Mayo Clinic Cancer Center

**A Phase 1/2 Trial of Carfilzomib and Melphalan and conditioning for autologous stem cell transplantation for multiple myeloma (CARAMEL)**

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**Drug Availability**
**Commercial Agents:** *Melphalan*
**Drug Company Supplied:** *Carfilzomib*

√Study contributor(s) not responsible for patient care.

| **Document History** | **(Effective Date)** |
|---|---|
| Activation | June 4, 2013 |
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**Protocol Resources**

| Questions: | Contact Name: |
|---|---|
| Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission | [redacted] Quality Assurance Specialist<br>Phone: [redacted]<br>E-mail: [redacted] |
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| Protocol document, consent form, regulatory issues | [redacted] Research Protocol Specialist<br>Phone: [redacted]<br>Email: [redacted] |
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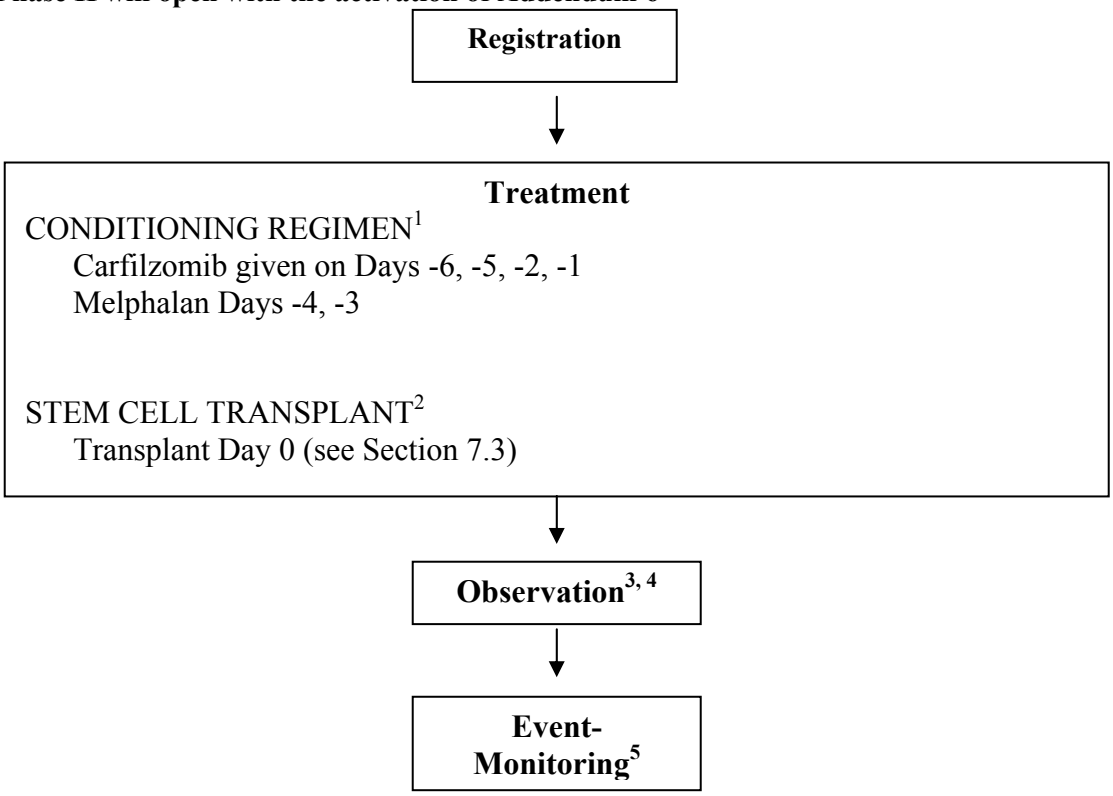
*No waivers of eligibility per NCI

**Index**

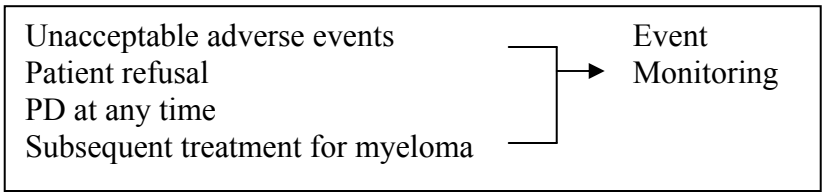
**Schema**

**Phase I MTD ( Dose level 3, 56 mg/m$^2$ Carfilzomib and 100 mg/m$^2$ Melphalan) has been reached and phase I permanently closed 12/29/2015**

**Phase II will open with the activation of Addendum 6**




1. Conditioning Regimen-Cycle 1: cycle = 6 days (days -6 to -1)
2. Stem Cell Transplant-Cycle 2: cycle = 31 days (days 0-30)
3. Post SCT Cycle 3: cycle = 70 days (days 31-100)
4. Post Day 100 Cycles 4 onwards: Every cycle will be 90 days
5. **With Addendum 8, patient follow-up no longer required**




| | |
|---|---|
| Generic name: Carfilzomib<br>Brand name(s):<br>Mayo Abbreviation: CARMIB<br>Availability: Onyx Pharmaceuticals, Inc. | Generic name: Melphalan<br>Brand name(s): Alkeran®<br>Mayo Abbreviation: LPAM<br>Availability: Commercial |

## 1.0 Background

1.1 High dose therapy and stem cell transplantation (SCT) remain the standard of care for patients with myeloma (MM) who are eligible to undergo the procedure.(Attal, Harousseau et al. 1996; Child, Morgan et al. 2003; Kumar 2009) It is an effective therapy, with improvement in overall survival and quality of life (time without symptoms and treatment) compared to conventional therapies. However, patients with MM undergoing SCT invariably suffer disease relapse after a median duration of 24 to 30 months. This is not surprising given that only a third of the patients achieve a complete response following induction therapy and SCT. Patients with high proliferative rates of tumor cells, those with high International Staging System (ISS) stage and those with adverse cytogenetic profile, such as presence of t(4;14) and t(14;16) are at a higher risk.(Gertz, Lacy et al. 2005) Strategies to improve the duration of response to SCT can contribute to improved patient wellbeing and potentially improve survival, and become an integral part of the therapeutic approach to MM. The high dose chemotherapy allows significant tumor control and the ability to overcome drug resistance. The condition regimen most commonly used for autologous transplantation is the melphalan 200 mg/m2, which has not changed significantly in the past decade. Attempts to improve upon the conditioning by escalating the dose to 280 mg/m2, or by adding amifostine to the melphalan, have met with no success. Single arm studies of bone targeting radiation using radioisotopes like samarium have shown interesting results. Several classes of new drugs have become available for the treatment of MM. Proteasome inhibitors, in particular, have been successful in terms of their efficacy in this disease.

1.2 Proteasome inhibitors for MM: The proteasome is a multi-catalytic 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 Studies have shown that addition of proteasome inhibitors to alkylating agents, such as cyclophosphamide or melphalan, can produce considerable synergy leading to better transplant outcomes in patients. In addition, at least 2 published trials have examined the role of adding bortezomib to melphalan conditioning.(Lonial, Kaufman et al. 2010; Roussel, Moreau et al. 2010) In both these single arm trials, the combination was well tolerated with no unexpected adverse events. In the Intergroupe Francophone du Myelome (IFM) phase 2 study, 54 untreated patients were enrolled to receive bortezomib (1 mg/m (2) x 4) and melphalan (200 mg/m (2)) as the conditioning regimen (Bor-HDM).(Roussel, Moreau et al. 2010) Overall, 70% of patients achieved at least a very good partial response (VGPR), including 17 patients with a complete response (CR) (32%) after SCT. No toxic deaths were observed. Bortezomib did not increase hematologic toxicity. Only one grade 3 to 4 peripheral neuropathy was reported. A matched control analysis was conducted comparing this cohort with patients from the IFM 2005-01 trial, which used melphalan alone. Patients were matched for response to induction therapy and type of induction: CR was higher in the Bor-HDM group (35% vs 11%; P = .001), regardless of induction

therapy. Lonial, et al conducted a randomized phase I/II trial designed to evaluate the safety and efficacy of combining the proteasome inhibitor bortezomib with high-dose melphalan as the conditioning for high-dose therapy and autologous transplant for myeloma.(Lonial, Kaufman et al. 2010) The study enrolled patients who did not achieve a very good partial remission (VGPR) following one or more induction regimens, and were randomized to receive a single escalating dose of bortezomib (1.0, 1.3, or 1.6 mg/m (2)), either 24 hours before or 24 hours after high-dose melphalan. Dose escalation was based on the escalation with overdose control, a Bayesian statistical model. Among 39 randomized patients, 20 received bortezomib after melphalan and 19 received bortezomib before - similar between the arms. The overall response rate for all patients was 87%, with 51% achieving a VGPR or better. Pharmacodynamic studies showed greater plasma cell apoptosis among patients who received bortezomib following melphalan. A single dose of bortezomib administered after high-dose melphalan was safe, with data suggesting improved efficacy.

