study activity

Screening – Subjects likely to meet eligibility criteria will be offered participation in the study after the investigator verifies UAB CTNMO registration. During the phase I portion, investigators should confirm with UAB availability of a cohort slot prior to offering study participation. Subjects will sign informed consent prior to any protocol associated procedure. Screening procedures are outlined in Table 7 and will 1) ensure that subject meets all the eligibility criteria, 2) obtain disease assessment to allow efficacy measurements, 3) assess baseline toxicity, and 4) provide initial biological samples for pharmacodynamic and correlative studies.

Conditioning Treatment- Subjects will receive the appropriate dose of carfilzomib on days -3 and -2. The Phase I portion of the study was completed and data was reviewed on October 28, 2013 concluding that the MTD was not reached and subsequent subjects would receive Carfilzomib doses outlined in cohort 4, 27 mg/m^2 on day -3 and 56 mg/m^2 on day -2. Carfilzomib will be infused over 30 minutes (±10 minutes) as described in section 6.1.1. On day -2, with 60 to 120 minutes of the end of infusion of carfilzomib, subjects will receive 200 mg/m^2 of intravenous melphalan as an intravenous push or a fast infusion, (see section 6.1.2). Prophylaxis of chemotherapy induced nausea and vomiting will follow institutional guidelines and SOPs.

Infusion of autologous cells- Infusion of autologous hematopoietic stem cells will occur on day 0 and follow institutional SOP.

Post AHSCT Follow-up phase – On day 1 following AHSCT, patients will receive either pegfilgrastim 6 mg subcutaneously (single dose) or filgrastim at 5 mcg/kg/day subcutaneously continuing at least until 2 days of absolute neutrophil count > 500/mm^3 as per institutional standard of care aiming at faster engraftment. The post-transplant follow up phase of the study will last 100 days and will consist of standard post transplantation supportive care and monitoring of AEs. For the phase I component of the study, dose-limiting toxicities will be captured during the first 30 days after transplantation (DLT period).

Post AHSCT Disease assessment- Disease assessment will occur at day 100 (+/- 7 days) and will consist of interim medical history and physical exam, serum protein electrophoresis, serum and urine immunofixation, 24h urine protein electrophoresis, serum free light chains, bone marrow aspiration and biopsy, complete blood counts and metabolic panel including uric acid phosphorus. Disease response will be categorized according to appendix B. Patients enrolled to the Phase I portion of the study will only be followed until the disease assessment visit at day 100 (+/- 7 days) and resolution of any treatment related toxicities to baseline or until toxicities have been deemed irreversible by the investigator.

MAINTENANCE THERAPY

(post day 100 disease assessment through a maximum of twelve 28 day maintenance cycles)

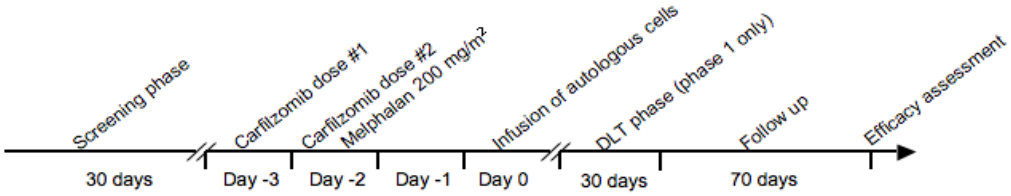
Applicable only to Phase IIa study activity

Screening for Maintenance Therapy – Patients must undergo day 100 disease assessment and be without disease progression in order to continue with maintenance therapy. Patients must be registered by the UAB CTNMO prior to starting any maintenance therapy. Maintenance registration forms are included in the UAB CTNMO case report form packet. Registration can occur any time after day 100 assessments are completed, but subjects must start maintenance therapy by day 120 after transplantation. At the time of registration, patients will be randomized to Arm 1 of Arm 2.

Maintenance Therapy- Maintenance regimen A will consist of carfilzomib 36 mg/m^2 infused over 30 minutes (±10 minutes) on days 1,8,15. Maintenance regimen B will consist of carfilzomib 36 mg/m^2 infused over 30 minutes (±10 minutes) on days 1, 2, 15 and 16. Each cycle will have 4 week duration. The first four maintenance therapy cycles will be dictated by a randomized assignment at time of study registration to maintenance therapy. Patients will either be randomized in blocks of two to either maintenance therapy **Arm 1= AABB** (two cycles of A followed by two cycles of B), or maintenance therapy **Arm 2= BBAA** (two cycles of B followed by two cycles of A). For both maintenance therapy arms, a patient preference questionnaire will be administered to the patient upon completion of the 4th cycle. The remaining 8 cycles (cycles 5-12) will be administered according to the regimen schedule preferred by the patient as documented on the patient preference questionnaire.

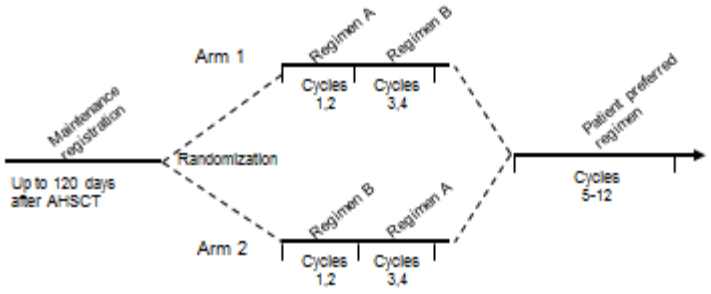
Maintenance Therapy Disease Assessment- During the maintenance therapy, disease assessments will occur at the end of each even cycle and consist of medical history and physical exam assessment, serum protein electrophoresis, serum and urine immunofixation, 24h urine protein electrophoresis, serum free light chains, complete blood counts and metabolic panel including uric acid and phosphorus. Bone marrow aspiration and biopsy will only be performed if needed to confirm complete response. Patients will complete Quality of Life assessments at the end of each even cycle.

Phases I and II transplant schema



	Carfilzomib dose #1	Carfilzomib dose #2
Cohort -1	20 mg/m²	20 mg/m²
Cohort 0	20 mg/m²	27 mg/m²
Cohort 1	27 mg/m²	27 mg/m²
Cohort 2	27 mg/m²	36 mg/m²
Cohort 3	27 mg/m²	45 mg/m²
Cohort 4	27 mg/m²	56 mg/m²

Phase II maintenance schema



	Carfilzomib dose	Treatment days
Regimen A	36 mg/m² over 30 minutes	1, 8, 15
Regimen B	36 mg/m² over 30 minutes	1, 2, 15, 16

3.6 PHARMACODYNAMIC AND CORRELATIVE ASSAYS

For our secondary objectives, we will perform pharmacodynamic assays to measure DNA fragmentation in peripheral blood mononuclear cells during the conditioning regimen. We also hypothesize that carfilzomib targets the Fanconi Anemia (FA) /BRCA pathway, and thus, enhances chemotherapeutic response of myeloma cells to melphalan. We will measure 11 genes that are involved in FA/BRAC pathway including brca1, brac2, fanca, fancc, fancd2, fance, fancf, fancg, fancl, rad51 and rad51c. The key end-points for our pharmacodynamics and mechanistic studies are:

-Expression of relevant genes of the FA/BRCA pathway in peripheral blood mononuclear cells utilizing quantitative RT-PCR;

-DNA fragmentation in peripheral blood mononuclear cells.

