



**A Phase I/II Trial of Carfilzomib, Pegylated Liposomal Doxorubicin, and Dexamethasone  
for the Treatment of Relapsed/Refractory Multiple Myeloma**

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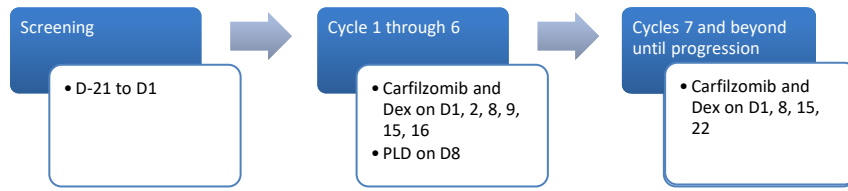
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## SCHEMA

Carfilzomib will be administered on Days 1, 2, 8, 9, 15, and 16 during Cycles 1 through 6, and on Days 1, 8, 15, and 22 beginning on Cycle 7 until disease progression or clinical relapse.

Pegylated liposomal doxorubicin (PLD) will be administered on Day 8 during Cycles 1 through 6.

Dexamethasone (Dex) will be administered on the same schedule as Carfilzomib (for patients in part 2 of phase 1 and phase 2.)



### Phase I

Part 1- A maximum of 24 participants eligible for Maximal Tolerated Dose (MTD) analysis will be enrolled to determine the MTD of carfilzomib in combination with pegylated liposomal doxorubicin (PLD) in participants with relapsed or refractory multiple myeloma.

Dose Level	Carfilzomib (mg/m <sup>2</sup> ) IV	PLD (mg/m <sup>2</sup> ) IV
-2	20	20
-1	20 on D1 and D2* 27 starting on D8	20
0 (Start)	20 on D1 and D2* 27 starting on D8	30
1	20 on D1 and D2* 36 starting on D8	30
2	20 on D1 and D2* 45 starting on D8	30
3	20 on D1 and D2* 56 starting on D8	30

\*- Please note that the D1 and D2 carfilzomib dose of 20mg/m<sup>2</sup> will only occur during Cycle 1. For all subsequent cycles, patients will receive the same dose of carfilzomib throughout at what is noted in this table to be the D8 dose.

Part 2- After the MTD of carfilzomib in combination with PLD has been determined, dose escalation will resume at the MTD of carfilzomib and PLD with the addition of dexamethasone. A maximum of 12 participants eligible for Maximal Tolerated Dose (MTD) analysis will be enrolled.

<b>Dose Level</b>	<b>Carfilzomib (mg/m<sup>2</sup>) IV</b>	<b>PLD (mg/m<sup>2</sup>) IV</b>	<b>Dex (mg) IV or PO</b>
-1	1 dose level below the MTD	1 dose level below the MTD	20
0 (Start)	MTD	MTD	20

## Phase II

Seventeen participants will be treated at the MTD of carfilzomib in combination with PLD and dexamethasone to evaluate the efficacy and toxicity in participants with relapsed or refractory multiple myeloma. Participants treated in phase 1 at the MTD will be counted as part of the phase two accrual.

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## 1.0 BACKGROUND AND RATIONALE

### 1.1 Multiple Myeloma

Multiple myeloma (MM) is a multifocal plasma cell neoplasm resulting from the clonal expansion of terminally differentiated B-cells. The disease is characterized by a serum or urine monoclonal protein and skeletal destruction with osteolytic lesions, bone pain, pathologic fractures and hypercalcemia. Recurrent infections from depressed normal immunoglobulin production, renal dysfunction from light chain production, and anemia from generalized marrow involvement are also common. In the United States, MM is the second most common hematologic malignancy behind non-Hodgkin's lymphomas with an estimated 15,270 new cases and 11,070 deaths in 2004.[1]

Progress in the management of MM has been modest since the introduction of melphalan more than 25 years ago. Melphalan combined with prednisone produces an objective response of 50-60% although median survival remains approximately 3 years with 5-10% of patients surviving 10 or more years[2]. More aggressive chemotherapy regimens, though associated with higher response rates, have had little impact on improving survival [3-8]. However, corticosteroids when used alone can induce a response in approximately 30% of patients, similar to rates seen with combination chemotherapy in refractory patients [9, 10]. Interferon  $\alpha$  (IFN- $\alpha$ ) in combination with chemotherapy is known to prolong the plateau phase of remission[11, 12]. The combination of IFN- $\alpha$  and corticosteroids has been shown to be better than IFN- $\alpha$  alone in improving progression free survival[13].

High dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT) has resulted in a higher rate of complete response (CR) (22% vs. 5%) and longer progression free survival (PFS) and overall survival (OS) (18-27 months and 37-60+ months, respectively) compared to standard dose chemotherapy [14]. However, high dose chemotherapy with transplant is not curative and currently there is great interest in developing therapies that prolong the remission duration following autologous transplantation for MM.

With the advent of novel targeted agents, the majority of patients have experienced improved survival outcomes in recent years. The immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib are routinely used as first line therapy and have thus improved the outcomes for myeloma patients. However, despite the availability of these newer therapies, the overall prognosis of patients with myeloma remains poor. Furthermore, patients who do respond and survive salvage chemotherapy will almost invariably relapse, underscoring the need for additional effective agents against myeloma.

## **1.2 Proteasome Inhibition and Bortezomib (Velcade®)**

### **1.2.1 The Proteasome**

The ubiquitin-proteasome pathway plays an essential role in cellular homeostasis. Eukaryotic cells target specific proteins for destruction by tagging them with ubiquitin. Polyubiquitinated proteins bind to the proteasome. The 26 S proteasome is an adenosine triphosphate-dependent multicatalytic protease which consists of a core 20S particle, which contains the catalytic proteinase function. This is symmetrically bound to 2 copies of a regulatory 19S particle, which recognizes the ubiquitinated substrates. The 26S proteasome performs a “housekeeping” role that acts to dispose of used up or damaged proteins and create antigenic peptides for presentation to immune effector cells.

In addition, the ubiquitin-proteasome pathway plays an important role in regulating the cell cycle, neoplastic growth and metastases.[15, 16] A number of key regulatory proteins are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway. The orderly degradation of these proteins is required for the cell to progress through the cell cycle and undergo mitosis. One of the targets is the tumor suppressor gene p53, which is required for the transcription of a number of genes involved in cell cycle progression and also plays an important role in apoptosis. Cyclins and cyclin-dependent kinase inhibitors p21 and p27 are other growth regulatory proteins degraded by the ubiquitin proteasome pathway.