1.4 Carfilzomib (PR-171) is a tetrapeptide keto-epoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome.(Kuhn, Chen et al. 2007; Parlati, Lee et al. 2009; Khan and Stewart 2011) Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor, bortezomib (Velcade®). In addition, when measured against a broad panel of proteases, including metallo-, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib.(Demo, Kirk et al. 2007; Arastu-Kapur, Shenk et al. 2008)

1.5 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 QD for five days, with nine days rest.(Kirk, Jiang et al. 2008) The administration of 12 $mg/m^2$ to rats, which was the toxic dose in 10% of animals ($STD_{10}$), resulted in > 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 toxicities 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 MM and solid tumors[3]. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity, including neuropathology, even at high doses. This is in stark contrast to that observed with bortezomib.(Bross, Kane et al. 2004) The DLTs of carfilzomib 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. The 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 achievable 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 achieve with bortezomib at its MTD, on a less intensive schedule.

1.6 ***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.(Demo, Kirk et al. 2007; Kuhn, Chen et al. 2007) 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. (Demo, Kirk et al. 2007; Kuhn, Chen et al. 2007)

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 a 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(Demo, Kirk et al. 2007).

1.7 **Phase I Experience with Carfilzomib as a Monotherapy:** A Phase I clinical trial, PX-171-002, testing carfilzomib in subjects with relapsed/refractory hematologic malignancies, is being completed.(Alsina, Trudel et al. 2007) 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 MM, Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia (WM), 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 MM experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were re-challenged 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 partial response (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.(Alsina, Trudel et al. 2007) 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 II studies.

1.8 **Phase II Experience with Carfilzomib as a monotherapy:** Two Phase II 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 increases in 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.(Jagannath, Vij et al. 2010)

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). (Jagannath, Vij et al. 2010)

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, and may form the basis for an accelerated approval NDA filing by the end of 2010. To date, this dosing schedule has been well tolerated.[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. 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 for superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were similar between the two cohorts, with Grade 3 neutropenia in ~5%, without any Grade 4 neutropenia to date.

In PX-171-004, a first cohort of patients received 20 mg/m2. 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).(Siegel, Wang et al. 2009; Wang, Siegel et al. 2009) The median time to progression (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 (minimal response) + (stable disease) 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/m2 in Cycle 2 or later based on tolerability, similar to that used in PX-171-003 – A1. Further information about the Phase II studies is presented in the Investigator's Brochure.

1.9a **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 escalating the dose 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 min 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 min 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 min was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced $C_{max}$ of carfilzomib vs 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 MM setting, particularly when administered as a 30 minute infusion. 27mg/m$^2$ of carfilzomib (bolus administration over 2-10 min.) is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities.

A phase I dose escalation study (PX-171-007) of single agent carfilzomib is ongoing, and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase II portion of the study at 36 mg/m2 (bolus administration over 2-10 min). A review of the tolerability of 36 mg/m2 carfilzomib in these patients indicates that this regimen was very well tolerated, with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m2 carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m2, with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for MM was added.

In the PX-171-007 trial, more recently 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/m$^2$, and so forth, are being investigated. Doses of 20/56 mg/m$^2$ are currently being given in two separate cohorts of patients with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose level (20/56 mg/m$^2$) have indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m$^2$, dexamethasone was increased from 4 mg/dose to 8 mg with the 56 mg/m$^2$ doses, in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56 mg/m$^2$ and are 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 mL/min, including patients on dialysis), without dose adjustment.(Badros, Vij et al. 2009) These data indicate that carfilzomib does not exacerbate underlying renal dysfunction, and confirms the “pre-renal” etiology of the BUN/creatinine elevations observed with IV bolus carfilzomib.

1.9b **Study Rationale**: Given the existing data, it is reasonable to consider the combination of carfilzomib, a new generation of proteasome inhibitors, with melphalan, as conditioning therapy for autologous stem cell transplant in myeloma. We have designed this phase I/II study of a novel conditioning regimen incorporating multiple anti-myeloma agents for patients with MM undergoing autologous stem cell transplantation. The phase I portion of the study is designed to determine the MTD of carfilzomib as part of the conditioning regimen. The phase II portion of the study is designed to assess the efficacy and toxicity of this approach.

## 2.0 Goals

2.1 Primary

2.11 **Phase I**: To determine the MTD of carfilzomib that can be added to high dose melphalan as part of conditioning chemotherapy for myeloma

2.12 **Phase II**: To determine the efficacy of the combination in patients with myeloma undergoing stem cell transplantation, as defined by achievement of complete response (CR).

2.2 Secondary

2.21 To examine the toxicities associated with addition of carfilzomib to high dose melphalan in patients with MM.

2.22 To determine the progression free rate at 1 and 2 years post registration.

2.3 Correlative Research

2.31 To determine the proportion of patients achieving a minimal residual disease (MRD) negative status.

2.32 To assess the HevyLite assay prior to and during treatment.

## 3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 The following laboratory values obtained ≤ 14 days prior to registration:
- Serum Creatinine ≤ 2 mg/dL
- Absolute neutrophil count ≥1000/μL
- Platelet count ≥ 50,000/μL
- Hemoglobin ≥ 8.0 g/dL

3.13 Diagnosis of symptomatic MM.

3.14 Measurable disease of multiple myeloma at the time of baseline values for disease assessment (see section 11.11) as defined by at least one of the following:
- Serum monoclonal protein ≥1.0 g/dL (see Section 11.1 for definition)
- ≥200 mg of monoclonal 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.
- Bone marrow plasma cells ≥ 30%

NOTE: For patients with no relapse prior to transplant, measurable disease at the time of diagnosis.

NOTE: For patients who have had a disease relapse prior to transplant, measurable disease at the time of the most recent relapse immediately prior to transplant. NOTE: If the patient had treatment for the relapsed disease prior to transplant, the patient must have measurable disease at the time of relapse prior to this therapy.

3.15 Patient is considered for autologous stem cell transplantation with full dose melphalan (200 $mg/m^2$).

3.16 ECOG performance status (PS) 0, 1 or 2 (Appendix I).

3.17 Recovered from toxicity of previous chemotherapy (excludes grade 1 neurotoxicity and hematological toxicity).

3.18 Provide informed written consent.

3.19a Adequate cardiopulmonary function
- Ejection fraction ≥ 45%
- Corrected pulmonary diffusion capacity of greater than or equal to 50%
- FEV1 ≥ 50%
- FVC ≥ 50%

3.19b Negative pregnancy test performed ≤7 days prior to registration, for women of childbearing potential only.

3.19c Willing to return to Mayo Clinic Rochester, Mayo Clinic Arizona, Mayo Clinic Florida for treatment.

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19d Willing to provide blood and bone marrow samples for correlative research purposes (see Sections 6.31 and 14.0).

3.2 Exclusion Criteria

3.21 Prior autologous or allogeneic bone marrow/peripheral blood stem cell transplant.

3.22 More than two prior regimens for therapy of MM.

3.23 Myocardial infarction within 6 months prior to enrollment, or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. NOTE: Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.

3.24 Seroreactivity for HIV, HTLV I or II, HBV, HCV.

3.25 Other active malignancy < 2 years prior to registration. **EXCEPTIONS**: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. **NOTE**: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.26 Any of the following:

- Pregnant women or women of reproductive capability who are unwilling to use effective contraception
- Nursing women
- Men who are unwilling to use a condom (even if they have undergone a prior vasectomy) while having intercourse with any woman, while taking the drug and for 28 days after stopping treatment.

3.27 Other co-morbidity, which would interfere with patient's ability to participate in the trial, e.g. uncontrolled infection, uncompensated lung disease.

3.28 Concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational. **NOTE:** Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

3.29 Known allergies to any of the components of the investigational treatment regimen or required ancillary treatments.

**4.0 Test Schedule**

| | **Active Monitoring** | | | | | |
|---|---|---|---|---|---|---|
| | Days Prior to Registration | | | | **Observation** | |
| | ≤30 days | ≤14 days | End of Cycle 1 (Day -1) | End of Cycle 2 (Day 30)[1] | End of Cycle 3 (Day 100)[10] | Every 90 days [1, 5, 11] |
| Complete medical history | X | | | | | |
| Adverse Event monitoring | | X | X | X | X | X[12] |
| Physical exam, including weight and vital signs | | X | X | X | X | |
| Height | | X | | | | |
| Performance status (ECOG scale) | | X | X | X | X | X |
| CBC with differential (neutrophil, platelets, hemoglobin) | | X | X | X | X | X |
| Prothrombin time (PT) | X | | | | | |
| Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; total and direct bilirubin; SGOT (AST); serum creatinine, calcium, albumin, urates, phosphorus | | X | X | X | X | X |
| LDH, $Beta_2$-microglobulin, C-reactive protein, Plasma cell assessment | X | | | | | |
| Electrophoresis of serum and urine | | X | | X | X | X |
| Affected serum immunoglobulin[8] | | X | | X | X | X |
| Immunofixation serum and urine | X | | | X | X[2] | X[2] |
| Immunoglobulin serum free light chains | | X | | X[6] | X[6] | X[6] |