During the maintenance treatment on the phase IIa we will measure the degree of proteasoma inhibition in peripheral blood mononuclear cells during regimen A and regimen B. Proteasoma inhibition samples will only be collected during the first cycle of each maintenance therapy regimen.

Additionally, for our secondary objectives, we will perform correlative assays to evaluate the possible association between biological parameters in the cancer cells and the magnitude of response to therapy. We reason that gene expression level in the FA/BRAC pathway and/or the unfolded protein response pathway would predict the response to carfilzomib + melphalan conditioning. The key end-points for our correlative studies are:

-Expression of genes in the FA/BRCA pathway by quantitative RT-PCR (genes that will be measured include: NK-kB, Rel/p50 and brca1, brac2, fanca, fancc, fancd2, fance, fancf, fancg, fancl, rad51 and rad51c);

-Expression of genes from the unfolded protein response pathway [genes that will be measured include: heat shock protein 90 and x-box binding protein-1 (XBP-1)].

Pharmacodynamic assays intend to verify if the hypothesized effects of the study drugs are indeed occurring in vivo. Tables 3 and 4 below summarizes the pharmacodynamic correlative assays completed for this study.

Table 3 - Pharmacodynamic (PD) and correlative assays (analyzed by MUSC)

PHASE I STUDY ACTIVITY CORRELATIVES		
Assay	**Material**	**Time points**
PD		
Expression of relevant genes in the FA/BRCA pathway	Peripheral blood mononuclear cells	D -3: Prior to CFZ and 1h after CFZ infusion completion. D-2: Prior to CFZ, 1h, 12h after Mel infusion completion (Mel infused immediately after CFZ) D 0: Immediately prior to infusion of cells
DNA fragmentation	Peripheral blood mononuclear cells	D -3: Prior to CFZ and 1h after CFZ infusion completion. D-2: Prior to CFZ, 1h, 12h after Mel infusion completion (Mel infused immediately after CFZ) D 0: Immediately prior to infusion of cells
PHASE I and Phase IIa STUDY ACTIVITY CORRELATIVES **Please note that *only MUSC patients* will be participating the in the Phase IIa portion of this study. As of April 2014, the MUSC correlative studies are closed to additional enrollment.**		
Correlatives		
Expression of genes in the FA/BRCA pathway	Plasma cells from bone marrow sample	Screening Day -1 (optional) Day 100 assessment
Expression of genes in the unfolded protein response pathway	Plasma cells from bone marrow sample	Screening Day -1 (optional) Day 100 assessment
DNA fragmentation	Plasma cells from bone marrow sample	Day -1 (optional)

Table 4 Pharmacodynamic (PD) and correlative assays during Phase IIa (analyzed by Onyx)

PHASE IIa CORRELATIVE STUDIES **Please note that only MUSC and MSKCC will participate in the Phase IIa Correlative Studies.**		
Assay	**Material**	**Time points**
PD (Proteasoma inhibition)	Peripheral blood mononuclear cells	*Regimen A:* Day 1: pre dose and 1 hour post dose Day 2: 24h +/- 1 hour after day 1 dose Day 8: pre dose and 1 hour post dose *Regimen B*: Day 1: pre dose and 1 hour post dose Day 2: pre dose and 1 hour post dose Day 8: at any time on day 8

All Phase I PD/mechanistic studies and correlative assays will be performed at the laboratory of Dr. Yubin Kang, MD. The phase IIa PD proteasoma inhibition assessment will be performed by Onyx. Only selected sites -MUSC and MSKCC- will participate in the Phase IIa PD studies. Please refer to the 101669 Correlative Study Manual for handling and processing details.

3.6.1 TIME POINTS OF SAMPLE COLLECTION

Please see the Tables 3 and Table 4 (pharmacodynamics and correlative assays) for the time points at which samples will be collected.

3.6.2 SAMPLE COLLECTION AND SHIPMENT

For peripheral blood samples collected during the phase I portion of the study, approximately 8ml of blood will be collected at each time point, (at least 4ml collected in yellow ACD tube and at least 4 ml collected in green sodium heparin tube). For bone marrow samples, a total of 4 ml of marrow aspirate will be collected in green sodium heparin.

For samples collected at MSKCC and MUSC,
the peripheral blood samples were processed within 24 hours of the time of blood collection to ensure specimen quality. Samples collected at MSKCC were shipped overnight to MUSC. The specific processing and shipping details are outlined within the 101669 correlative studies manual. At the time of issue of Amendment 6 all sample collection for correlative studies has been completed. Samples will be processed and analyzed by Dr. Yubin Kang (Duke University, Division of Hematological Malignanices & Cellular Therapy, 2400 Pratt Street, DUMC 3961, Durham, NC 27710, LAB Location: GSRB1, Rm# 4040)"

.*For PD samples (proteasoma inhibition) collected during maintenance therapy.*

Only MUSC and MSKCC will participate in these pharmacodynamic studies during maintenance therapy. Samples for pharmacodynamic studies will be obtained only during the first cycle of each regimen- A and B (e.g. Cycle 1 and Cycle 3). See Table 4 for schedule of pharmacodynamics samples. Up to 10 evaluable patients will participate. If a patient discontinues therapy or has a dose reduction prior to completing cycle 3, then the subject will be replaced. All proteasoma inhibition samples will be analyzed by Covance. See the 101669 correlatives manual for details.

3.6.3 ASSAYS

-- Cellular Proteasome Activity Assay:

Whole peripheral blood will be collected in yellow ACD tube and mononuclear cells will be obtained using Histopaque-1077 (Sigma-Aldrich) gradient separation. Cell lysates will be prepared by hypotonic lysis (BD Pharmalyse; BD Pharmingen) and the cell lysates will be mixed with 7-Amino-4-methycoumarin (AMC)-conjugated fluorogenic proteasome substract (Boston Biochem). The proteasome activities are determined by the initial rate (first 10 min) of AMC product formation.

-- Gene expression measurement by quantitative RT-PCR:

Genes that will be measured in this protocol include those that are involved in FA/BRCA pathway and those in the unfolded protein response pathway. These genes are: NK-kB, Rel/p50 and brca1, brac2, fanca, fancc, fancd2, fance, fancf, fancg, fancl, rad51, rad51c; HSP90 and XBP-1. The samples will be peripheral blood mononuclear cells or bone marrow mononuclear cells as indicated in Table 3.

Total RNA will be isolated from mononuclear cells using the Trizol (Invitrogen) as per manufacturer's instruction. First-strand cDNA will be synthesized with the iScript cDNA synthesis kit (Bio-Rad) using 20 µl reaction mixture containing 1 µg total RNA, 4 µl 5x iScript reaction mixture, and 1 µl iScript reverse transcriptase. The complete reaction is cycled for 5 min at 25 °C, 30 min at 42 °C, and 5 min at 85 °C. The reverse transcription reaction mixture is then diluted with nuclease-free water in the ratio 1:10 and used for PCR amplification of genes of interest, and β- actin control gene. Primers will be purchased from Invitrogen. The primers for control gene (β- actin) are □-Actin F (ACCTTCTACAATGAGCTGCG) and □-Actin R (CCTGGATAGCAACGTACATGG).