The ubiquitin-proteasome pathway is also required for transcriptional regulation. Nuclear factor kappa-B is a key transcription factor, whose activation is regulated by the proteasome-mediated degradation of the inhibitor protein I-kappa B. NF- $\kappa$ B regulates the expression of adhesion molecules such as E-selectin, intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1 (VCAM 1). These adhesion molecules in turn direct the adhesion and extravasation of tumor cells. NF- $\kappa$ B is also required by a variety of cells to maintain cell viability due to the production of anti-apoptotic proteins like bcl-2 or growth factors such as interleukin-6.

### **1.2.2 Bortezomib (Velcade®)**

Bortezomib is the first proteasome inhibitor developed to be used in routine clinical practice for myeloma treatment. It is a reversible inhibitor of the proteasome blocking signal transduction pathways mediated by NF- $\kappa$ B resulting in the stimulation of apoptosis by inhibiting the proteasome degradation of I $\kappa$ B. It has been shown to be effective in the first line setting as well as in patients with relapsed and refractory myeloma.

In newly diagnosed elderly patients, the phase III VISTA trial compared

bortezomib plus melphalan plus prednisone versus melphalan plus prednisone and demonstrated a 52% reduction in the risk of disease progression and a median time to progression (TTP) of 24 months versus 16.6 months (P<0.001). After a median follow-up of 25.9 months, the 3-year survival rates were also better with the bortezomib-containing regimen (72% vs. 59%, p=0.003).[17]

In the relapsed/refractory population, the phase III APEX trial demonstrated the superiority of a bortezomib plus high dose dexamethasone versus high-dose dexamethasone alone. The median TTP was longer (6.2 vs. 3.5 months), p<0.001, more patients experienced a  $\geq$ PR (38% vs. 18%; p<0.001) and CR (6% vs. <1%, p<0.001), and the overall 1 year survival was improved (80% vs. 66%; p=0.003).[18]

## **1.3 Carfilzomib**

### **1.3.1 Overview of Carfilzomib**

Carfilzomib is a novel inhibitor of the proteasome. It is an irreversible tetrapeptide ketoepoxide-based inhibitor of the chymotrypsin-like activity of the 20S proteasome, which is structurally and mechanistically different from the dipeptide boronic acid reversible proteasome inhibitor bortezomib. It is more selective for the chymotrypsin-like protease, having less inhibitory activity against the other two active subunits. 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.

### **1.3.2 Pre-clinical Studies of Carfilzomib**

Based upon *in vitro* and *in vivo* studies, it is anticipated that more intense and longer duration of proteasome inhibition can be achieved with carfilzomib relative to bortezomib, resulting in enhanced anti-tumor activity. Continuous (72-hour) exposure to carfilzomib was associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture [19]. Incubation of hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib was also cytotoxic in bortezomib-resistant tumor cell lines.[20]

Preclinical studies in rats and monkeys have been performed administering carfilzomib intravenously (IV) for 5 consecutive days followed by 9 days of rest for 2 cycles. Proteasome inhibition of more than 80% was achieved, suggesting that high-level inhibition of the proteasome with the epoxyketone class is possible, affording new opportunities to escalate dose to optimize anti-tumor effects. This finding was in contrast to preclinical testing with the boronic class of inhibitors that prohibited uninterrupted daily dosing due to lethal toxicity.



### 1.3.3 Non-Clinical Pharmacodynamics and Pharmacokinetics of Carfilzomib

#### 1.3.3.1 Pharmacodynamics

The *in vivo* pharmacodynamics (PDn) and efficacy of carfilzomib have been evaluated using direct measurement of proteasome enzyme activity in a variety of tissues and determination of the antitumor response in mice bearing established subcutaneous tumors.

The PDn of carfilzomib has been determined by measurement of chymotrypsin-like proteasome activity in tissue extracts following IV bolus administration in rats. Dose-dependent proteasome inhibition was observed 1 hour after dose administration in all tissues examined, with the exception of brain (Demo 2007). Proteasome activity recovered in nucleated tissues with a half-life of approximately 24 hours. With a 12 mg/m<sup>2</sup> (2 mg/kg) dose (the STD10 on a QDx5 schedule), proteasome inhibition exceeded 80% in multiple tissues (blood, adrenal, heart, lung, and bone marrow). Equivalent levels of proteasome inhibition were seen in blood and tissues when carfilzomib was delivered as a bolus administration or a 30-minute infusion indicating that the biodistribution and PDn of carfilzomib are a function of the total dose administered and not the maximum plasma concentration (C<sub>max</sub>).

#### 1.3.3.2 Pharmacokinetics

The pharmacokinetics (PK) of carfilzomib was examined following IV bolus administration to Sprague-Dawley rats and cynomolgus monkeys. There was a dose-dependent increase in the area under the curve (AUC) and a biphasic distribution profile following administration. The terminal half-life ( $t_{1/2}$ ) was calculated to be 5 to 17 minutes in rats and 7 minutes in monkeys. The plasma clearance of carfilzomib is 195 to 319 mL/min/kg in rats and 187 to 286 mL/min/kg in monkeys, which is higher than the liver blood flow for both species, indicating that clearance occurred largely extrahepatically in these species.

When carfilzomib was given as 30-minute IV infusion at 8 mg/kg to rats, the concentration at steady state was approximately 28-fold lower than the C<sub>max</sub> with IV bolus at the equivalent doses. Other PK parameters (clearance, AUC, and  $t_{1/2}$ ) were comparable between bolus and infusion dosing. Similar PDn (proteasome inhibition in blood and tissues) between bolus and infusion dosing supported accessibility of carfilzomib to target tissues using the 30-minute infusion protocol.

### 1.3.3.3 Metabolism, Distribution, and Excretion

#### 1.3.3.3.1 Metabolism

Carfilzomib is rapidly and extensively metabolized following IV administration to rats, monkeys, and humans. The predominant metabolites are carfilzomib diol as well as peptide fragments and amino acids derived from carfilzomib, with no unique metabolites identified in humans, suggesting that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism in all these species. The metabolites do not inhibit proteasome activity. Cytochrome P450-mediated pathways are not significant in the overall metabolism of carfilzomib.

Carfilzomib is also rapidly metabolized by peptidases and epoxide hydrolases *in vitro* upon incubation with rat blood and tissue homogenates derived from the lung, kidney, and liver, further corroborating the extrahepatic mechanisms of metabolism *in vivo*.