**Test Schedule continued on the following page.**

| | **Active Monitoring** | | | | | |
|---|---|---|---|---|---|---|
| | Days Prior to Registration | | | | **Observation** | |
| | ≤30 days | ≤14 days | End of Cycle 1 (Day -1) | End of Cycle 2 (Day 30)[1] | End of Cycle 3 (Day 100)[10] | Every 90 days [1, 5, 11] |
| Metastatic skeletal survey | X | | | | X [4] | X [4] |
| Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, plasma cell proliferation, and flow cytometry[9] | X | | | | X | X[7] |
| Chest x-ray, ECHO, PFT | X | | | | | |
| Serum pregnancy test | | X[3] | | | | |
| Research Bone marrow aspirate[R] | X | | | | X | X[7] |
| Research blood[R] | X | | | | X | X[7] |

1) ± 14 days
2) Immunofixation (IF) needed only in the absence of M-spike.
3) For women of childbearing potential only. Must be done ≤7 days prior to registration.
4) Every 168 days (6 months). This is not required for patients unable to return to the study site for follow-up visits.
5) For up to 1 year from the time of registration, or until progression or subsequent treatment after transplant, whichever occurs first
6) Only required to document stringent CR or for patients who are followed by light chains for response.
7) At physician's discretion at time of suspected CR. This is not required for patients unable to return to the study site for follow-up visits.
8) Affected immunoglobulin refers to the baseline M-protein type, that is, IgM, IgG, IgA, or IgD. Not applicable if patient "non-secretory", or if patient has no heavy chain, i.e. light chain MM or AL.
9) FISH and cytogenics are required only at baseline.
10) ± 40 days
11) May be performed by local MD and results faxed to study site if patient is unable to return to the study site for follow-up visits.
12) Patient who is completing local labs – a nurse will contact to assess AEs and medication changes.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

**5.0 Grouping Factor:**

5.1 Phase: I (Dose Escalation Group, permanently closed 12/29/15) vs. II (MTD)

**6.0 Registration Procedures**

6.1 Phase I – Mayo Clinic Institutions Only

**Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.**

6.11 Registration Procedures

6.111 To register a patient, [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II

6.21 Mayo Clinic Institutions Registration Procedures

6.211 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.3 Phase I and II

6.31 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 14.0).

6.32 Prior to accepting the registration, registration/randomization application 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

6.33 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.34 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of Multiple Myeloma at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.35 Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Arizona, Mayo Clinic Florida under the supervision of a hematologist/oncologist.

6.36 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration. Exception: If therapy must be started when the MCCC Registration Office is closed, the registration office must be notified immediately upon the next business day. Under no circumstances will un-registered patients be retrospectively eligible for the study.

6.37 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.38 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.39b Study drug is available on site.

## 7.0 Protocol Treatment

7.1 Treatment Schedule: The treatment phase of the protocol consists of 2 distinct cycles, with a total duration of 37 days.

| | Duration | Transplant day number | |
|---|---|---|---|
| Cycle 1 | 6 days | -6 to -1 | Conditioning regimen |
| Cycle 2 | 31 days | 0 to +30 | Hematopoietic stem cell infusion and engraftment.<br>Assessment of DLT for Phase I and toxicity for Phase II<br>Disease assessment. |

7.11 Cycle 1 (Days -6 to -1) (Conditioning for stem cell transplant)

Phase I (Dose Escalation phase)

| Agent | Dose | Route | Day | Cycle length |
|---|---|---|---|---|
| Carfilzomib[1] | As assigned by MCCC Registration Office | IV | -6, -5, -2, and -1 | |
| Melphalan[2] | 100 mg/m$^2$ | IV | -4 and -3 | |

[1] Carfilzomib is administered as a continuous IV infusion in 50 mL or 100 mL of 5% dextrose in water over 30 minutes after pre-hydration with 500 mL NS iv over 1 hour. On day -6, Solu-Medrol 125 mg iv should be administered 1 hour prior to carfilzomib.
[2] Melphalan is administered as a continuous IV infusion in 1000 mL of 0.9% sodium chloride over 1 hour.

Phase II (Phase II studies at MTD)

| Agent | Dose | Route | Day | Cycle length |
|---|---|---|---|---|
| Carfilzomib[1] | 56 mg/m$^2$ | IV | -6, -5, -2, and -1 | |
| Melphalan[2] | 100 mg/m$^2$ | IV | -4 and -3 | |

[1] Carfilzomib is administered as a continuous IV infusion in 50 mL or 100 mL of 5% dextrose in water over 30 minutes after pre-hydration with 500 mL NS iv over 1 hour. On day -6, Solu-Medrol 125 mg iv should be administered 1 hour prior to carfilzomib.
[2] Melphalan is administered as a continuous IV infusion in 1000 mL of 0.9% sodium chloride over 1 hour.

7.111 Doses will be calculated using the lesser of actual or corrected ideal body weight (CIBW) (see appendix IV).

7.12 Cycle 2 (Day 0) (Stem Cell Transplant)

| | Day 0 |
|---|---|
| Bone marrow or peripheral blood stem cell infusion | X |

7.2 Dose Escalation: This study will use a two-stage accelerated design (Simon et al, 1997). The first stage will be an accelerated dose escalation with a cohort of one patient. The second stage will resume the standard cohort of three phase I study design. The dose levels to which patients will be assigned in sequential cohorts are described below. Decisions on when and how to dose escalate are described below.

| Dose Level | Carfilzomib[1] | Melphalan |
|---|---|---|
| 0* | 27 mg/m$^2$ | 100 mg/m$^2$ |
| 1 | 36 mg/m$^2$ | 100 mg/m$^2$ |
| 2 | 45 mg/m$^2$ | 100 mg/m$^2$ |
| 3 | 56 mg/m$^2$ | 100 mg/m$^2$ |

* Starting dose
[1] Subjects with a BSA > 2.2 m$^2$ will receive a dose based on 2.2 m$^2$ BSA.

7.3 Phase I – Dose Escalation and Determination of MTD

7.31 MTD Determination

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD.

7.32 Stage 1 (Accelerate cohort of 1 patient)

7.321 Assign one patient at a dose level and observe for at least 2 cycles (37 days) to assess toxicity, where toxicity is defined as an adverse event at least possibly related to treatment.

•If this patient has not had a DLT and <2 patients have experienced grade ≥3 non-hematologic toxicities during the first 2 cycles over all dose levels, then escalate dose to the next higher dose level

- •Repeat Stage 1 if the next higher dose level is not the highest level of the treatment
- •Enter Stage 2 if the next higher dose level is the highest level of treatment

•If this patient has had a DLT or ≥2 patients have experienced grade ≥3 non-hematologic toxicities during the first 2 cycles over all dose levels, then expand the current cohort to 3 patients and enter Stage 2

7.322 As of Addendum 4, the phase I study design will be modified to the standard cohort of 3 design. Stage 1 with accelerated dose escalation will no longer apply and accrual will continue in Stage 2 with the standard cohort of 3 design. Due to issues with accruing potential patients, it is felt that a cohort of 3 design will be more beneficial to the patients and to study accrual. In addition, the study entered Stage 2 of the design in error and it is felt that it will be more appropriate to continue with standard cohorts of 3 patients.

7.33 Stage 2 (Standard cohort of 3 patients)

7.331 Three patients will be treated at a given dose level combination and observed for at least 2 cycles (37 days) to assess toxicity.

7.332 If DLT is not seen in any of the 3 patients treated at a certain dose level, up to 3 new patients will be accrued and treated at the next higher dose level, or at the same dose level if the current dose level is the highest level being tested. If DLT is seen in at least 2 patients treated at a given dose level, then 3 total patients will be treated at the next lower dose level.

7.333 If a DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥ 2 of 6), the MTD will have been exceeded and further accrual will cease to this cohort. If DLT is not seen in any of the 3 additional patients, 3 new patients will be accrued and treated at the next highest dose level.

7.334 If DLT is observed in at least 2 of 6 patients after enrolling 6 patients on a specific dose level, then the MTD will have been exceeded and defined as the previous dose, unless ≤ 3 patients were treated at the lower dose level. In such cases, a total of 6 patients are treated at the MTD to more fully assess the toxicities with the MTD.

7.34 Dose De-Escalation

If DLT is seen in at least 2 patients at the starting Dose Level 0, then the dose level will be closed and the study will need to be amended.

7.35 If a patient fails to complete the initial 2 cycles of therapy (conditioning and transplant) for reasons other than toxicity, the patient will be regarded as uninformative with respect to the goals of the study and an additional patient will be treated at the current dose level.

7.4 Definition of dose limiting toxicity (DLT for Phase I portion)

7.41 For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event occurring in the first 2 cycles attributed (definitely, probably, or possibly) to the study treatment, and meeting one of the following criteria:

| **Toxicity** | **DLT Definition** |
|---|---|
| Hematologic | Absolute neutrophil count engraftment* delayed beyond day 21 or Platelet engraftment* delayed beyond day 30. |
| Neurologic | ≥ Grade 3 sensory, motor |
| Other | ≥ Grade 4 non-neurologic or non-hematologic excluding nausea, vomiting, diarrhea |

* For the purposes of this protocol, engraftment is defined as an absolute neutrophil count > 500 on 3 consecutive days and platelets ≥ 20,000/μL, without transfusion, on 3 consecutive days (see Section 11.16).