Real-time PCR will performed in duplicate using 25 µl reaction mixture that contains 1.0 µl RT mixture, 0.2 µM of both primers, and 12.5 µl iQ SYBR Green Supermix (Bio-Rad) to be run in the iCycler real-time detection system (Bio-Rad) with a two-step method. The hot-start enzyme is activated (95 °C for 3 min) and cDNA is then amplified for 40 cycles consisting of denaturation at 95 °C for 10 s and annealing/extension at 58 °C for 30 s. A melt curve is then performed (55 °C for 1 min and then temperature is increased by 0.5 °C every 10 s) to detect the formation of primer-derived trimmers and dimmers. Data will be analyzed using the iCycler iQ software (Biorad Laboratories, USA) and adjusted against β- actin.

-- DNA fragmentation assay:

The DASH assay captures and detects damage-induced low molecular-weight DNA fragments as diffuse halos in an agarose microgel. The peripheral blood mononuclear cells will be washed with PBS and embedded in low melting agarose. The embedded cells are lysed for 10 min under alkaline conditions, and DNA is precipitated and visualized with SYBR Green fluorogenic dye (Molecular Probes). Fifty images will be randomly captured per slide, and the logarithmic radius of each nucleoid is calculated using the tail-length parameter of the Loats Associates comet analysis software.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Age ≥ 18 years (or age of majority at participating site, whichever is greater) and ≤ 70 years.
2. Life expectancy ≥ 12 months.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
4. Diagnosis of symptomatic multiple myeloma[38], relapsed after initial therapy.
5. At least minimal response (defined as 25% decrease in the M protein in serum or urine) to the most recent treatment regimen.
6. Evaluable disease prior to the most recent reinduction regimen as defined by at least one of the following:

   -Serum monoclonal (M) protein ≥ 0.5 g/dl by protein electrophoresis
   ->200 mg of M protein in the urine on 24 hour electrophoresis
   - Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio
   - Monoclonal bone marrow plasmacytosis ≥30%
7. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 μmol/L) within 14 days prior to registration.
8. Hemoglobin ≥ 8 g/dL (80 g/L) within 14 days prior to registration (subjects may be receiving red blood cell [RBC] transfusions in accordance with institutional guidelines).
9. Creatinine clearance (CrCl) ≥ 40 mL/minute within 14 days prior to registration, either measured or calculated using a standard formula (eg, Cockcroft and Gault).
10. Prior storage of at least 2 x 10^6 CD34+ cells/kg available for autologous transplantation. During the phase I component of the study, at least the same amount of cells is required as "back up" in the unlikely event of non-engraftment.
11. Subjects may have had a prior AHSCT for the treatment of MM as long as it was performed greater than 12 months from study registration.
12. Subjects must meet institutional general eligibility criteria for autologous transplantation.
13. Written informed consent in accordance with federal, local, and institutional guidelines.
14. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception.
15. Male subjects must agree to practice contraception.
16. Prior therapy with carfilzomib is allowed as long as subject did not experience disease progression while on carfilzomib or within 90 days of treatment discontinuation for any reason..

4.2 EXCLUSION CRITERIA

1. Pregnant or lactating females.
2. Major surgery within 30 days prior to start of treatment.
3. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to registration.
4. Known human immunodeficiency virus infection.
5. Active hepatitis B or C infection.
6. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
7. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration.
8. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.
9. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to registration.
10. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
11. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration.
12. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

4.3 CRITERIA FOR REGISTRATION FOR MAINTENANCE (PHASE IIa ONLY)

In order for patients to continue to maintenance therapy within the Phase IIa portion of the study, patients must be meet the following eligibility criteria and be registered via the UAB CTNMO.

1. Adequate graft function consisting of hemoglobin ≥ 10 g/dL (100 g/L), platelets ≥ 75,000/mm3, absolute neutrophil count ≥ 1,000/mm3 within 14 days prior to registration.
2. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 μmol/L) within 10 days prior to registration.

3. Creatinine clearance (CrCl) ≥ 40 mL/minute within 10 days prior to registration, either measured or calculated using a standard formula (eg, Cockcroft and Gault).
4. Absence of progressive disease on day 100 (+/- 7 days) disease assessment.
5. Absence of any exclusion criteria outlined in 4.2

5 SUBJECT ENROLLMENT

Once a patient is identified as a candidate for the trial the investigator will contact the UAB CTNMO registration office (205-975-5387) prior to obtaining informed consent (phase I only). This process is intended to verify if a "slot" is available in the current cohort. Registration will be completed upon submission of documentation of eligibility to the registration office and issuance of a registration confirmation email.

Prior to accepting the registration, the registration office will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Pretreatment tests and procedures must be completed within the guidelines specified in the test schedule, including assessment of baseline symptoms.
- Study drugs availability on site (for initial site patient only; Local site is responsible for assessing drug available for subsequent site enrollments)

Phase IIa Registration Procedures:

When the Phase IIA portion of the study begins, the following patient registration procedures must be followed prior to any start of conditioning therapy.

Registration will be completed upon submission of documentation of eligibility to the registration office and issuance of a registration confirmation email. Prior to accepting the registration, the registration office will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Pretreatment tests and procedures must be completed within the guidelines specified in the test schedule, including assessment of baseline symptoms.

- Study drugs availability on site (for initial site patient only; Local site is responsible for assessing drug available for subsequent site enrollments)

Effective on approval of Amendment 6, the registration office will be transferred to UAB CTNMO Phone No: 205- 975-5387, Fax No: 205-975-9875.

An enrolled patient is expected to undergo a second registration prior to starting any maintenance therapy. Registration will be completed upon submission of documentation of eligibility to the registration office and issuance of a registration confirmation email. The registration confirmation email will include the maintenance arm randomization. Prior to accepting the registration, the registration office will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- All required procedures will be performed as day 100 (+/-7days) assessment per Table 7. Registration can occur any time after assessment completed, but subjects must start maintenance therapy by day 120 after transplantation.

6 TREATMENT PROCEDURES

6.1 DRUG PREPARATION AND ADMINISTRATION

6.1.1 CARFILZOMIB

- 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 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 the discretion of the investigator, patients thought to be at particularly high risk for the development of TLS, based on high tumor burden, **oral hydration** should be given as follows, at least 48 hours before Day -3,: 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.
- **IV hydration** will be given immediately prior to carfilzomib. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (eg, ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.
- 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 30 minutes (±10 minutes). The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain under observation for at least 1 hour following each dose of carfilzomib during conditioning therapy. 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.
- During the maintenance component of the study carfilzomib will be administered over approximately 30 minutes (±10 minutes). IV hydration with 250 ml of normal saline will be

administered prior to carfilzomib. No post carfilzomib hydration nor observation are necessary during maintenance.