#### 1.3.3.3.2 Distribution

The  $V_{ss}$  was 0.3 to 2.0 L/kg and 0.3 to 1.1 L/kg, respectively, for rats and monkeys. Due to metabolism in a variety of tissues and the irreversible, covalent binding of carfilzomib to the 20S proteasome, the  $V_{ss}$  values may underestimate the extent of tissue distribution of carfilzomib. Potent proteasome inhibitory effects in a variety of tissues following IV administration to rats at different dose levels and detection of radioactivity in a variety of tissues with an IV administration of [3H-Phe]-carfilzomib to rats at 2 mg/kg (12 mg/m<sup>2</sup>) indicated rapid and wide distribution of carfilzomib to tissues except brain.

An *in vitro* protein-binding study using equilibrium dialysis demonstrated that approximately 97% of carfilzomib is bound to human plasma proteins, similar to rats and monkeys.

#### 1.3.3.3.3 Elimination

Excretion of [3H-Phe]-carfilzomib was determined by quantitative whole-body autoradiography in rats receiving a single IV bolus administration of 2 mg/kg (12 mg/m<sup>2</sup>). Urine and feces accounted for 14.1% and 18% of the dosed radioactivity, respectively, at 168 hours post-dose. Approximately 44% of the administered radioactivity remained in tissues, indicating slow elimination of drug-derived radioactivity, likely due to incorporation of 3H-

phenylalanine into cellular proteins.

Excretion was also determined in bile duct-cannulated rats following a single IV bolus administration of 2 mg/kg. Carfilzomib was excreted mainly in the form of metabolites, with less than 1% of the dose excreted intact. About 57% of the dose was recovered within 24 hours of dosing in both bile and urine samples. The limited recovery was likely due to target binding in cells unable to synthesize new proteasomes (e.g., red blood cells [RBCs]) and peptidic metabolites that cannot be differentiated from endogenous components.

### **1.3.4 Clinical Pharmacokinetics, Metabolism, Distribution, and Excretion**

#### **1.3.4.1 Pharmacokinetics**

Following IV administration of carfilzomib at  $\geq 15 \text{ mg/m}^2$  to patients with hematological malignancies (PX-171-001 and PX-171-002), carfilzomib was rapidly cleared from the systemic circulation with a half-life  $< 1$  hour. The systemic clearance, which ranged from 2.7 to 30 L/minute, exceeded liver blood flow, suggesting that carfilzomib is largely cleared non-hepatically.

Assessment of the PK of carfilzomib in MM patients with varying levels of renal dysfunction, including those on dialysis, is currently ongoing (PX-171-005). As of the data transfer cutoff date of 10 July 2009, 16 patients have been evaluated for PK and there has been no apparent effect of renal dysfunction on PK in preliminary analysis. Based on currently available data, carfilzomib can be administered to patients with MM and substantial renal dysfunction without need for dose adjustment.

Carfilzomib was also rapidly cleared in patients with solid tumors following IV administration (PX-171-007) with a half life of  $< 1$  hour and systemic clearance exceeding hepatic blood flow. There was no systemic accumulation of carfilzomib after repeat doses. Both  $C_{\text{max}}$  and AUC increased dose-proportionally from 20 to 36  $\text{mg/m}^2$ , indicating linear PK in the dose range tested.

#### **1.3.4.2 Metabolism**

Similar to the metabolic profile in rats and monkeys, the most abundant metabolites of carfilzomib in human plasma and urine collected from the patients with hematological malignancies were peptide and amino acid fragments of carfilzomib and carfilzomib diol, indicating that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism of IV administered carfilzomib in humans. No significant oxidative

metabolites mediated by cytochrome P450 enzymes were detected. None of these metabolites have significant proteasome inhibition (or other known biological) activity.

#### **1.3.4.3 Distribution**

The  $V_{ss}$  of carfilzomib ranged from 10 L to 228 L in patients with hematological cancers. However, due to metabolism in tissues and irreversible binding of carfilzomib to the 20S proteasome, the  $V_{ss}$  value may underestimate the actual tissue distribution of carfilzomib. The potent proteasome inhibitory effects in a variety of tissues in rats and broad distribution of the radioactivity in the quantitative whole body autoradiography study in rats following IV administration demonstrated wide tissue distribution of carfilzomib except brain. The *in vitro* binding of carfilzomib to human plasma proteins averaged 94% over the concentration range of 0.5–5  $\mu$ M.

#### **1.3.4.4 Excretion**

Carfilzomib is eliminated primarily in the form of inactive metabolites (mainly as peptide fragments). Renal excretion accounts for 20%–30% of the total dose and appears not to be affected by renal dysfunction (PX-171-005).

### **1.3.5 Current Clinical Experience with Carfilzomib**

#### **1.3.5.1 Summaries of Phase I Studies**

Two Phase 1 studies have been completed; both evaluated carfilzomib in subjects with refractory or relapsed hematologic malignancy following at least 2 prior therapies. In the first study (Study PX-171-001, N = 29), the MTD was established at 15 mg/m<sup>2</sup> as an IV bolus over 1 to 2 minutes. At the 20 mg/m<sup>2</sup> dose, 2 of 5 subjects experienced DLTs of Grade 3 febrile neutropenia and chills (1 subject) and Grade 4 thrombocytopenia (1 subject) during Cycle 1. In the second study (Study PX-171-002, N = 48), DLTs of renal failure, fatigue, and hypoxia were observed at different dose levels; no dose level (through 27 mg/m<sup>2</sup>) met the criteria for the MTD of carfilzomib. However, based on the safety information available, further dose escalation beyond 27 mg/m<sup>2</sup> as an IV bolus over 2 minutes was not pursued. The expansion cohort received starting doses of 20 mg/m<sup>2</sup> in Cycle 1 on Days 1, 2, 8, 9, 15, and 16, escalating up to 27 mg/m<sup>2</sup> in Cycle 2 as tolerated on Days 1, 2, 8, 9, 15, and 16.

Three Phase 1 studies are ongoing. One study is being conducted in multiple myeloma subjects with end stage renal disease and another in subjects with relapsed advanced malignancies who have varying degrees

of hepatic impairment, both testing the 56 mg/m<sup>2</sup> dose (by Cycle 2 and beyond in subjects that tolerate the 20 and 27 mg/m<sup>2</sup> doses) administered as a 30-minute infusion. The third study is evaluating once-weekly carfilzomib in combination with lenalidomide and dexamethasone in subjects with newly diagnosed or relapsed multiple myeloma.