7.5 Phase II portion

Enrollment to the phase II portion will begin once the MTD has been determined as defined in Section 7.31. If all dose levels are safely tested and an MTD has not been determined, enrollment will begin in phase II at the highest dose level tested in phase I (Dose Level 4). A total of 6 phase I patients must be treated at the dose level that will be brought forward to the phase II portion.

7.6 Treatment by a local medical doctor (LMD) is not allowed.

## 8.0 Dosage Modification Based on Adverse Events

8.1 There is no anticipated dose modification (other than the anticipated in the carfilzomib dose escalation) for any of the drugs used in the conditioning regimen. However, administration of the study drug can be held at the treating physician's discretion for prior life threatening acute side-effect (e.g. allergic or infusion reaction with carfilzomib).

## 9.0 Ancillary Treatment/Supportive Care

9.1 Investigators will follow the institutional guideline for supportive care in patients receiving Hematopoietic stem cell transplant (HCT). Substitution of the medications below based on standard practice is acceptable, for example oral or IV equivalent.

9.2 Patients may receive concurrent treatment with a bisphosphonate.

9.3 Patients may continue on low level/stable steroid doses for replacement or inhalation therapy.

9.4 The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy
- Any other systemic anti-neoplastic therapies, including, but not limited to, immunotherapy or monoclonal antibody therapy
- Any external beam radiotherapy

9.5 Antiemetics may be used at the discretion of the attending physician.

9.6 Solumedrol 125 mg iv can be administered prior to, during, or after administration of carfilzomib for fevers, rigors, rash, dyspnea, or other signs of a hypersensitivity reaction

9.7 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.

9.71 Administration of only leukocyte depleted, irradiated blood products.

9.72 Transfusion of red blood cells if hemoglobin < 8g/dl or if patient has symptoms of anemia.

9.73 Transfusion of apheresis platelets, if platelet count <10 x 109/liter, or ≤ 20 x 109/liter and patient is febrile and/or with extensive mucositis, and/or receiving low molecular weight heparin.

9.8 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications, such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.9 Diarrhea: This can be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and/or other antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea, or any diarrhea associated with severe nausea or vomiting, **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.9a Standard infectious disease prophylaxis

9.9a1 Anti-bacterial prophylaxis with levofloxacin 500 mg by mouth once daily or by IV, beginning on day –1 and continuing until absolute neutrophil count (ANC) $>0.5x10^9$/liter x 2 days. May be held during therapeutic antibiotics. Equivalent antibacterial prophylaxis may be substituted for drug allergy or MD discretion. Penicillin VK 500 mg by mouth twice daily, starting on day -1 through day +365, unless held for therapeutic antibiotics. Equivalent antibacterial prophylaxis may be substituted for drug allergy or at MD discretion.

9.9a2 Anti-fungal prophylaxis with fluconazole 400 mg by mouth or IV once daily, from the start of conditioning regimen continuing until ANC $>0.5x10^9$/liter x 2 days. Equivalent antifungal prophylaxis may be substituted at the physician discretion.

9.9a3 Prophylaxis of Pneumocystis jiroveci infection with TMP-SMX DS, 1 tablet by mouth twice daily from admission until day -1, then resume TMP-SMX SS when ANC $>1$ x$10^9$/liter at a dose of one tablet by mouth daily until day +100. Equivalent prophylaxis may be substituted for drug allergy or MD discretion.

9.9a4 Prophylaxis of HSV and HZV with Acyclovir 400 mg by mouth twice daily, or by IV from day –6 to day +365. Equivalent prophylaxis may be substituted for drug allergy or MD discretion.

9.9a5 Empirical broad spectrum antibiotic therapy for patients with fever and neutropenia. Introduction of anti-fungal agents, if fever persists or findings suggestive of fungal infection.

## 10.0 Adverse Event (AE) Reporting and Monitoring

### 10.1 Adverse Event Characteristics

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

### 10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

**NOTE**: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

**Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.**

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

**NOTE:** The combination of an investigational agent with a commercial agent is considered investigational.

**Routine Reporting**

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.52.

  **NOTE:** When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

**Expedited Reporting**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

- Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via MedWatch.

- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

## 10.32 Special Situations for Expedited Reporting

**Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events[1]**

An expedited report may not be required for specific Grade 1, 2, 3, and 4 Serious Adverse Events where the AE is listed in Section 15.0 of the protocol as **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e., Nadir/adverse events form]: see footnote 1):

| System Organ Class (SOC) | Adverse event/ Symptoms | CTCAE Grade at which the event will not be reported in an expedited manner. |
|---|---|---|
| Blood and lymphatic system disorders | Febrile neutropenia | ≤ 4 |
| | Anemia | ≤ 3 |
| Investigations | Neutrophil count decreased | ≤ 4 |
| | Platelet count decreased | ≤ 4 |
| | Lymphocyte count decreased | ≤ 4 |
| | White blood cell decreased | ≤ 4 |
| Gastrointestinal disorders | Mucositis oral | ≤ 3 |
| | Diarrhea | ≤ 3 |
| | Nausea | ≤ 3 |
| | Vomiting | ≤ 3 |
| Metabolism and nutrition disorders | Dehydration | ≤ 3 |

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.321 **Persistent or Significant Disabilities/Incapacities**
Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.322 **Death**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

- Any death occurring **greater than 30 days** after the last does of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

10.323 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.324 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.325 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, Amgen Global Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Amgen Global Safety Contact information in Section 10.4). 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 Amgen Global Safety.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

10.4 Expedited Reporting Requirements for IND/IDE Agents

### 10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes |
|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 7 Calendar Days | 24-Hour 3 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | |

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.32 of the protocol.
**Expedited AE reporting timelines are defined as:**

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-hour notification followed by complete report within 3 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional instructions:

1. Notify Amgen Global Safety of **all** expedited safety reports/serious unexpected suspected adverse reactions (SUSARs) and **all** non-expedited SAEs via the contact information listed below. This applies to all subjects receiving carfilzomib treatment, regardless of whether the event is determined to be related or unrelated to carfilzomib. **All report must include the SAE Report Cover Page (see forms packet).**
   **Please note these important SAE reporting timelines:**
   - **Expedited Safety Reports/SUSARs**: These notifications must be provided to Amgen Global Safety **in parallel** to the Health Authority submissions within **seven (7) calendar days for any fatal or life-threatening SUSARs and within fifteen (15) calendar days for all other SUSARs**, but in no case any later than one (1) business day from the submission date.
   - **All other SAEs:** These notifications must be provided to Amgen Global Safety **no later than thirty days (Day 30) from the time the site or Principal Investigator becomes aware of the SAE.**

   **Send Reports to:**
   Drug Safety Reporting Fax: [redacted] (US toll-free fax)

2. Use FDA Medwatch (Form 3500A) available in forms packet for Investigational agents or commercial/investigational agents on the same arm. Submit to Amgen Global Safety (see #1).

   Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

   Non-MCCC Institutions: Provide copies by fax [redacted] to the MCCC SAE Coordinator who will forward to the MCCC IND Coordinator to determine if FDA submission is needed.

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

| System Organ Class (SOC) | Adverse event/Symptoms | Baseline | Each evaluation |
|---|---|---|---|
| Vascular Disorders | Hypotension | X | X |
| Investigations | Blood bilirubin increased | X | X |
| | Creatinine increased | X | X |
| Nervous System Disorders | Peripheral motor neuropathy | X | X |
| | Peripheral sensory neuropathy | X | X |

10.52 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation – The International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al, 2011) will be used to assess response to therapy.

### 11.1 Multiple Myeloma Patients

11.11 Terms and definitions

- **Baseline values for disease assessment**: All disease response measurements will be based on the values obtained at the time of diagnosis if there has been no relapse prior to transplant. If patients had a disease relapse prior to transplant, the baseline values will be those obtained at the time of relapse immediately prior to the transplant. If patient had treatment for the relapsed

disease prior to transplant, the values will be from prior to this therapy, ie, the time of relapse.

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria. In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177mM/L)
6. Hyperviscosity

NOTE: If the patient does not meet the IMWG criteria for clinical relapse but the patient has increasing M protein leading to a change in clinical management, this will also be considered a relapse at the discretion of the treating physician.

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same M-protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

**FLC estimation** is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.

  - Serum M-protein ≥1 g/dl
  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥ 30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine M-protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-protein, serum free light chain, or urine M-protein.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.12 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

**Table 11.12**

**Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])**

| On Study Baseline Value | SPEP[4] | 24 hr UPEP[2] | Ig FLC | BM Bx |
|---|---|---|---|---|
| Serum M-protein ≥1 g/dl, and urine M-protein≥ 200 mg/24 hrs | X | X | | |
| Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs | X | | | |
| Serum M-protein <1 g/dl, and urine M-protein≥ 200 mg/24 hrs | | X | | |
| Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL | | | X | |
| Serum M-protein < 1 g/dl, urine M-protein< 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells | | | | X[3] |

[1] ***SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy*** *are required to document CR regardless of registration values, and in addition* ***FLC*** *measurement and* ***bone marrow immunophenotyping*** *is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.*

[2] *For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category*

[3] *At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.*

[4] *If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.*

11.13 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.

- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.12

11.14 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.15 Response and Progression

Criteria for response and progression are listed in Table 11.15. Progressive disease for all patients as defined in Table 11.15.

Table 11.5

| CATEGORY | RESPONSE CATEGORY [a] |
|---|---|
| Stringent Complete Response (sCR) [b] | • CR as defined *plus*<br>• Normal FLC ratio *and*<br>• Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [i] |
| Complete Response (CR) [b,j] | • Negative immunofixation of serum and urine [c] *and*<br>• Disappearance of any soft tissue plasmacytoma *and*<br>• <5% PCs in Bone Marrow *and*<br>• If the only measurable disease is FLC, a normal FLC ratio [d] |
| Very Good Partial Response (VGPR) | • Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or*<br>• ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c]<br>• If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels |
| Partial Response (PR) | • If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c]<br>• If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels<br>• If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%)<br>• If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas |
| Minor Response (MR) | • If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and*<br>• If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma *and*<br>• No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response) |

| | |
|---|---|
| Progressive Disease (PD) [b, h] | Increase of 25% from lowest value in any of the following [f, g]:<br>• Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or*<br>• Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or*<br>• If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or*<br>• If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e]<br><br>Or any one or more of the following:<br>• Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma<br>• Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder |
| Stable Disease (SD) | Not meeting criteria for sCR, CR, VGPR, PR, MR or PD |

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

**[b]** CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

**[c]** If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

**[d]** In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

**[e]** Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[h] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

[j] If a patient has already achieved a complete response prior to registration as a result of the induction therapy or stem cell transplant, the patient will be considered a continued complete response if they continue to meet the complete response criteria at the next assessment. Reconfirmation of complete response is not required.

11.16 Criteria for engraftment (for hematopoietic stem cell transplant studies only)

Engraftment is defined as:

- The first day of three consecutive days on which the absolute neutrophil count (ANC) >500/mm$^3$

**and**

- The first of three consecutive days with an un-transfused platelet count >20,000/mm$^3$.

## 12.0 Descriptive Factors

12.1 Prior Immunomodulatory agents (IMiDs): Yes vs. no

12.2 Prior Alkylators: Yes vs. no

12.3 Prior Proteasome inhibitors: Yes vs. no

12.4 Response to last treatment: Yes vs. no

12.5 Timing of transplant: < 12 months from diagnosis vs. ≥ 12 months from diagnosis

12.6 Dose Level (to be assigned by Registration Office): 0 vs. 1 vs. 2 vs. 3 vs. 4

12.7 Parameters followed for hematologic response (pick one): serum M-spike ≥ 1 g/dL and urine M-spike ≥200 mg/24 hours vs. serum M-spike ≥1g/dL only vs. urine M-spike ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL vs. bone marrow plasma cells ≥ 30%. Distinguish between SPEP measurement versus quantitative IgA measurement for serum M-spike. All measurements are based on those at the time of Baseline values for disease assessment as defined in Section 11.11.

12.8 Relapse status category as a descriptive factor: No relapse prior to transplant vs. Disease relapse prior to transplant with no treatment for most recent relapse vs. Disease relapse prior to transplant with treatment for most recent relapse.

## 13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) will continue the conditioning regimen and stem cell transplant per protocol.

13.2 Observation: If the patient has achieved sCR, CR, VGPR, PR, or SD, (or usCR, uCR, uVGPR, uPR) at the post-transplant evaluation, the patient will be observed at 100 days post-transplant and then every 90 days for up to1 year from time of registration. The follow-up visit may be performed by local MD if the patient is unable to return to the study site. If the patient develops progressive disease or receives subsequent treatment for myeloma while in observation then the patient will go to the event-monitoring phase per Section 18.0.

13.3 Criteria for Patient Initiation of Event Monitoring
**As of Addendum 8, patient follow-up is no longer required.**

Patients will go to event monitoring for the following reasons:

- Progressive multiple myeloma
- Subsequent treatment for multiple myeloma
- Patient withdraws consent to continue in the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over the course of one year.)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early.

13.4 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.5 Phase I Portion only: If a patient fails to complete treatment (conditioning and transplant) for reasons other than toxicity, the patient will be regarded as not evaluable and will be replaced.

13.6 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

## 14.0 Body Fluid Biospecimens

### 14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

| Correlative Study (Section for more information) | Mandatory or Optional | Blood or Body Fluid being Collected | Type of Collection Tube (color of tube top) | Volume to collect per tube (# of tubes to be collected) | Visit 1: Study Entry | Visit 2: End of cycle 3 (Day 100) | Visit 3: At suspected CR | Process at site? (Yes or No) | Temperature Conditions for Storage /Shipping |
|---|---|---|---|---|---|---|---|---|---|
| Minimal residual disease | Mandatory | Bone marrow aspirate | EDTA (lavender) | 3 mL (1) | X | X | X[1] | No | Ambient |
| HevyLite Assay® | Mandatory | Plasma | ACD (yellow) | 6 ml (2) | X | X | X[1] | No | Ice pack |

1. Not required for patients who are unable to return to the study site.

14.2 Collection and Processing

14.21 Minimal residual disease evaluation: This will be performed on bone marrow aspirate following a wash no lyse method on fresh samples.

14.22 HevyLite Assay®: This will be performed on plasma samples as per manufacturer's guidelines.

14.3 Shipping and Handling

14.31 Minimal Residual Disease

14.311 Draw 1-2 mL of bone marrow aspirate into one 2 mL lavender top EDTA tube. It is important to thoroughly mix the blood with the anticoagulant agent by gently inverting the tube not less than five times. Carefully unstop the EDTA tube and using the pipette provided transfer 1 mL of aspirate into the provided 1 mL Cyto-Check tube. Gently invert vial by hand 3 times to mix. Immediately ship ambient via overnight delivery to the address below. A kit will be shipped to the participating site (see Appendix V).

Please plan to obtain samples for bone marrow aspirates on Monday through Thursday only.

14.32 HevyLite Assay®

14.321 The peripheral blood sample will be collected in ACD tubes (2 tubes). A kit will be shipped to the participating site.

14.33 Shipping Specimens: Samples can be shipped on ice. They should be shipped overnight taking care to avoid Friday collection and shipping.

Please notify Mayo Clinic by email [redacted] or phone, [redacted] to ensure that samples are received.

[redacted]

14.4 Background and Methodology

14.41 Minimal residual disease evaluation: Currently 30-40% of patients achieve a CR with initial therapy. In most cases, patients classified as CR in reality have minimal residual disease (MRD) since (i) many such patients relapse, and (ii) residual clonal disease is detectable in most by more sensitive techniques such as multiparameter flow cytometry and PCR based techniques.(Sarasquete, Garcia-Sanz et al. 2005; Mateo, Montalban et al. 2008; Paiva, Vidriales et al. 2009). We will determine

minimal residual disease positivity at various stages of treatment, among patients achieving a conventional complete response. Bone marrow aspirates will be evaluated for presence of clonal plasma cells a well as the ratio of clonal to non-clonal plasma cells after 3 cycles and whenever a CR is suspected and a marrow is done.

MRD detection will be done on BM samples as previously described32. Plasma cells are identified by their characteristic CD45/CD38/CD138 staining pattern with light chain restriction and CD19/CD56 phenotype on each case. One ml (milliliter) of BM (bone marrow) is subjected to flow cytometry on a Cantos Flow Cytometer. Samples are collected ungated, up to one million events per tube.

14.42 HevyLite Assay®: Immunoparesis may be a valuable biomarker of the presence of residual malignant disease. However, immunoparesis of uninvolved immunoglobulins (Igs) lacks precision. The novel Hevylite™ assay measures levels of each distinct Ig subtype (i.e., IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, and IgMλ,) and enables us for the first time to determine if suppression of isotype-specific Ig of the opposite LC type is occurring. We have found that suppression of isotype specific M protein (i.e., IgGκ in IgGλ MGUS) is associated with a significantly increased risk of progression in MGUS indicating ability to detect malignant phenotype.(Katzmann, Clark et al. 2009) In the studies proposed here, we will determine if suppression of isotype specific Ig level can help identify patients who have persistent MRD.

## 15.0 Drug Information

### 15.1 Carfilzomib (PR-171, Kyprolis™)

15.11 **Background**: Carfilzomib is an analog of epoxomicin and eponemycin; a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in vitro in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

15.12 **Formulation**: Carfilzomib for Injection is supplied as a white to off-white lyophilized cake or powder in a 60 mg single-use vial. Upon reconstitution, Carfilzomib for Injection consists of 2 milligram per milliliter (mg/mL) carfilzomib, 100 mg/mL sulfobutylether-beta-cyclodextrin (SBECD), and 1.9 mg/mL citrate buffer (pH3 to 4).

15.13 **Preparation and storage**: Unopened vials of carfilzomib are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). Retain carfilzomib in the original package to protect from light. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution.