6.1.2 MELPHALAN

- Melphalan is commercially available and supplied as a sterile, freeze-dried powder. Each vial contains 50 mg melphalan hydrochloride and the inactive ingredient, povidone 20 mg. Reconstitute per manufacturer instructions using the diluent provided. Further dilution and administration per institutional standards. The manufacturer recommends completion of administration of melphalan within 60 minutes of reconstitution.
- The dose (200 mg/m^2) will be calculated using the lesser of the subject's actual (AW) or corrected ideal body weight (CIBW). CIBW= IBW + 0.25(AW-IBW). The ideal body weight (IBW) is calculated using the formula: Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet. Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
- Solution Preparation: Vial/50 mg: Constitute with 10 ml of the special diluent to yield a 5 mg/ml melphalan concentration. May be further diluted per institutional guidelines.
- Melphalan must be infused intravenously utilizing a central vein catheter and infusion completed within one hour of reconstitution.
- **IV hydration** will be given immediately after melphalan per institutional guidelines.
- Intravenous melphalan is commercially available and will not be provided by the sponsor.

6.2 DOSE REDUCTIONS/ADJUSTMENTS

6.2.1 TRANSPLANT COMPONENT

Since each subject will only undergo one "cycle" of therapy, the possibility of intra patient dose reduction/adjustment for subsequent cycles does not apply.

Since subjects will receive carfilzomib on days -3 and -2 of treatment, subjects experiencing significant immediate toxicity after day -3 dose will have day -2 dose omitted according to Table 5.

Table 5 – Adverse events requiring omission of day -2 dose of carfilzomib.

Symptom	Recommended Action regarding Carfilzomib
Allergic reaction/hypersensitivity, grade 2 or greater	Omit day -2 dose
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	Omit day -2 dose
"First dose effect" of any grade (see section 6.3) ≥ Grade 2	Omit day -2 dose
Any other non-hematologic immediate toxicity assessed as carfilzomib-related ≥ Grade 3	Omit day -2 dose

6.2.2 MAINTENANCE COMPONENT

During maintenance therapy one level dose reduction will be allowed for carfilzomib related toxicity according to Table 6. The reduced dose will consist of carfilzomib 27 mg/m2. Subjects requiring further dose reduction will have experimental therapy discontinued.

Dose reductions during maintenance component will carry forward to all subsequent cycles for both regimens A and B.

Omitted doses will not be replaced. Patients who interrupt therapy due to toxicity will resume therapy as outlined in Table 6 receiving any remaining doses on the ongoing cycle. If no remaining doses on the current cycle, then treatment will resume after the cycle is completed, 28 (+/- 2) days from the initiation of the prior cycle.

Table 6 – Dose adjustments during maintenance therapy

Hematologic toxicity	CTC 4.0 grade	Action

Thrombocytopenia	Grade 3	Hold therapy until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 or bleeding	First occurrence - Hold carfilzomib until resolution to grade ≤ 2 and no bleeding. Resume therapy at one level dose reduction. Second occurrence- Discontinue therapy
Anemia	Grade 3	Hold therapy until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 or transfusion requirement	First occurrence - Hold carfilzomib until resolution to grade ≤ 2. Resume therapy at one level dose reduction Second occurrence- Discontinue therapy.
Neutropenia	Grade 3	Hold therapy until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 or grade 3 with infection	First occurrence - Hold carfilzomib until resolution to grade ≤ 2. Resume therapy at one level dose reduction

		Second occurrence- Discontinue therapy.
Non-hematologic toxicity	**CTC 4.0 grade**	**Action**
Any	Grades 2	No action is required. Investigator is allowed to hold study drug for up to two weeks and then resume at same dose. On second occurrence, the investigator has the option to resume therapy at reduced dose.
	Grade 3	Hold therapy until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4	First occurrence - Hold carfilzomib until resolution to grade ≤ 2. Resume therapy at one level dose reduction. Second occurrence- Discontinue therapy.

6.3 SAFETY CONSIDERATIONS

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, the following observations are noted:

- A "first dose effect" has been seen with carfilzomib, 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 the following day, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.
- Dexamethasone at least 4 mg PO/IV will be administered prior to all carfilzomib doses.

- Should a "first dose effect" occur after day -3 dose of carfilzomib, 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.

- Acyclovir, or a similar medication, should be given to all subjects, per institutional prophylaxis guidelines, unless contraindicated.

- CrCl changes are mostly transient, reversible, and non-cumulative. All subjects 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 and reviewed prior to each dose of carfilzomib. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.

- Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with carfilzomib until the infection has resolved and, if being treated with anti-infective, the course of antibiotics has been completed.

- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetic or antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration.

- The treatment with melphalan as outlined in this protocol constitutes standard of care. The dose of 200mg/m^2 of melphalan is myeloablative, therefore subjects are expected to develop grade 4 thrombocytopenia requiring transfusion, grade 4 neutropenia with near 100% risk of neutropenic fever and anemia requiring transfusion of red blood cells. Subjects will be monitored for need of transfusional support and for fever and other complications until engraftment.

- Melphalan at the doses employed in this protocol will cause nausea, vomiting and mucositis manifested mostly as oral pain, dysphagia and diarrhea. Subjects will receive antiemetic and antidiarheal medications according to institutional guidelines.

6.3.1 GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF TUMOR LYSIS SYNDROME (TLS)

TLS, which may be associated with multiorgan failure, has been observed in treatment cycles 1 and 2 in some patients with MM who have been treated with carfilzomib.

The following safety measures are mandatory for all subjects. In addition, MM subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk. Please see **section 6.1.1** for hydration requirements.

6.3.1.1 Laboratory Monitoring

Appropriate chemistries, including creatinine and complete blood counts (CBC) with platelet count, should be obtained and reviewed prior to carfilzomib dosing. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

6.3.1.2 Management of Tumor Lysis Syndrome

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

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

6.4 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before

Day -3 through the end of the subject's study participation. Any change in concomitant medications must be recorded.

6.4.1 REQUIRED CONCOMITANT MEDICATIONS

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

Dexamethasone at least 4 mg PO/IV will be administered prior to all carfilzomib doses.

On Day 1 of AHSCT subjects will receive either single dose of pegfilgrastim at 6mg subcutaneously or start filgrastim at 5 mcg/kg/day subcutaneously and continue until ANC is greater than 500/mm^3 on two consecutive days.

Subjects should receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone during the period of neutropenia according to institutional guidelines. In addition, subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis until day 100 as per institutional guidelines. Subjects receiving maintenance therapy in the phase IIa portion of the study will continue acyclovir or similar for the entire duration of maintenance.

6.4.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO daily on days -3, -2, -1 and 0 (total of 4 days).

Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

6.4.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed. Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

7 STUDY TESTS AND OBSERVATIONS

Table 7 – Study Evaluations: Conditioning Therapy and AHSCT

	Screening		Treatment				Follow up		Disease assessment
	Within 30 days from registration	Within 14 days from registration	Day -3[8]	Day -2	Day -1	Day 0	Recovery of blood counts[4, 5]	Twice weekly until day 21	Day+100 (+/- 7 days)
History and Physical	X		X	X	X	X		X	X
Vitals	X		X	X	X	X		X	X
Weight	X		X	X	X	X		X	X
Height	X								
Complete blood counts		X	X	X	X	X	X[4, 5]	X	X
Metabolic panel (Na, K, Cr, BUN, Cl, Bicarbonate)		X	X	X	X	X		X	X
Calcium, Phosphorus, Uric acid		X	X	X	X	X		X	X
LFTs (bilirubin, AST, ALT, alkaline phosphatase)		X	X	X	X	X		X	X
Serum protein electrophoresis		X							X
24h urine protein electrophoresis[9]		X							X
Serum free light chains		X							X
Serum and urine Immunofixation		X							X
Bone marrow aspiration and biopsy[1, 2]	X[2]								X[2]
Pharmacodynamics sample[3]			X	X		X			
Adverse Events Assessment[6]	X	X	X	X	X	X		X	X
Concomitant Medications Review[7]		X	X	X	X	X		X	X
Serum pregnancy test		X							

1- Bone marrow correlative studies will be performed in each of these specimens as described in section 3.6 and table 3. During the Phase I portion of the study only MUSC and MSKCC will participate. During the Phase IIa portion of the study, up to 4 patients, from MUSC ONLY,, will participate. The Day -1 bone marrow aspiration and biopsy is optional As of April 2014, the Day -1 bone marrow correlative study completed.

2 - Conventional cytogenetics and FISH for myeloma-associated abnormalities are to be performed. The screening bone marrow biopsy can be performed after registration and prior to study treatment.

3-These studies are only applicable only to Phase I as described in section 3.6 and table 3.Please note that only MUSC and MSKCC will participate in these PD samples during the Phase I portion of this study. When the Phase IIa portion of the study opens, these Phase IIa patients will not participate in these PD studies.
4- **During the Phase I portion of the study**, complete blood counts will be performed daily until the following is achieved: a) platelet ≥ 20,000/mm3 for 3 consecutive days without transfusions in the past 7 days and b) neutrophil count ≥ 500/mm3.
5 - **During the Phase IIa portion of the study**, complete blood counts will be performed until the following is achieved: a) platelet ≥ 20,000/mm^3 without transfusions for 3 consecutive measurements and b) neutrophil count ≥ 500/mm^3.
6-AEs should be assessed using CTCAE v4.0 from date informed consent signed until 30-days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever comes first. See Section 9.3.
7-Concomitant Medications should be assessed 14 days before Day-3 through the end of study participation.
8- It is recommended that study treatment begin within 7 days after study registration. If an event occurs that prevents the patient from beginning Day -3 treatment within 7 days of registration, the investigator must repeat a history and physical, CBCD, CMP, Calcium, Phosphorus, Uric acid, LFTs (bilirubin, AST, ALT, alkaline phosphatase) to ensure the patient meets the institutional general eligibility criteria for autologous transplantation and laboratory values as outlined within the study's eligibility criteria.
9- When the total protein <10g/dL, urine protein electrophoresis is not required.

Table 8 – Study Evaluations: Maintenance Therapy (Applicable to Phase IIa Only)

	Registration[1]	Regimen A cycle			Regimen B cycle				At end of cycle 4	Disease assessment	End of Study[8]
		Day 1	Day 8	Day 15	Day 1	Day 2	Day 15	Day 16		At the end of each even cycle	
History and Physical	X	X			X					X[3]	X
Vitals	X	X			X					X[3]	X
Weight	X	X			X					X[3]	X
Height	X										
Complete blood counts	X	X		X	X		X			X[3]	X
Metabolic panel (Na, K, Cr, BUN, Cl, Bicarbonate)	X	X		X	X		X			X[3]	X
Calcium, Phosphorus, Uric acid	X	X		X	X		X			X[3]	X
LFTs (bilirubin, AST, ALT, alkaline phosphatase)	X	X		X	X		X			X[3]	X
Serum protein electrophoresis	X									X[3]	
24h urine protein electrophoresis[5]	X									X[3]	
Serum free light chains	X									X[3]	
Serum and urine Immunofixation	X									X[3]	
Bone marrow aspiration and biopsy	X									X[3, 4]	
Pharmacodynamics sample		X[2]	X[2]		X[2]	X[2]					
Adverse Events Assessment		X	X	X	X	X	X	X		X	
Concomitant Medications Review		X	X	X	X	X	X	X		X	
Patient completion of Preference Questionnaire[6]									X		
Patient completion of Quality of Life Questionnaires[7]										X	

1- All required procedures will be performed as day 100 (+/-7days) assessment per Table 7. Registration can occur any time after assessment completed, but subjects must start maintenance therapy by day 120 after transplantation.
2- Only MUSC and MSKCC will participate in these pharmacodynamic studies during maintenance therapy in Phase IIa. Samples for pharmacodynamic studies will be obtained only during the first cycle of each regimen- A and B (e.g. Cycle 1 and Cycle 3. Note that Regimen A includes a Day 2 collection and Regimen B includes a Day 8

collection. See Table 4 for schedule of pharmacodynamics samples. Up to 10 evaluable patients will participate. If a patient discontinues therapy or has a dose reduction prior to completing cycle 3, then the subject will be replaced.
3- Disease assessment procedures may be combined with day 1 assessment of subsequent cycle.
4- Bone marrow aspiration and biopsy required only to confirm complete response.
5- When the total protein <10g/dL, the urine protein electrophoresis is not required.
6- Refer to Appendix C.
7- Refer to Appendix D and Appendix E. Quality of Life questionnaires will be administered at the end of each even cycle.
8- End of Study – these assessments are required in the event that the patient discontinues maintenance therapy due to early termination (eg. withdraws consent, toxicity, etc.).

8 STUDY DISCONTINUATION

Reasons for study discontinuation may include, but are not limited to:

- ≥ 2 subjects experience DLT in cohort -1 as indicated in section 3.1.1.
- Safety concerns
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

9 ADVERSE EVENTS

9.1 ADVERSE EVENTS DEFINITIONS

An AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory findings), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered “unexpected”.

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs (see Appendix D). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.

For AEs not adequately addressed in the CTCAE, the severity Table 9 below may be used:

Table 9. Adverse Event Severity

Severity	Description
GRADE 1 – Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
GRADE 2 – Moderate	Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
GRADE 3 – Severe	Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL.
GRADE 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated.
GRADE 5 – Fatal	Death related to AE.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

9.2 CAUSALITY

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

Yes: The event is suspected to be related if:

- there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
- there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

No:

- the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
- the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
- the event is unlikely to be related to the investigational product(s)

9.3 ADVERSE EVENTS REPORTING PROCEDURES

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate form.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.

AEs should be reported from the time the subject signs consent through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever occurs first. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject is registered but discontinues the study prior to receiving any study drug, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone and documented in the subject's source document. AEs continuing at 30 days post-last dose should have a comment in the source document by the Investigator that the event has stabilized or is not expected to improve.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI-CTCAE grading scale v4.0.

All Grade 3 and 4 adverse events must be recorded as AEs on the CRF. Grade 1 and 2 adverse events should only be recorded if considered clinically significant by the Investigator.

The Principal Investigator may delegate these duties to Sub-investigators and must ensure that these Sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572.

9.4 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is one that meets the following criteria:

- Death
- Life threatening experience defined as any adverse experience that places the subject, in the view of the Investigator, at immediate risk of death at the time of occurrence; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated causes such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE, when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the Sponsor as an SAE.

9.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.

If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The sponsor is responsible for notifying the appropriate Regulatory Agencies, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports. Generally, these are all SAEs that are judged to be unexpected and related to study drug(s), as specified in ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports. However, certain Regulatory Agencies may have additional requirements for expedited safety report submissions.