### **1.3.5.2 Phase 2 Experience with Carfilzomib as a monotherapy**

The initial Phase 1 studies administered carfilzomib as monotherapy on 5 consecutive days with a 14-day cycle; this resulted in sustained proteasome inhibition and a favorable safety profile[22]. Subsequent Phase 1 and 2 studies of carfilzomib monotherapy utilized twice-weekly dosing for 3 weeks in a 28-day cycle and have achieved higher tolerated doses with promising anti-tumor activity. The most common adverse events have been non-hematologic, including fatigue, nausea, diarrhea, upper respiratory tract infection, and reversible elevations in creatinine. Severe peripheral neuropathies were rare: 2 cases of grade 3 in >200 myeloma patients treated, most with pre-existing neuropathy. Hematologic toxicities were seen, including anemia, transient thrombocytopenia (cyclical, similar to bortezomib), and neutropenia with or without fever. The level of grade 3 neutropenia is ~10% and appears to be lower than that observed with bortezomib.

Two Phase 2 clinical studies are ongoing with carfilzomib in MM patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM. In both studies, patients were dosed with 20 mg/m<sup>2</sup> 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. No further cases of TLS have been reported. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased 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[23].

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). A “stepped up” dosing schedule, referred to as 20/27 mg/m<sup>2</sup>, 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<sup>2</sup> for the first cycle and 27 mg/m<sup>2</sup> thereafter. To date, this dosing schedule has been well tolerated. 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. The most common adverse events were similar to the A0 portion of the study. A decrease in cases of renal impairment was observed from 47% all grades with 15% Grade 3/4 in A0 to 35% all grades and 2.2% Grade 3/4 in A1. This is most likely due to the implementation of guidelines for hydration. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 15% Grade 1/2 and no Grade 3 or 4 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. Rates of thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date[23]. As of May 2009, over 160 patients with relapsed and refractory multiple myeloma have received the 20/27 stepped-up dosing schedule in the PX-171-003-A1 study. Phase 1b/2 solid tumor study patients are also receiving a stepped up dosing schedule using 20/36 mg/m<sup>2</sup>. In this study, the stepped up dose is administered on Day 8 of Cycle 1 and for all subsequent doses. As of April 2009, no MTD has been reached in this study and dose escalation to 45 mg/m<sup>2</sup> is to be initiated.

In PX-171-004, the subset of patients (N=14) that had not seen bortezomib had an ORR of 57% (7% CR, 14% VGPR and 36% PR), while the bortezomib treated patients (N=17) had an ORR of 18% (18% PRs)[24]. The median TTP was 11.1 and 8.3 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 substantial anti-tumor activity is observed even in bortezomib-treated patients. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability, and cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

Based on the results of these trials, in July 2012 carfilzomib received FDA approval for patients who had relapsed/refractory multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.[40]

#### 1.4 Pegylated Liposomal Doxorubicin (Doxil® or Lipodox)

Pegylated liposomal doxorubicin (PLD) was first compared with conventional doxorubicin in a randomized, phase III multicenter trial of metastatic breast cancer (MBC). Two hundred ninety-seven patients with MBC and no prior chemotherapy for metastatic disease were randomized to receive either 60 mg/m<sup>2</sup> of PLD or conventional doxorubicin, in combination with 600 mg/m<sup>2</sup> of cyclophosphamide, every 3 weeks until disease progression or unacceptable toxicity. The study showed an improved toxicity panel compared to doxorubicin with significantly reduced cardiotoxicity and less grade 4 neutropenia, while providing comparable antitumor efficacy.[25] This was confirmed in subsequent trials as O'Brien and colleagues compared the use of PLD at a dose of 50 mg/m<sup>2</sup> (every 4 weeks) to doxorubicin 60 mg/m<sup>2</sup> (every 3 weeks). Cardiac event rates were based on reductions in left ventricular ejection fraction as a function of cumulative anthracycline dose. This study demonstrated that in first-line treatment of women with MBC, the efficacy of [progression-free survival (PFS)] of PLD is non-inferior to doxorubicin with significantly less cardiotoxicity, myelosuppression, nausea, and vomiting.[26]

Multicenter randomized phase III trials in multiple myeloma showed that PLD-containing chemotherapy regimens (DVD – PLD (Doxil), vincristine (Oncovin), dexamethasone) compared to a similar doxorubicin-containing regimen (VAD – vincristine (Oncovin), doxorubicin (Adriamycin), dexamethasone) provided similar responses and survival, but that the DVD regimen was associated with significantly less toxicity and supportive care.[27,28] PLD was associated with significantly less grade 3/4 neutropenia or neutropenic fever (10% vs. 24%; p=0.01), less antibiotic use, lower incidence of sepsis, decreased need for central venous access (p<0.0001) and growth factor support (p=0.03) and less alopecia compared to the doxorubicin regimen.[27] A similar decreased toxicity and equivalent tumor response was seen in phase II trials incorporating PLD for doxorubicin in the CHOP regimen for older patients with aggressive (stage III/IV) NHL, in low-grade NHL and in previously untreated aggressive diffuse large B cell lymphoma[28-31]

In a Phase III international study comparing the efficacy and safety of a combination of pegylated liposomal doxorubicin (PLD) plus bortezomib with bortezomib monotherapy in patients with relapsed or refractory multiple myeloma, 646 patients were randomly assigned to receive either intravenous bortezomib 1.3 mg/m<sup>2</sup> on Days 1, 4, 8, and 11 of an every 21-days cycle, or the same bortezomib regimen with PLD 30 mg/m<sup>2</sup> on Day 4. Median time to progression was increased from 6.5 months for bortezomib alone to 9.3 months with the PLD + bortezomib combination (P = 0.000004; hazard ratio, 1.82 [monotherapy v combination therapy]; 95% CI, 1.41 to 2.35). The 15 month survival rate for PLD + bortezomib was 76% compared with 65% for bortezomib alone (P=0.03). The complete plus partial response rate was 41% for bortezomib and 44% for PLD + Bortezomib, a difference that was not statistically significant. Median duration of response was increased from 7 to 10.2 months (P=0.0008) with PLD + bortezomib.

Grade 3 and 4 adverse events were more frequent in the combination group (80% vs. 64%), with safety profiles consistent with the known toxicities of the two agents.