**Reconstitution/Preparation Steps**:
1. Remove vial from refrigerator just prior to use.
2. Aseptically reconstitute each vial by slowly injecting 29 mL Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. Do not use alternative diluents, such as 0.9% Sodium Chloride Injection, USP, for reconstitution.
3. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides.
4. After reconstitution, carfilzomib is ready for intravenous administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product.
5. When administering in an intravenous bag, withdraw the calculated dose from the vial and dilute into 50 mL or 100 mL 5% Dextrose Injection, USP intravenous bag. If required, an equivalent volume of D5W could be withdrawn prior to dilution of carfilzomib.
6. Immediately discard the vial containing the unused portion.

Onyx does not have any data to support the use of closed-system drug transfer devices other than a standard syringe needle, therefore use of closed-system drug transfer devices are to be avoided. However, institutions must comply with internal procedures and guidelines for preparation of oncologic drugs when preparing carfilzomib. Therefore, use of these systems may be required by these procedures.

Prepared IV bags are stable in the refrigerator for 24 hours, or at room temperature for 4 hours. Total time from reconstitution to administration should not exceed 24 hours.

15.14 **Administration:**
Current clinical experience indicates that carfilzomib can be safety administered IV over 2 to10 minutes, or at rates of approximately 10 mL/minute for doses up to 27 mg/m$^2$; higher doses (>27 mg/m$^2$) are most often administered as a 30-minute infusion.

The IV administration line should be flushed with 5% dextrose in water or normal saline, immediately before and after carfilzomib administration. Carfilzomib should not be administered as a bolus.

The dose is calculated using the less of actual or corrected ideal body weight (see Appendix IV). Patients with a BSA greater than 2.2 $m^2$ will receive a dose based upon a BSA of 2.2 $m^2$.

15.15 **Pharmacokinetic information**:

a) Absorption – The $C_{max}$ and AUC following a single IV dose of 27 $mg/m^2$ was 4232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 $mg/m^2$, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 $mg/m^2$, there was a dose-dependent increase in exposure. There are no apparent differences in carfilzomib clearance, AUC, and Cmax between subjects with normal and those with varying levels of renal functional impairment following single- or repeat-dose administration.

b) Distribution – The mean $V_{ss}$ of a 20 $mg/m^2$ dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

c) Metabolism – Carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

d) Excretion – Following intravenous administration of doses ≥ 15 $mg/m^2$, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Within 24 hours following administration of a single 27 $mg/m^2$ IV dose of carfilzomib to subjects with multiple myeloma or solid tumors, approximately 30% of the administered dose of carfilzomib was excreted in urine as metabolites.

15.16 **Potential Drug Interactions**: Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities. The drug-drug interaction potential of carfilzomib is expected to be low. In cultured fresh human hepatocytes, carfilzomib did not induce human CYP1A2 and CYP3A4. In a study conducted in subjects with solid tumors (PX-171-008), single and repeat dosing of carfilzomib at 27 mg/m2 did not affect the PK of midazolam, a sensitive CYP3A substrate. Together, the in vitro and in vivo results indicate a low potential for carfilzomib to inhibit the metabolism of CYP3A4/5 substrates and other CYP450 substrates in human subjects. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib; thus, the potential impact of other concomitant medications on carfilzomib PK is expected to be low.

Since it is unknown whether carfilzomib is an inducer of CYP2C9 at relevant therapeutic concentrations, the current data cannot exclude that the efficacy of oral contraceptives may be reduced during carfilzomib treatment. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, such as oral contraceptives.

Carfilzomib is a substrate of efflux transporter P-glycoprotein (P-gp), but it only showed marginal inhibitory effect to P-gp at concentrations as high as 3 micromoles and is not a BCRP substrate. Given that carfilzomib is administered IV and is extensively metabolized, the PK profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

In vitro, carfilzomib does not inhibit OATP1B3, OAT1, OAT3, OCT2, or BSEP at concentrations up to 3 μM. The risk of clinically relevant interactions with substrates of OATP1B1 and UGT1A1 is low.

15.17 **Known potential toxicities**: Most commonly reported adverse reactions (incidence ≥30%) are fatigue, anemia, thrombocytopenia, and diarrhea.
**Common known potential toxicities, > 10% -** <30%:
Central nervous system: Headache, dizziness, insomnia, peripheral neuropathy
Gastrointestinal: Vomiting, constipation, abdominal pain, nausea
Hematologic: Lymphopenia, neutropenia, leukopenia
Metabolism and Nutrition: Anorexia, hypokalemia, hyperglycemia
Neuromuscular & skeletal: Back pain, arthralgia, muscle spasms, pain in extremity
Renal: Increased creatinine
Respiratory: Dyspnea, cough, respiratory tract infection, pneumonia, nasopharyngitis
Vascular: Hypertension
General Disorders: Asthenia, peripheral edema, and pyrexia

**Less common known potential toxicities, 1% - 10%**:
Cardiovascular: Cardiac failure, tachycardia, palpitations, atrial fibrillation
Central nervous system: Paresthesia, anxiety, hypoesthesia
Dermatologic: Rash, pruritus, erythema, hyperhidrosis
Endocrine & metabolic: Elevated uric acid, low albumin levels
Gastrointestinal: Dyspepsia
Hematologic: Febrile neutropenia, leukopenia, platelet count decreased, lymphocyte count decreased
Hepatic: ALT increased, AST increased, hyperbilirubinemia, increased gamma glutamyltransferase
Infections: Urinary tract infections, sepsis, bronchitis, influenza, viral infection

Metabolism and Nutritional disorders: Hypocalcemia, hypercalcemia, hypophosphatemia, hyponatremia, dehydration, hyperkalemia, hypomagnesemia, hyperuricemia
Neuromuscular & skeletal: Myalgia, musculoskeletal pain, musculoskeletal chest pain, muscular weakness, bone pain
Ocular: Blurred vision, cataracts
Respiratory: Epistaxis, pulmonary edema, oropharyngeal pain, dysphonia, wheezing, pulmonary hypertension, rhinitis
Vascular: Hypotension, DVT, PE, flushing
Other: Pain, increased C-reactive protein, toothache, chills, infusion site reaction

**Rare known potential toxicities, <1% (Limited to important or life-threatening):**

Cardiovascular: Cardiac arrest, myocardial infarction, myocardial ischemia, pericardial effusion, ejection fraction decreased
Hepatic: Hepatic failure, cholestasis
Respiratory: Pneumonitis, acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, lung infection, pulmonary hemorrhage
Vascular: Thrombotic thrombocytopenic purpura, thrombotic microangiopathy
Other: Tumor lysis syndrome, posterior reversible encephalopathy syndrome, multi-organ failure, cerebrovascular accident, intracranial hemorrhage, hypertensive crisis/emergency, hemorrhage, drug hypersensitivity

Potential risks (unknown if there is a causal association between the event and carfilzomib):
Herpes zoster infections (The risk of herpes zoster infections can be minimized with antiviral prophylaxis).

Detailed safety information for carfilzomib, including contraindications, warnings, and precautions, adverse reactions, and overdose can be found in the current prescribing information. Carfilzomib should be administered under the supervision of a physician experienced in the use of anti-neoplastic therapy.

15.18 **Drug procurement:** Drug is provided to the study free of charge by Onyx Pharmaceuticals, Inc.

15.19 **Nursing Guidelines:**

15.191 Fatigue is the most commonly reported side effect. Instruct patient in energy conserving lifestyle and monitor for effectiveness.

15.192 Anemia and thrombocytopenia are also commonly seen. Monitor CBC closely and instruct patient to report any unusual bruising or bleeding to the health care team.

15.193 GI side effects are commonly seen, but are usually mild in nature (nausea, diarrhea). Treat symptomatically and monitor for effectiveness.

15.194 Pneumonia and pulmonary hypertension have been seen. Instruct patient to report any shortness of breath, cough and/or chest pain to the study team.

15.195 Elevated creatinine and isolated cases of renal failure (some associated with tumor lysis syndrome) have been seen. Make sure patient is well hydrated prior to administration and monitor creatinine levels closely. Urinary tract infections can also be seen, instruct patient to report signs and symptoms to study team.

15.196 Take a detailed history of patient's concomitant medications including OTC and herbal preparations. Instruct patients not to start any new medications without checking with the study first.

15.197 Cardiac side effects, including peripheral edema, hypertension, hypotension, DVT and PE can be seen. Instruct patient to report any signs or symptoms to health care team.

15.198 Monitor LFT's and instruct patient to report any hepatic symptoms (abdominal pain, jaundice) to study team immediately.

15.199a The IV line should be flushed with D5W or NS immediately before and after carfilzomab administration. Do not administer as a bolus.

15.199b Dosing is calculated using patient's actual body surface area (BSA). Patients with a BSA greater than 2.2 $m^2$ should receive dose based upon a BSA of 2.2 $m^2$.

15.199c Monitor electrolytes. Administer replacement doses as ordered and follow labs for effectiveness.

15.2 **Melphalan (Alkeran®, LPAM)**

15.21 **Background**: Melphalan is an alkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of

carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.

15.22 **Formulation**: Commercially available for injection as:
Injection, powder for reconstitution: 50 mg [diluent contains ethanol and propylene glycol]

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature. Protect from light.