This submission of IND Safety Reports (North America) or Suspected Unexpected Serious Adverse Reactions (SUSARS [Europe]) will be cross referenced according to local regulations to Onyx Investigational Compound Number (IND, CSA, etc) at the time of submission.

The Investigator is also responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), in accordance with local regulations, of all SAEs.

Additionally, the Investigator is responsible for reporting adverse events to Onyx as described below:

Expedited Reporting by Investigator to Onyx

The Investigator must inform Onyx Drug Safety in writing by Fax at the contact information listed below of all Expedited Safety Reports submitted to the relevant Regulatory Agencies. These notifications should be performed in parallel to the Regulatory Agency submissions [e.g., within 7 calendar days for any Fatal or Life-threatening SUSARs and within 15 calendar days for all other SUSARs], but in no case any later than 1 business day from the submission date. This must be documented on a FDA 3500A MEDWATCH form. This form must be completed and supplied to Onyx Drug Safety in English and accompanied by the global IST SAE Report Cover Page.

The initial report must be as complete as possible, at a minimum including the serious adverse event term(s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up FDA 3500A MEDWATCH form and submitted to Onyx Drug Safety in the same timelines as outlined above. The Onyx protocol number (IST-CAR-536) and the institutional protocol number should be included on all reports to Onyx Drug Safety.

All other serious adverse events regardless of drug causality will be reported to Onyx Drug Safety on a FDA 3500A Medwatch form no later than 30 days from the time the sponsor-investigator becomes aware of the SAE. Onyx reserves the right to review the CRFs or source documents in response to any inquiries by regulatory agencies that the sponsor may receive.

Onyx Drug Safety and Pharmacovigilance Contact Information:

Drug Safety Hotline: 650.266.2501
Drug Safety Fax: 1-805-480-9205 or US Toll Free 1-888-814-8653

With Copy to: UAB CTNMO
(Reference IST-CAR-536/UAB #XXXX)
Fax: 205-975-9875
Phone: 205-975-5387
Email: pamdixon@uab.edu

9.6 PREGNANCY

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of carfilzomib, Onyx Drug Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Onyx Drug Safety and Pharmacovigilance Contact information above). If the subject is pregnant, carfilzomib must be withheld.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to report the results to Onyx Drug Safety.

All pregnancies are considered a SAE and will require expedite reporting. Investigators will follow the outcome of the pregnancy for (spontaneous abortion,(any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly..

10 STATISTICAL ANALYSIS

10.1 STUDY DESIGN

The study has a phase I/IIa design. The first phase I portion will be a standard 3+3 dose escalation study to include between 9 and 30 patients. However, it is highly unlikely that 30 patients will be enrolled (this would occur if dose expansion to 6 patients per level occurred at all of dose levels 0 through 4) and expected enrollment is expected to be 18 or fewer. The phase IIa portion of the study will expand the MTD cohort (or cohort 4 if MTD not reached) to enroll a total of 28 patients using a single stage design. Due to the 100 day lag between treatment and evaluation, an interim analysis for the primary endpoint is not feasible.

10.2 STUDY ENDPOINTS

10.2.1 PRIMARY ENDPOINTS

Phase I – The primary endpoint in phase I is the occurrence of a dose-limiting toxicity as defined in section 3.1.1.1.

Phase IIa – Rate of very good partial response (VGPR) + complete response (CR) in patients with relapsed MM treated with the melphalan + MTD of carfilzomib as determined in the phase I component of the study.

10.2.2 SECONDARY ENDPOINTS

Phase I and IIa – Pharmacodynamic effects of this combination at the proposed doses and schedule: changes in expression of Fanconi anemia/BRCA DNA repair genes and DNA fragmentation.

Phase IIa – Rate of overall response, defined as CR+VGPR+PR (Appendix B). Rate of PFS 12 months after AHSCT in the setting of carfilzomib + melphalan conditioning and carfilzomib maintenance therapy. Pharmacodynamic effect of maintenance regimens A and B assessed by proteasome inhibition in peripheral blood mononuclear cells. Subject's preference for regimens A and B. Measurement of proteasome inhibition is described in section 3.6.

10.2.3 SAFETY ENDPOINTS

Both phase I and phase IIa, transplant component – Engraftment kinetics, described by the median time for neutrophil and platelet engraftment (as defined in section 3.1.1.1) and the rate of engraftment by day 30. Frequency and nature of grades 3 and 4 non-hematologic AEs and SAEs.

Phase IIa, maintenance component – Frequency and nature of AEs and grades 3 and 4 AEs.

10.3 SAMPLE SIZE CONSIDERATIONS

The phase I sample size is determined based on the occurrence of DLTs at each dose level and the expansions. The minimum number of patients treated would be 6 (with 3 patients at each of dose levels 0 and -1) and the maximum would be 30 (with an expansion to 6 patients at each of dose levels 0 to 4). These are both unlikely and it is expected that the number of patients treated in the phase I portion will be between 12 and 18.

Patients will be enrolled in the phase 2 portion of the study to expand the MTD cohort (or cohort 4 if MTD is not reached) in order to reach 28 patients. There is little preliminary data to suggest a historical control response rate to the proposed treatment regimen. As a result, we are choosing to enroll 28 patients in order to be able to estimate the response rate with sufficient precision. More specifically, N=28 provides a half width of <0.20 for the 95% confidence interval for any response rate. This precision will provide sufficient information to determine if the regimen is sufficiently promising, in conjunction with the safety information learned in the phase IIa portion.

The phase IIa maintenance portion of the study is included to describe additional endpoints including proteasome inhibition in two different regiments of treatment, and patient preference. There will be no hypothesis testing performed and so there is no power calculation. No additional patients are enrolled specifically for the objectives addressed by the maintenance phase.

10.4 INTERIM AND SAFETY ANALYSIS

There is no interim analysis in Phase IIa for futility or efficacy. However, there will be continuous monitoring for safety. A sequential probability ratio test (SPRT) approach will be

used. If there is strong evidence that the rate of grade 4 toxicities is 0.30 or above, as compared to a null rate of 0.15, the study will be stopped. The stopping boundary is based on the likelihood ratio comparing the null rate of 0.30 versus the alternative rate of 0.15 using binomial likelihoods. If the ratio favoring a rate of 0.30 (vs. 0.15) ever exceeds 10, then the study will be stopped. A likelihood ratio of 10 is similar to a significance level of 0.05. The stopping criteria for this approach are listed in Table 10 below.

Table 10. Stopping criteria for early stopping due to excessive toxicity. For example, if four of the first six patients experience a grade 4 toxicity, the study will be stopped. The last boundary (9 grade 4 toxicities in 28 patients) would not stop the study (because the maximum N is 28); but at the end of the study, the treatment would be deemed to toxic to take to the next phase of research.