Based on the results of this trial the combination of bortezomib and liposomal doxorubicin (Doxil) received FDA approval for patients who had relapsed/refractory multiple myeloma who had failed at least one line of therapy and had not received prior bortezomib therapy.[17]

In response to a critical shortage of (Doxil), the FDA approved temporary importation of a replacement drug Lipodox (doxorubicin hydrochloride liposome injection) in February 2012. Lipodox has not been approved by the FDA, and therefore, cannot be considered a “generic” of Doxil but has the same active ingredient, dosage, strength, and route of administration. Lipodox is manufactured in a facility that has been inspected by the FDA and found to be in compliance with current good manufacturing practices.

### **1.5 Dexamethasone**

There is increasing data on the superiority of three-drug regimens in the treatment of relapsed and refractory multiple myeloma. Dexamethasone is commonly incorporated in these three-drug regimens because of its ability to improve response rates and duration of response without adding toxicity.

The combination of bortezomib, PLD, and dexamethasone (VDD) has been shown to be efficacious and well tolerated. The overall response and duration of response of VDD exceeds that of the two drug regimens bortezomib-PLD, and bortezomib-dexamethasone suggesting a synergistic effect.[42]

Dexamethasone has been added to carfilzomib, with and without additional agents, in many ongoing clinical trials. These clinical trials have indicated that adding dexamethasone may increase efficacy and tolerability of carfilzomib containing regimens. Many clinical trials that have incorporated dexamethasone into carfilzomib regimens have exceeded the MTD of the single-agent carfilzomib studies.

### **1.6 Rationale**

Based on the further need to improve the therapeutic interventions for multiple myeloma, the previous experience with proteasome inhibition, the potentially improved efficacy of carfilzomib over bortezomib, and the success of bortezomib combination with PLD, the natural next step is to combine carfilzomib with PLD. Furthermore, proteasome inhibitors have the ability to enhance the chemosensitivity in both *in vitro* and *in vivo* preclinical models.[32] Mechanistic studies have indicated that this effect is at least in part due to the inhibition of NF- $\kappa$ B, since many chemotherapeutics activate NF- $\kappa$ B, which can lead to the induction of anti-apoptotic survival proteins such as members of the Bcl-2 family[33]. Several models utilizing anthracyclines in combination with a proteasome inhibitor have shown enhanced anti-tumor activity, including solid tumor models as well as multiple myeloma. Our aim would be to first determine the maximal



tolerated dose of the combination in participants with relapsed/refractory myeloma and then to establish the efficacy of this novel combination[34, 35].

## 1.7 Correlative Studies Background

The correlative studies will focus on two areas:

- (1) evaluation of markers of response
- (2) evaluation of effects of carfilzomib, PLD, and dexamethasone on clonogenic myeloma cells

In order to do so, we will collect bone marrow, peripheral blood, and plasma samples prior to treatment, at time of response, and/or at end of study. The first objective is to determine tumor characteristics that predict at least very good partial response (VGPR). VGPR has been associated with longer progression survival and overall survival. The second objective is to investigate the effects of carfilzomib and PLD on clonogenic myeloma cells. It is hypothesized that inability to cure the disease is related to the inability of eradicating chemoresistant clonogenic myeloma cells or myeloma stem cells. The effect of carfilzomib and its combinations on these cells is not known.

## 2.0 OBJECTIVES

### 2.1 Primary Objectives

- **Phase 1: Part 1-** To determine the Maximal Tolerated Dose (MTD) of carfilzomib in combination with pegylated liposomal doxorubicin (PLD), in participants with relapsed or refractory multiple myeloma. **Part 2-** To determine the Maximal Tolerated Dose (MTD) of carfilzomib in combination with PLD and dexamethasone, in participants with relapsed or refractory multiple myeloma.
- **Phase 2:** To evaluate the efficacy and toxicity of carfilzomib in combination with PLD and dexamethasone in participants with relapsed or refractory multiple myeloma.

### 2.2 Secondary Objectives

- To evaluate the safety of carfilzomib in combination with PLD and dexamethasone in participants with relapsed or refractory multiple myeloma.
- To evaluate the effect of dexamethasone co-administration on the MTD of carfilzomib and PLD
- To evaluate time to tumor progression, progression-free survival, and overall survival in this population treated with carfilzomib in combination with PLD and dexamethasone.

## 3.0 PARTICIPANT SELECTION

### 3.1 Inclusion Criteria

A participant must meet all of the following criteria to be eligible for enrollment.

- 3.1.1** Histologically confirmed diagnosis of multiple myeloma with a measurable disease parameter at time of screening. A measurable disease parameter is defined as one or more of the following:
- Serum monoclonal protein  $\geq 0.5$  g/dl.
  - 24 hour urine monoclonal protein  $\geq 0.2$  g/24 hour
  - Serum free light chain ratio  $> 5x$  normal ratio with an absolute difference of 10mg/dl between the involved and uninvolved free light chain.
  - Soft tissue plasmacytoma  $\geq 2$  cm measurable by either physical examination and/or applicable radiographs (e.g. MRI, CT, etc).
  - Bone Marrow Plasma Cells  $\geq 30\%$ .
- 3.1.2** Documentation of at least one line of prior myeloma therapy now with relapsed or refractory disease requiring re-treatment.
- 3.1.3**  $\geq 18$  years of age at time of signing the informed consent.

*Note:* No dosing or adverse event data are currently available on the use of carfilzomib in combination with PLD in participants  $< 18$  years of age. Thus, children and adolescents are excluded from this study but will be eligible for future pediatric phase 2 combination trials.

- 3.1.4** Performance status of ECOG  $\leq 2$  or Karnofsky  $\geq 60$  % (see Appendix A and B).

*Note:* Participants with lower performance status based solely on bone pain secondary to multiple myeloma will be eligible.

- 3.1.5** Required Laboratory Values
- ALT (SGPT) and AST (SGOT)  $< 2.5$  x the upper limit of the institutional normal value (ULN).
  - Total bilirubin  $\leq 1.5$  x ULN.
  - ANC  $\geq 1,000$ .
  - Hemoglobin  $\geq 8$  g/dl.
  - Platelets  $\geq 50,000$ .
  - Creatinine clearance  $> 15$  ml/minute using Cockcroft-Gault formula (See Appendix C).
  - For those participants receiving warfarin (Coumadin), unfractionated heparin, or low-molecular weight heparin therapy, the applicable

coagulation parameter that is being monitored must be within the accepted therapeutic ranges for those indications.

*Note:* Transfusions and/or growth factor dependent participants are not excluded if the above parameters can be achieved with such support.