**The time between reconstitution/dilution and administration of parenteral melphalan must be kept to a minimum (manufacturer recommends <60 minutes) because reconstituted and diluted solutions are unstable.** Dissolve powder initially with 10 mL of diluent to a concentration of 5 mg/mL. Shake vigorously to dissolve. This solution is chemically and physically stable for no more than 90 minutes at room temperature. Immediately dilute dose in 0.9% Sodium Chloride to a concentration of ≤ 0.45 mg/mL. Solution should be administered within 60 minutes of dilution. DO NOT REFRIGERATE solution; precipitation occurs.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Melphalan is administered as a continuous I.V. infusion over one hour in 1000 mL 0.9% Sodium Chloride.

15.25 **Pharmacokinetic information**:
**Distribution:** $V_d$: 0.5-0.6 L/kg throughout total body water, low penetration into CSF
**Protein binding:** 60% to 90%; primarily to albumin, 20% to $\alpha_1$-acid glycoprotein
**Metabolism:** Hepatic; chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan
**Half-life elimination:** Terminal: I.V.: 75 minutes
**Time to peak, serum:** ~1-2 hours

15.26 **Potential Drug Interactions**:
**Increased Effect/Toxicity:** Risk of nephrotoxicity of cyclosporine is increased by melphalan. Concomitant use of I.V. Melphalan may cause serious GI toxicity. Cisplatin may increase the levels/effects of I.V. melphalan. Melphalan may increase risk of vaccinal infection.
**Decreased Effect:** Melphalan may decrease the levels/effects of digoxin.
**Ethanol/Herb Interactions**: Avoid ethanol (due to GI irritation).

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information. **U.S. Boxed Warnings include: bone marrow suppression, hypersensitivity,**

**chromosomal changes potentially mutagenic and leukemogenic.**

**Common known potential toxicities, > 10%**:
Gastrointestinal: Vomiting
Hematologic: Myelosuppression, leukopenia, thrombocytopenia
Miscellaneous: Secondary malignancy

**Less common known potential toxicities, 1% - 10%**:
Miscellaneous: Hypersensitivity

**Infrequent, frequency undefined, Postmarketing, and/or case reports:**
Agranulocytosis, allergic reactions, alopecia, amenorrhea, anaphylaxis, anemia, bladder irritation, bone marrow failure (irreversible), diarrhea, hemolytic anemia, hemorrhagic cystitis, hemorrhagic necrotic enterocolitis, hepatic veno-occlusive disease, hepatitis, interstitial pneumonitis, jaundice, nausea, ovarian suppression, pruritus, pulmonary fibrosis, radiation myelopathy, rash, secondary carcinoma, secondary leukemia, secondary myeloproliferative syndrome, SIADH, skin hypersensitivity, skin necrosis, skin ulceration (injection site), skin vesiculation, sterility, stomatitis, testicular suppression, transaminases increased, vasculitis

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

15.291 Hematologic toxicity is a major and dose-limiting adverse effect and is principally manifested by leukopenia and thrombocytopenia. Myelosuppression usually occurs 2-3 weeks after therapy and may persist for 6 weeks or more. Monitor CBC frequently. Instruct patient to report any signs/symptoms of infection, unusual bruising or bleeding to the health care team.

15.292 Assess for nausea and vomiting and treat symptomatically. Severe nausea and vomiting has been reported with high dose treatment. Pre-medicate with antiemetics before high dose IV treatment. Occasional diarrhea and stomatitis has been reported also. Treat symptomatically. Encourage good oral care.

15.293 Assess for pulmonary toxicity. Instruct patient to report any unusual cough, chest pain, or respiratory difficulties.

15.294 Anaphylaxis is possible with IV administration. Have anaphylaxis tray and necessary emergency equipment nearby when administering IV. Monitor for signs symptoms of hypersensitivity reaction, which include, rash, diaphoresis, difficulty breathing, and hypotension.

15.295 Drug is an irritant. Avoid extravasation. Establish IV patency before and throughout administration.

15.296 Monitor renal function tests.

## 16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase I/II study of a novel conditioning regimen incorporating carfilzomib and melphalan for multiple myeloma patients undergoing autologous stem cell transplantation. The phase I portion of this study is designed to determine the maximum tolerated dose (MTD) of carfilzomib and melphalan conditioning in patients with multiple myeloma. The phase II portion of this study will use a one-stage design to assess the efficacy of carfilzomib and melphalan conditioning in patients with multiple myeloma.

16.11 Endpoint: The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD). For the phase II portion of this trial, the primary endpoint is the proportion of complete responses. A complete response is defined as a CR noted as the objective status on two consecutive evaluations. Complete response will be evaluated using all cycles. Note that a patient may have already achieved a complete response prior to registration from induction therapy. In this case, a continued complete response will be considered a complete response for the primary endpoint.

16.12 Sample Size: This phase I portion of this study is expected to require a minimum of 10 (one patient each at dose levels 0-3 plus 6 patients at dose level 4) and a maximum of 30 (6 patients at each dose level 0-4) evaluable patients. The 6 patients treated at the MTD in the phase I portion will also be included in the phase II portion. An additional 33 evaluable patients will be accrued for a maximum of 39 evaluable patients in the phase II portion of this study. We anticipate accruing 5 additional patients (2 phase I, 3 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the study is expected to accrue a maximum of 32 patients in phase I, 36 patients in phase II, and 68 patients overall.

As of Addendum 4, the number of dose levels in the phase I portion will be reduced. A total of 5 patients have been accrued as of August 2014. We expect a maximum of 9 additional evaluable patients to be accrued in phase I. The new overall maximum sample size is 51 patients (14 patients total in phase I + 33 patients in phase II + 4 additional patients to account for patients who are replaced).

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2-3 evaluable multiple myeloma patients per month. At this rate, it will likely take about 2 months (cohort of 1 patient) to 3 months (cohorts of 3 patients) to enroll, treat, and evaluate each cohort in the phase I portion of this study. The phase I portion is expected to take between 14 and 30 months. The phase II portion of this study will accrue in the subsequent

1.5 years. The maximum total study duration is expected to be approximately 4.5 years, or until the last patient accrued has been observed for at least 6 months.

As of Addendum 4, phase I accrual will continue with the standard cohort of 3 design. The phase I portion is expected to take an additional 6-9 months. Therefore, the maximum study duration is expected to be approximately 3 years after Addendum 3 is implemented.

**Phase I Portion**

16.2 Study Design: This portion of the study will consist of a phase I trial to determine the MTD of carfilzomib and melphalan conditioning. A two-stage accelerated design will be utilized (Simon et al, 1997). The first stage is an accelerated dose escalation with a cohort of one patient as in Section 7.32. Once one DLT has been observed or ≥2 patients have experienced grade 3+ non-hematologic toxicities during the first 2 cycles over all dose levels, the second stage will resume the standard cohort of three design as in Section 7.33. A total of 6 patients will be enrolled and treated at the dose level prior to the one where the two DLTs occurred; i.e. at the MTD.

As of Addendum 4, the phase I study design will be modified to the standard cohort of 3 design. The first stage with accelerated dose escalation will no longer apply and accrual will continue in the second stage with the standard cohort of 3 design. Due to issues with accruing potential patients, it is felt that a cohort of 3 design will be more beneficial to the patients and to study accrual. In addition, the study entered the second stage of the design in error and it is felt that it will be more appropriate to continue with standard cohorts of 3 patients.

16.21 MTD Determination: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). See section 7.3 for the MTD determination algorithm and section 7.4 for DLT definitions.

16.22 Primary Outcome Analyses:

16.221 Adverse Events Profile: The number and severity of all adverse events will be tabulated and summarized in this patient population. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.222 Toxicity Profile: The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

**Phase II Portion**

16.3 Statistical Design:

16.31 Decision Rule: In a Mayo Clinic database study that captured data prospectively into a continuously updated database, 178 multiple myeloma patients received a stem cell transplant within 12 months of diagnosis.(Kumar, Lacy et al. 2011) All of these patients received conditioning with single agent melphalan. The complete response rate to stem cell transplant was 35%. Since patients in this study are expected to receive a stem cell transplant within 12 months of diagnosis, an increase in complete response rate to greater than 35% with the addition of carfilzomib to melphalan in the conditioning regimen for patients with multiple myeloma would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 35%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 55%. The following one-stage binomial design uses 39 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 35%.

16.311 Final Decision Rule: If 17 or fewer successes are observed in the first 39 evaluable patients, we will consider this regimen ineffective in this patient population. If 18 or more successes are observed in the first 39 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.312 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.44.

16.32 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

| If the true success proportion is... | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 |
|---|---|---|---|---|---|
| Then the probability of declaring that the regimen warrants further study is… | 0.10 | 0.27 | 0.50 | 0.74 | 0.90 |

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.4 Analysis Plan

16.41 Primary Outcome Analyses:

16.411 Definition: The primary endpoint in the phase II portion of this trial is the proportion of complete responses. A complete response is defined as a CR noted as the objective status on two consecutive evaluations. Complete response will be evaluated using all cycles. Note that a patient may have already achieved a complete response prior to registration as a result of the induction therapy. In this case, a continued complete response will be considered a complete response for the primary endpoint. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportion will be calculated.