Number of Grade 4 toxicities	Number of Patients Treated	Observed toxicity rate	Likelihood Ratio (favoring 30% toxicity rate)
4	6	67%	10.9
5	10	50%	12.1
6	15	40%	11.2
7	20	35%	10.3
8	24	33%	11.5
9	28	32%	12.8

10.5 PLANNED METHODS OF ANALYSIS

The primary objective of the phase I portion of the study is determination of the maximum-tolerated dose (MTD). This will be determined based on the algorithmic dose finding approach where the highest dose at which 0 or 1 of 6 patients experiences a DLT is designated as the MTD. The properties of this design are shown in Table 11 below where dose is escalated if either (a) 0 out of 3 evaluable patients experience a DLT, or (b) 1 out of 6 patients experience a DLT.

Table 11: Probability of escalation based on true DLT rates ranging from 10% to 60%. We assume that DLT rates of 30% and below are acceptable. For DLT rates that are 40% or greater, we have a relatively low chance of escalation, especially when the DLT rate is as high as 50% or 60%.

True DLT rate	Probability of escalation
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

The primary objective of the phase IIa portion of the study is to estimate the response rate. This will be done by estimating the proportion of patients who experience a response (defined above) with its 95% confidence interval.

The secondary objectives of the study include describing toxicities in both the phase I and IIa portions, and describing the pharmacodynamics effects of the treatment in phase I and phase IIa. This will be done by tabulating toxicities by type and grade in each phase. Pharmacodynamic measures will be quantified by changes in quantitative measures (e.g. expression) between baseline and follow-up. These will be summarized using graphical displays and summary statistics. PFS will be graphically displayed using Kaplan-Meier curves and 12 month PFS will be estimated with its 95% confidence interval.

For those patients in the maintenance phase of the phase IIa portion of the study, proteasome inhibition will be treated as a continuous variable and summarized by treatment arm using graphical displays and summary statistics. Preference for A vs. B and completion rates will be estimated by proportions with exact 95% confidence intervals. Given that the number of patients in the maintenance portion of the study is expected to be small (20-22), hypothesis testing will not be performed to compare patients who receive A first versus those who receive B first.

11 INVESTIGATIONAL PRODUCT

11.1 CARFILZOMIB DESCRIPTION

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

11.2 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®).

11.3 CARFILZOMIB STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel.

11.4 CARFILZOMIB ACCOUNTABILITY

Onyx, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of UAB, Onyx and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of UAB, Onyx and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

This study uses an Onyx-supported Interactive Response Technology System (IRT) for study drug ordering. Training will be provided to investigators and their designees at the different sites at or prior to study initiation visit.

11.5 MELPHALAN DESCRIPTION

Melphalan (L-phenylamine mustard, L-PAM, L-Sarcolysin) is an alkylating agent coupled to an amino acid. The molecular formula is $C_{13}H_{18}C_{12}N_2O_2$ and the molecular weight is 305.

11.6 MELPHALAN FORMULATION

Melphalan is commercially available and supplied as a sterile, freeze-dried powder. Each vial contains 50 mg melphalan hydrochloride and the inactive ingredient, povidone 20 mg. Reconstitute per manufacturer instructions using the diluent provided. Further dilution and administration may be done per institutional standards. The manufacturer recommends completion of administration of melphalan within 60 minutes of reconstitution.

11.7 MELPHALAN STORAGE

The intact packages of melphalan for intravenous administration should be stored at room temperature (15 - 30°C) protected from light. Shelf life surveillance of the intact dosage form is ongoing.

11.8 MELPHALAN SUPPLIER

Intravenous melphalan is commercially available for purchase by a third party. Its use in the clinical setting addressed by this protocol (high dose chemotherapy and autologous hematopoietic stem cell transplantation) is standard of care practice.

12 REGULATORY OBLIGATIONS

12.1 INFORMED CONSENT

The investigator will obtain written informed consent from all participating patients or their authorized representatives. Obtaining informed consent must be done according to International Conference on Harmonization- Good Clinical Practice Guidelines (ICH GCP). Copies of the signed document will be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

12.2 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Onyx with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Onyx as follows:

Onyx Inc.
Regulatory Department
2100 Powell St.

Emeryville, CA 94608

With copy to: UAB CTNMO

Name: Pamela Dixon
Address: 1824 6th Avenue South; WTI 110C; Birmingham, AL 35294
Phone No: 205- 975-5387
Fax No: 205-975-9875
Email Address: pamdixon@uab.edu

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

Onyx will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study.

Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee and Onyx with a summary of the trial's outcome.

12.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Participating study sites cannot begin enrollment until an initiation letter has been issued from the UAB CTNMO. Each center is required to participate in an initiation conference call.

Before the start of this study and the shipment of study drug to a participating study site, the following documents must be on file at UAB CTNMO. Participating sites will be responsible for forwarding the initiation documents toUAB CTNMO.

All start-up documents can be submitted via electronic mail to pamdixon@uab.edu or via fax at (205) 975-9875. Please ensure that the fax cover page clearly identifies the site, study identifier and is addressed to ATTN: UAB CTNMO.

These documents are required to be submitted by each participating center:

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center.

2. The names of any sub-investigators at the participating center must appear on e 1572. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.

3. Current curricula vitae and documentation of professional licensure of the Principal Investigator and sub-investigators listed on the 1572.

4. Resumes and human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel).

5. A signed and dated investigator brochure acceptance form.

6. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.

7. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the UAB CTNMO prior to submission to the site's designated IRB.

8. A signed Confidentiality Agreement.

9. A signed Clinical Trial Agreement for each site.

10. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.

11. The UAB CTNMO site specific forms as specified in the investigator-initiated multicenter manual.

12.4 SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Onyx, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY COMPLETION

13.1.1 PROTOCOL AMENDMENTS

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

13.1.2 STUDY COMPLETION

The following data and materials are required by UAB CTNMO and Onyx before a study can be considered complete or terminated:

1. Copies of protocol amendments and IRB approval/notification, if appropriate.
2. Copies of the IRB final report, documentation of submission to the IRB.
3. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract).
4. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site).

13.2 STUDY DOCUMENTATION AND ARCHIVE

13.2.1 DATA RECORDING

The Clinical Research Coordinator and Investigator will be responsible for the recording of all data on the Case Report Forms (CRFs).

The Investigator will provide access to his/her original records to permit a representative from the funding or auditing institution(s) to verify the proper transcription of data. Data submission will be electronically via the REDCap database.

13.2.2 RECORD RETENTION

Federal law requires that an Investigator maintain all study records for two years after the investigation is discontinued.

13.3 STUDY MONITORING AND DATA COLLECTION

13.3.1 MONITORING

UAB CTNMO will be responsible for the monitoring of study patient data and records. Monitoring will be performed centrally. All monitoring reports will be kept by the UAB CTNMO to ensure that all reports are contained in a central study file. The CTNMO manager or UAB internal auditor will be responsible for conducting the review of monitoring packets. A final monitoring report will be generated and issued to the site and will be kept in the central study file by the UAB CTNMO. The UAB CTNMO will be responsible for forwarding the final monitoring reports to the UAB Data Safety Monitoring Committee (DSMB) for review.

13.3.1.1 Frequency of Reviews

The each patient at each participating center will have their eligibility criteria reviewed prior to enrollment by the UAB CTNMO.

During the course of the study, each site will be selected for an audit by the UAB Quality Assurance Committee approximately once a year. Audit will include 100% of the subjects enrolled at the site. In addition to the once yearly QA audit, monitoring for each patient entered into this trial will be 100%. Sites are to send source information on each patient to the UAB CTNMO office where a shadow chart will be maintained on each subject for this trial. Source will be verified to data entered into the RedCap database.