- 3.1.6** Females of childbearing potential (FCBP) must agree to refrain from becoming pregnant while on study drug and for 3 months after discontinuation from study drug, and must agree to use adequate contraception including hormonal contraception, (i.e. birth control pills, etc), barrier method contraception (i.e. condoms), or abstinence during that time frame.

FCBP must agree to regular pregnancy testing during this timeframe (see section 10.1). Inclusion of FCBP requires two negative pregnancy tests prior to enrollment.

*Note:* all women, regardless of age, should be considered FCBP unless they are surgically sterile (post hysterectomy, post bilateral oophorectomy, etc) or have been naturally post menopausal for  $\geq 24$  consecutive months.

- 3.1.7** Men engaging in sexual intercourse with a FCBP must agree to use adequate contraception including hormonal contraception, (i.e. birth control pills, etc), barrier method contraception (i.e. condoms), or abstinence while on study drug and for 3 months after discontinuation from study drug

- 3.1.8** Ability to understand and willing to sign a written informed consent document.

## **3.2 Exclusion Criteria**

A participant must not meet any of the following criteria to be eligible for enrollment.

- 3.2.1** POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
- 3.2.2** Plasma Cell Leukemia.
- 3.2.3** Waldenstrom's macroglobulinemia.
- 3.2.4** Pregnant or lactating females.
- 3.2.5** Use of any anti-myeloma drug therapy within 14 days of initiation of study drug treatment excluding corticosteroids if given for an indication other than myeloma.

*Note:* Bisphosphonates are not considered anti-myeloma drugs.

- 3.2.6** Participation in an investigational therapeutic study within 14 days of initiation of study drug treatment.
- 3.2.7** Radiotherapy to multiple sites or immunotherapy within 14 days of initiation of study drug treatment (localized radiotherapy to a single site at least 7 days before start is permissible).
- 3.2.8** Major surgery within 14 days of initiation of study drug treatment.
- 3.2.9** Participants in whom the required program of PO and IV fluid hydration is contraindicated.
- 3.2.10** Prior history of a hypersensitivity reaction to PLD, doxorubicin, bortezomib, carfilzomib, or liposomal drug formulations other than PLD.

History of reactions to liposomal drug formulations other than PLD should be evaluated individually and if their reactions were felt to have been due to the encapsulated agent, rather than the liposomal component itself they should be excluded at the discretion of the investigators.

- 3.2.11** Participants who are known to have active hepatitis A, B, or C viral infection may not participate in this study. Active disease is defined as participants with a known viral hepatitis whose liver function tests are elevated beyond the criteria indicated in Section 3.1.5.
- 3.2.12** Known HIV-seropositive and are taking anti-retrovirals may not participate in this study because of potential interactions between these medications and the investigational agent. Participants who are HIV-seropositive and not on anti-retroviral therapy and who otherwise meet the inclusion/exclusion criteria will be eligible for the study.
- 3.2.13** Compromised cardiovascular function defined as any of the following:
  - EKG evidence of acute ischemia.
  - EKG evidence of medically significant conduction system abnormalities.
  - History of myocardial infarction within the last 6 months.
  - Unstable angina pectoris or cardiac arrhythmia.
  - History of Class 3 or Class 4 New York Heart Association Congestive Heart Failure
  - Left ventricular ejection fraction (LVEF) < 55% by either echocardiography or radionuclide-based multiple gated acquisition (Echo or MUGA).

**3.2.14** Uncontrolled concurrent illness including: other hematologic or non-hematologic malignancy, active infection, or uncontrolled diabetes

**3.2.15** Any significant psychological, medical, or surgical condition thought to compromise the participant, the study, or prevent informed consent.

### **3.3 Inclusion of Women and Minorities**

Both men and women and members of all races and ethnic groups are eligible for this trial.

## **4.0 REGISTRATION PROCEDURES**

**Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.**

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

### **4.1 Confirmation of Patient Eligibility**

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

### **4.2 Patient Registration in the Siteman Cancer Center Database**

All patients must be registered through the Siteman Cancer Center database.

### **4.3 Assignment of UPN**

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

## 5.0 TREATMENT PLAN

### 5.1 Overview

Carfilzomib will be administered on Days 1, 2, 8, 9, 15, and 16 during Cycles 1 through 6, and on Days 1, 8, 15, and 22 beginning on Cycle 7 until disease progression or clinical relapse. Participants treated prior to approval of amendment 1, will have carfilzomib administered on Days 1, 2, 8, 9, 15, and 16 during Cycles 1 and 2 and on Days 1, 8, 15, and 22 beginning on Cycle 3. PLD will be administered on Day 8 during Cycles 1 through 6. Dexamethasone will be administered on the same schedule as carfilzomib (patients treated in part 2 of phase 1 or phase 2).

Participants that have PLD or dexamethasone discontinued for toxicity may remain on study to receive the planned study drug doses at the PI's discretion.

### 5.2 Phase I

Part 1- A phase I dose escalation of carfilzomib and PLD will be performed using a standard 3 + 3 design with a maximum of 4 dose levels (24 participants). The carfilzomib dose will be determined using a modified Fibonacci dose escalation, with a goal of three participants at each dose level.

Dose Level	Carfilzomib (mg/m <sup>2</sup> ) IV	PLD (mg/m <sup>2</sup> ) IV
-2	20	20
-1	20 on D1 and D2* 27 starting on D8	20
0 (Start)	20 on D1 and D2* 27 starting on D8	30
1	20 on D1 and D2* 36 starting on D8	30
2	20 on D1 and D2* 45 starting on D8	30
3	20 on D1 and D2* 56 starting on D8	30

\*- Please note that the D1 and D2 carfilzomib dose of 20mg/m<sup>2</sup> will only occur during Cycle 1. For all subsequent cycles, patients will receive the same dose of carfilzomib throughout at what is noted in this table to be the D8 dose.

Part 2- After the MTD of carfilzomib in combination with PLD has been determined, dose escalation will resume at the MTD of carfilzomib and PLD with the addition of dexamethasone. A maximum of 12 participants eligible for Maximal Tolerated Dose (MTD) analysis will be enrolled.

Dose Level	Carfilzomib (mg/m <sup>2</sup> ) IV	PLD (mg/m <sup>2</sup> ) IV	Dex (mg) IV or PO
-1	1 dose level below the MTD	1 dose level below the MTD	20
0 (Start)	MTD	MTD	20

### 5.2.1 Dose Escalation Rule

Number of Participants with a DLT at a Dose Level	Escalation Decision Rule
0	Enter 3 participants at the next dose level.
1 out of 3	Enter 3 more participants at this dose level.  If none of the additional participants experiences a DLT, then proceed to the next dose level. If $\geq 1$ of the additional participants experiences a DLT, then dose escalation is stopped and the level below is declared the MTD.
$\geq 2$	Dose escalation is stopped. Enter 3 more participants at the next lower dose level if only 3 participants had previously been treated at that dose level.