16.42 Secondary Outcome Analyses

16.421 The complete response rate at day 100 will be estimated by the total number of patients who achieve a complete responses by day 100 post-transplant divided by the total number of evaluable patients. All evaluable patients will be used for this

analysis. Exact binomial 95% confidence intervals for the true complete response rate at day 100 will be calculated.

16.422 Time to progression is defined as the time from registration to the earliest date with documentation of disease progression If a patient dies without a documentation of disease progression, the patient will be considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of time to progression will be estimated using the method of Kaplan-Meier.(Kaplan and Meier 1958) The progression-free rate at 1 year and 2 years will be assessed.

16.425 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.43 Correlative Analyses

16.431 Minimal residual disease will be assessed on bone marrow aspirate in all patients achieving CR. The proportion of patients who achieve MRD negative status will be estimated by the number of patients who are MRD negative divided by the total number of evaluable patients who achieve a CR. Exact binomial 95% confidence intervals for the true MRD negative rate will be calculated.

16.432 The HevyLite assay will be assessed prior to treatment, at the end of cycle 3 (day 100), and at the time of suspected CR. Patients will be categorized by whether they have an abnormal ratio (yes vs. no) and uninvolved immunoglobulin suppressed (yes vs. no) at each time point. The correlation of these categories with whether MRD is present (yes vs. no) will be evaluated using Fisher's exact test. In addition, the relationship between these categories and time to progression will be evaluated using Kaplan-Meier methods and log-rank statistics. Due to the limited sample size, these analyses will be considered exploratory.

16.44 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.5 Data & Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules (includes all phase II patients, including phase I patients treated at the MTD): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 15 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 4.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

**Accrual Estimates by Gender/Ethnicity/Race**

| **Ethnic Category** | **Sex/Gender** | | | |
|---|---|---|---|---|
| | **Females** | **Males** | **Unknown** | **Total** |
| Hispanic or Latino | 0 | 1 | 0 | 1 |
| Not Hispanic or Latino | 17 | 33 | 0 | 50 |
| **Ethnic Category: Total of all subjects*** | 17 | 34 | 0 | **51** |
| **Racial Category** | | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 0 | 2 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 | 0 |
| White | 16 | 33 | 0 | 49 |
| **Racial Category: Total of all subjects*** | 17 | 34 | 0 | **51** |

**Ethnic Categories:** **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

**Not Hispanic or Latino**

**Racial Categories:**

**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

**Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

**Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

**17.0 Pathology Considerations/Tissue Biospecimens: None.**

**18.0 Records and Data Collection Procedures**

18.1 Submission Timetable

**Initial Material(s)**

| **Case Report Form (CRF)** | **Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0) |
|---|---|
| On-Study Form | ≤2 weeks after registration |
| Baseline Adverse Event Form | |
| Pretreatment Measurement Form (Registration Values) | |
| Pretreatment Measurement Form Baseline Values for Disease Assessment | |
| Pretreatment Measurement Form Baseline Values at Time of Diagnosis | |
| SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey, PCLI, Cytogenetic, FISH on study reports | |
| Research Blood Submission Form (see Section 14.0) | |
| Research Bone Marrow Aspirate Submission Form (see Section 14.0) | |
| End of Active Treatment/Cancel Notification Form | Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy |

**Test Schedule Material(s)**

| CRF | Active-Monitoring Phase (Compliance with Test Schedule Section 4.0) | | |
|---|---|---|---|
| | At each evaluation during treatment | At end of treatment | Observation |
| Evaluation/Treatment Form | X[2] | X | |
| Evaluation/Observation Form | | | X[1] |
| Nadir/Adverse Event Form | X | X | X[3] |
| Measurement Form | X | X | X |
| SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey | X[4] | X[4] | X[4] |
| Cycle 2 Transplant and Engraftment Data Form | X[5] | | |
| Research Blood Submission Form | | | X |
| Research Bone Marrow Aspirate Submission Form | | | X |
| End of Active Treatment/Cancel Notification Form | | X | |
| ADR/AER | At each occurrence (see Section 10.0) | | |

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at Cycle 1 only.
3. Only when required by the Test Schedule (see Section 4.0).
4. Submission of these reports is only required for documentation of CR or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation of progression, submit one report for one of the measures where progression was seen. Attention: QAS for MC1185.
5. Complete once at the end of Cycle 2.

**Follow-up Material(s)**

| CRF | Event Monitoring Phase[1] | | | | |
|---|---|---|---|---|---|
| | q. 3 months until PD or subsequent treatment for MM[2] | At PD or subsequent treatment for MM | q. 3 months after PD or subsequent treatment for MM | Death | New Primary |
| Event Monitoring Form | X | X | X | X | At each occurrence |

1. If a patient is still alive 5 years after registration, no further follow-up is required. **As of Addendum 8, patient follow-up is no longer required**
2. Submit copy of documentation of progression. Attention: QAS for MC1185, [redacted]

## 19.0 Budget

19.1 Costs charged to patient: Melphalan, Stem cell transplant, Routine physical exams and blood and urine tests, Bone marrow aspirate and biopsy, X-ray skeletal survey, Chest x-ray, Pulmonary function tests, ECHO, Pregnancy tests for women of childbearing potential.

19.2 Tests to be research funded: Minimal residual disease testing and HevyLite Assay®.

19.3 Other budget concerns: Protocol administration, data management and statistical analysis efforts will be by funded by Onyx Pharmaceuticals. Carfilzomib will be provided free of charge from Onyx Pharmaceuticals.

## 20.0 References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**Appendix I**
**ECOG Performance Status Scale**



| SCORE | DESCRIPTION |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. |
| **2** | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **3** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| **5** | Dead. |

## Appendix II

## NYHA Classification



Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

**Appendix III**
**Multiple Myeloma Diagnostic Criteria**



Standard criteria for a diagnosis of multiple myeloma are as follows (Kyle et al *British Journal of Haematology. 121(5):749-57, 2003)*

**Multiple Myeloma**
Monoclonal protein present in serum ≥ 3 g/dl
and/or
Bone marrow clonal plasma cells ≥ 10%

**Myeloma-related organ or tissue impairment (ROTI)**
Calcium 1 mg/dL (0.25 mmol/L) above the upper limit of normal
Creatinine > 2 mg/dL (173 mmol/L)
Lytic bone lesions or osteoporosis

**Asymptomatic myeloma**
Multiple myeloma and absence of ROTI

**Symptomatic myeloma**
Multiple myeloma and presence of any ROTI that can be attributed to myeloma.

**Appendix IV**
**Chemotherapy Dosing Information**

## Principle: Use the lesser of actual or *corrected* ideal body weight (CIBW) for all chemotherapy dosing.

For patients who are overweight, a corrected ideal body weight should be calculated and used to calculate chemotherapy doses. Ideal body weight (IBW) can be calculated as follows:

1. Males: IBW = 50 kg + (2.3 x number of inches over 5 feet)

2. Females: IBW = 45.5 kg + (2.3 x number of inches over 5 feet)

The corrected ideal body weight can then be calculated by the following formula:

1. Corrected IBW = IBW +0.25 (actual body weight - IBW)

The lesser of actual or corrected ideal body weight is then used in the Gehan and George BSA formula to calculate carfilzomib and melphalan dosing

| **The Gehan and George formula** |
| --- |
| $BSA\ (m^2) = 0.0235 \times Height(cm)^{0.42246} \times Weight(kg)^{0.51456}$ |

Gehan EA, George SL, Estimation of human body surface area from height and weight. *Cancer Chemother Rep* 1970 54:225-35.

**Appendix V**
**Blood Collection Kit: Specimen Checklist and Shipping Instructions**

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

**Kit Contents:**

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- 7ml ACD (yellow top) collection tubes
- Streck Cell Preservative® screw-top vial
- Absorbent tube holder
- Zip lock biohazard specimen bag

**Packing and Shipping Instructions:**

1. Collect the following specimens:
    1. Peripheral blood – Draw 14ml of peripheral blood into two (2) ACD tubes.
    2. Bone marrow aspirate – Draw 1ml of a 'redirect' bone marrow aspirate and place in the Streck Cell Preservative® screw-top vial. Gently mix by inversion 3 times.
2. All specimens are to be clearly labeled with the protocol number MC1185, the patient's initials (last, first, middle) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock biohazard specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Patient Information Form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please e-mail [redacted] to notify the laboratory when samples are being shipped. Indicate protocol number MC1185, the Fed Ex tracking number, name and phone number of the contact person. The samples in prepared kits should be shipped to the following:

[redacted]

**Patient Information Form**

Specimen Date: / /

Patient Initials (last name, first name):

Hospital ID #:

Protocol #: MC1185

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

Please indicate which samples are being shipped at this time:

1. Study Entry
2. Post Cycle Three (Day 100)
3. At Suspected CR

Any questions concerning these samples or to obtain blood collection kits for the MC1185 study, please contact:

Kim Henderson

[redacted]

Affiliates who anticipate participating in this study should please call in advance for kits.