13.3.2 PROTOCOL DEVIATIONS AND SAFETY REPORTING

A Protocol Deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval.

Any protocol deviation or serious adverse event will be reported by the subsite within 10 days of notification. Protocol Deviations will be reported by completion of the hard copy Protocol Deviation Report form. Serious Adverse Events will be reported by completion of a MedWatch 3500A form and hard copy Serious Adverse Event form. For both Protocol Deviations and Serious Adverse Events, all required forms and any supporting clinical documentation should be submitted to the UAB CTNMO office within 10 days of notification.

13.3.3 DATA SAFETY MONITORING BOARD

The University of Alabama Comprehensive Cancer Center Data Safety Monitoring Board will have oversight of the protocol. The UAB CCC DSMB will meet at a minimum on a monthly basis to discuss hematology related trials.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the UAB CCC DSMB for review during the DSMB monthly meetings. The coordinating center will review protocol deviation and SAE events for form completion and provide assistance in communicating to the subsite if more information is warranted. The UAB CTNMO will report the event report to the UAB CCC DSMB so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action.

13.3.4 DATA COLLECTION

Data collection will be managed by the UAB CTNMO staff via the study database which is housed and maintained at the Hollings Cancer Center along with the MUSC datacenter. The majority of study data will be reported by electronic case report forms in the REDCap database. A description of the data collected within the REDCap system includes information regarding the administration of study drug, adverse events, response assessments, safety evaluations per the protocol study calendar and patient relevant and current medical history.

REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-

institutional consortium which includes MUSC and was initiated at Vanderbilt University. The database is hosted at the MUSC Datacenter. The system is protected behind a login and Secure Sockets Layer (SSL) encryption. Data collection is customized for each study or clinical trial based on a study-specific data dictionary defined by the research team with guidance from the SCTR Informatics REDCap administrator at MUSC.

Time sensitive information such as patient registration, serious adverse events reporting, and protocol deviation reporting will be collected via completed hard copy form. These forms are available from the UAB CTNMO. . Information collected will be reviewed and processed by the UAB CTNMO.

The data will be initially reviewed for quality assurance purposes to identify any discrepancies or missing data. The staff of the UAB CTNMO will notify the participating site of any data queries and manage the overall data quality of the study. If data received relates to a serious adverse event or protocol deviation, the information will be processed for report to the UAB CCC DSMB for review. The sponsor- investigator, Luciano Costa, MD and the assigned MUSC statistician, Elizabeth Garrett-Mayer, PhD will also have access to study data for quality assurance and analysis purposes. During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed. The study will be subject to a yearly internal audit via the UAB CCC Quality Assurance Committee at a minimum and audits may occur more frequently at the request of the QA Committee.

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APPENDIX A: NCI-CTCAE VERSION 4.0

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v4.0

Publish Date: June 14, 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX B: RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response category	Criteria
Stringent complete response (sCR)	• CR as defined below plus all of the following • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete response (CR)	• Negative immunofixation of the serum and urine • If only the measurable non-bone marrow parameter was FLC, normalization of FLC ratio • < 5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas.
Very good partial response (VGPR)	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥ 90% or greater reduction in serum M-component • Urine M-component <100 mg per 24 hour
Partial response (PR)	One of the following: • If serum and urine measurable, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. • If only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein. • If urine measurable (but serum not), a reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. • If only the measurable non-bone marrow parameter was FLC, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio • If the bone marrow was only measurable parameter, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if a plasmacytoma is present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or PD
Progressive Disease (PD)	Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be $\geq$ 0.5 g/dL), and/or • Urine M-component (absolute increase must be $\geq$ 200mg/24 h), and/or • Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10mg/dL) • Only in patients without measureable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

APPENDIX C: PATIENT PREFERENCE QUESTIONNAIRE

(see next page)

PATIENT PREFERENCE QUESTIONNAIRE

Version date April 15, 2013

Patient Study ID: 101669- _____ **Date of Completion (MM-DD-YYY**): _____

To be completed by the patient:

During your maintenance treatment period, you were given the study drug- carfilzomib in two different ways (or regimens). Below is the description of two ways carfilzomib was provided to you during the previous cycles. We would like to get your opinion of which regimen you liked best. Based on your response, your doctor will complete the remaining eight cycles of treatment based on the treatment regimen you like best. Please answer the questions below. There are no wrong or right answers.

Regimen A:	***Regimen B:***
• The study drug carfilzomib was given at a dose of 36mg/m2 infused over 30 minutes. • The days of treatment happened on **days 1, 8, 15** every 28 days.	• The study drug carfilzomib was given at a dose of carfilzomib 36mg/m2 infused over 30 minutes. • The days of treatment happened on **days 1, 2, 15 and 16** every 28 days.
<u>Question 1</u>. Please mark beside the statement below that best fits you. (select only one)	
_____ I liked Regimen **A** the best.	_____ I liked Regimen **B** the best.

<u>Question 2</u>: Circle the response below to describe how strongly you liked the regimen you chose above.

5	**4**	**3**	**2**	**1**
I **strongly liked** this over the other.		I **liked** this regimen over the other		I liked both regimens almost equally. It was hard for me to choose.

<u>Question 3</u>: Can you describe why you chose the regimen over the other?

Signature of the participant: _____ Date completed: _____

To be completed by the study personnel:

Name of study personnel administering form: _____

APPENDIX D: QUALITY OF LIFE QUESTIONNAIRE (QLQ-C30)

(see next page)

THE QLQ-C30 VERSION 3.0

PT STUDY NUMBER: 101669 - __ __ __ __ __ - __ __

DATE COMPLETED (MM/DD/YYY):_____

WE ARE INTERESTED IN SOME THINGS ABOUT YOU AND YOUR HEALTH. PLEASE ANSWER ALL OF THE QUESTIONS YOURSELF BY CIRCLING THE NUMBER THAT BEST APPLIES TO YOU. THERE ARE NO "RIGHT" OR "WRONG" ANSWERS. THE INFORMATION THAT YOU PROVIDE WILL REMAIN STRICTLY CONFIDENTIAL.

	Not at all	A little	Quite a bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a **long** walk?	1	2	3	4
3. Do you have any trouble take a **short** walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need rest?	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with you daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your **family** life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your **social** activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

29. How would you rate your overall **health** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX E: QUALITY OF LIFE QUESTIONNAIRE (QLQ-MY20)

(see next page)

THE EORTC QLQ-MY20

PT STUDY NUMBER: 101669 - __ __ __ __ __ - __ __

DATE COMPLETED (MM/DD/YYY):_____

PATIENTS SOMETIMES REPORT THAT THEY HAVE THE FOLLOWING SYMPTOMS OR PROBLEMS. PLEASE INDICATE THE EXTENT TO WHICH YOU HAVE EXPERIENCED THESE SYMPTOMS OR PROBLEMS DURING THE PAST WEEK. PLEASE ANSWER BY CIRCLING THE NUMBER THAT BEST APPLIES TO YOU.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
45. Have you had acid indigestion or heartburn?	1	2	3	4

46. Have you had burning or sore eyes?	1	2	3	4
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4