Only after the last participant on at each dose level completes one cycle of treatment will the first participant in the next dose level be enrolled.

### 5.2.2 Definition of Maximum Tolerated Dose

The maximum tolerated dose (MTD) is defined as the dose level immediately below the dose level at which 2 participants of a cohort (of 2 to 6 participants) experience dose limiting toxicity (DLT) during the first cycle of treatment. (See Section 6.0 for information on what constitutes a DLT.) Dose escalation will proceed until the MTD has been reached.

## 5.3 Phase II

Having established an MTD in phase I, phase II will be conducted to assess the efficacy and toxicity of carfilzomib in combination with PLD and dexamethasone in participants with relapsed or refractory multiple myeloma.

Seventeen participants will be treated at the MTD of carfilzomib in combination with PLD and dexamethasone. Participants treated in phase 1 at the MTD will be counted as part of the phase two accrual. If  $\leq 5$  successes (CR, VGPR, or PR) are observed, we will

consider this regimen ineffective in this participant population and will not recommend further testing.

#### **5.4 Requirements to Start Treatment (Cycle 1 Day 1)**

- ALT (SGPT) and AST (SGOT) < 2.5 x the upper limit of the institutional normal value (ULN).
- Total bilirubin  $\leq$  1.5 x ULN.
- ANC  $\geq$  0.5.
- Platelets  $\geq$  25,000.
- Creatinine clearance > 15 ml/min using Cockcroft-Gault formula (See Appendix C).

#### **5.5 Accrual**

The anticipated accrual rate for the phase I portion is 1 participant per calendar month, with a total accrual time of two years. The anticipated accrual rate for the phase II portion is 1-2 participants per calendar month, with a total accrual time of one year.

### **6.0 DOSE-LIMITING TOXICITIES/DOSE MODIFICATIONS**

#### **6.1 Definition of Dose-limiting Toxicity**

Participants will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.0. A DLT is defined as any of the below treatment emergent toxicities with attribution to one or both of the study drugs that occur during Cycle 1. Toxicities that occur in subsequent cycles will be handled through dose modifications (Section 6.2) but will not be considered DLTs or figure into the definition of MTD.

As the study uses a lead in dose of 20mg/m<sup>2</sup> of Carfilzomib for days 1 and 2 for all dose levels, toxicity that requires dose reduction or doses to be held prior to Day 8 of cycle 1 will not be considered a DLT, but will result in the participant being ineligible for MTD analysis. The participant may remain on protocol therapy at the PI's discretion, and an additional participant will be enrolled into the cohort for MTD analysis.

In Phase 1, inability to receive >80% of Carfilzomib doses and 100% of PLD doses in Cycle 1 for reasons other than toxicity will result in the participant being ineligible for MTD analysis. The participant may remain on protocol therapy at the PI's discretion, and an additional participant will be enrolled into the cohort for MTD analysis.

Inability to receive >80% of Dex doses for reasons other than toxicity will result in the participant being ineligible for MTD analysis (only patients treated in part 2).

#### Hematologic DLTs

- $\geq$  Grade 4 thrombocytopenia



- $\geq$  Grade 4 neutropenia
- $\geq$  Grade 3 febrile neutropenia (fever  $\geq$  38.5 degrees C and ANC  $<$ 1000k/cumm)

#### Non-Hematologic DLTs

- $\geq$  Grade 2 neuropathy with pain
- $\geq$  Any grade 3 non-hematologic toxicity (excluding nausea, vomiting, diarrhea)
- $\geq$  Grade 3 nausea, vomiting, or diarrhea for  $>$  3 days despite maximal antiemetic/antidiarrheal therapy
- Any non-hematologic toxicity requiring a dose reduction within Cycle 1
- Inability to receive Day 1 dose of Cycle 2 due to drug-related toxicity persisting from Cycle 1 or drug-related toxicity newly encountered on Day 1 of Cycle 2
- Delay of  $>$  14 days in initiating Day 1 of Cycle 2 due to drug-related toxicity

## **6.2 Dosing Modifications**

### **6.2.1 Overview**

Dose modifications for hematologic and non-hematologic toxicities are summarized in sections 6.2.2 and 6.2.3 respectively. Participants who have treatment delayed for greater than four weeks should discontinue protocol therapy.

A maximum of 2 dose reductions of carfilzomib or Dex and 1 dose reduction of PLD will be allowed for each participant. More than two dose reductions of Dex or one dose reduction of PLD will require the agent be discontinued. Participants that permanently discontinue Dex or PLD due to toxicity can remain on study and receive the other planned study drug doses at the investigator's discretion. Participants requiring a third dose reduction of carfilzomib will have treatment discontinued.

If the participant tolerates the reduced dose for one cycle, the participant may be dose escalated to the study drug dose(s) prior to reduction at the discretion of the Investigator.

Dose modifications should be followed directly for Cycle 1 for all patients treated in the phase I portion of the study. In Cycles 2+ for patients treated in the phase I portion, and for any cycle for patients treated in the phase II portion, dose modifications and delays different from those stated in the protocol for management of toxicities will be permitted at the discretion of the Principal Investigator.

### **6.2.2 Dosing Modifications for Hematologic Toxicities**

#### **6.2.2.1 Thrombocytopenia**

Only thrombocytopenia determined to be related to one or both study

drugs require dose reductions or adjustments as described in this section. Platelet transfusion support is permissible at the discretion of the treating physician. Participants who have treatment delayed for greater than four weeks should discontinue protocol therapy.

Dose modifications for thrombocytopenia should be instituted as follows:

Grade	Platelet	Modification
4	< 25,000	<p><b>First episode:</b> Hold therapy until platelets resolve to grade <math>\leq 1</math> or baseline, then reduce carfilzomib by one dose level</p> <p><b>Second episode:</b> Hold therapy until platelets resolve to grade <math>\leq 1</math> or baseline, then further reduce carfilzomib by one more dose level and reduce PLD by one dose level</p> <p><b>Third episode:</b> Discontinue protocol therapy.</p>

#### 6.2.2.2 Neutropenia

Only neutropenia determined to be related to one or both study drugs require dose reductions or adjustments as described in this section. Colony-stimulating factor support (such as G-CSF or GM-CSF) for neutropenia is permissible at the discretion of the treating physician, but should not be given prophylactically. Participants who have treatment delayed for greater than four weeks should discontinue protocol therapy.

Dose modifications for neutropenia should be instituted as follows:

Grade	ANC	Modification
4	< 500	<p><b>First episode:</b> Hold therapy until ANC resolves to grade <math>\leq 1</math> or baseline, then reduce carfilzomib by one dose level</p> <p><b>Second episode:</b> Hold therapy until ANC resolves to grade <math>\leq 1</math> or baseline, then further reduce carfilzomib by one more dose level and reduce PLD by one dose level</p> <p><b>Third episode:</b> Discontinue protocol therapy.</p>

#### 6.2.2.3 F

#### **febrile Neutropenia (Fever > 38.5 degrees Celsius and ANC < 1000)**

Colony-stimulating factor support (such as G-CSF or GM-CSF) for neutropenia is permissible at the discretion of the treating physician, but should not be given prophylactically. Participants who have treatment delayed for greater than four weeks should discontinue protocol therapy.

Dose modifications for febrile neutropenia should be instituted as follows:

Grade	Modification
≥ 3	<p><b>First episode:</b> Hold therapy until participant recovers, then reduce carfilzomib by one dose level</p> <p><b>Second episode:</b> Hold therapy until participant recovers, then further reduce carfilzomib by one more dose level and reduce PLD by one dose level</p> <p><b>Third episode:</b> Discontinue protocol therapy.</p>

### 6.2.3 Dosing Modifications for Non-Hematologic Toxicities

Dose modification guidelines for treatment related non-hematologic toxicities are as follows:

Toxicity	Grade	Modification
<b>Allergic reaction/hypersensitivity</b>	2 or 3	<p><b>First episode:</b> Hold suspected drug(s) until ≤ grade 1, resume treatment at full dose.</p> <p><b>Second episode:</b> Discontinue suspected drug(s).</p>
<b>Allergic reaction/hypersensitivity</b>	4	Discontinue suspected drug(s).
<b>Congestive heart failure (CHF)</b>	Any	Any participant with new symptoms of CHF worsening symptoms of baseline CHF or LVEF < 45% should have <b>all</b> drugs held until resolution or return to baseline regardless of attribution, once resolved Carfilzomib may continue at the original dose, reduced dose or discontinued at the investigator's discretion, but PLD must be discontinued
<b>Creatinine Clearance ≤ 15 mL/min</b> (by Cockcroft-Gault formula, see Appendix C)	N/A	Hold <b>all</b> drugs until > 15mL/min regardless of attribution, then reduce suspected drug(s) by one dose level.
<b>Herpes simplex virus (HSV) or herpes zoster</b>	Any	Hold <b>all</b> drugs until HSV lesions are dry then resume treatment at full dose.

<b>Infection</b>	$\geq 3$	Hold <b>all</b> drugs until infection is adequately controlled with systemic therapy regardless of attribution, then resume treatment at full doses. Patients with recurrent infection should have carfilzomib or PLD dose reduced at the investigator's discretion.
<b>Nausea, Vomiting, or Diarrhea</b> <i>persisting <math>\leq 3</math> days following adequate treatment of antiemetics or antidiarrheals</i>	3	No dose modification required.
<i>persisting <math>&gt; 3</math> days following adequate treatment of antiemetics or antidiarrheals</i>	3	Hold suspected study drug(s) until toxicity resolves to $\leq$ grade 1 or baseline, then reduce suspected drug(s) by one dose level.
<b>Neuropathy</b> <i>Moderate symptoms; limiting instrumental ADL but not painful</i>	2	Continue treatment. Patients on Pyridoxine should have it discontinued
<i>Moderate symptoms with associated pain; limiting instrumental ADL</i>	2	Continue treatment. Patients on Pyridoxine should have it discontinued. If neuropathy persists for more than two weeks, hold suspected drug(s) until resolved to $\leq$ grade 2 without pain, then reduce suspected drug(s) by one dose level.
<i>Severe symptoms; limiting self care ADL</i>	3	Continue treatment. Patients on Pyridoxine should have it discontinued. If neuropathy persists for more than two weeks, hold suspected drug(s) until resolved to $<$ grade 2 without pain, then reduce suspected drug(s) by one dose level.
<i>Life-threatening consequences; urgent intervention indicated</i>	4	Discontinue treatment.

<p><b>Palmar-Plantar Erythrodyesthesia (PPE)</b>  <i>Erythema, desquamation, or swelling interfering with but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter</i></p> <p><i>Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing</i></p> <p><i>Diffuse or local process causing infectious complications, a bed-ridden state or hospitalization</i></p>	<p>2</p> <p>3</p> <p>4</p>	<p><b>First episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume at the same dose.</p> <p><b>Second episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume carfilzomib at same dose level a reduce PLD by one dose level.</p> <p><b>Third episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume carfilzomib at same dose and discontinue PLD</p> <p><b>First episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume carfilzomib at same dose level a reduce PLD by one dose level.</p> <p><b>Second episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume carfilzomib at same dose and discontinue PLD.</p> <p><b>First episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 regardless of attribution, then resume carfilzomib at same dose and discontinue PLD.</p>
<p>Stomatitis  <i>Painful erythema, edema, or ulcers, but can eat</i></p> <p><i>Painful erythema, edema, or ulcers, and cannot eat</i></p>	<p>2</p> <p>3</p>	<p><b>First episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 then resume at the same dose.</p> <p><b>Second episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 then resume carfilzomib at the same dose and PLD at 20 mg/m<sup>2</sup>.</p> <p><b>Third episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 then discontinue PLD and resume carfilzomib at the same dose.</p> <p><b>First episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 then resume carfilzomib at the same dose and PLD at 20 mg/m<sup>2</sup>.</p> <p><b>Second episode:</b> Hold <b>all</b> drugs until resolved to <math>\leq</math> grade 1 then discontinue PLD and resume carfilzomib at the</p>

<i>Requires parenteral or enteral support</i>	4	same dose. Hold <b>all</b> drugs until resolved to $\leq$ grade 1, then discontinue PLD and resume carfilzomib at the same dose.
Tumor lysis syndrome, defined as $\geq 3$ of following:  $\geq 50\%$ increase in creatinine $\geq 50\%$ increase in uric acid $\geq 50\%$ increase in phosphorus $\geq 30\%$ increase in potassium $\geq 20\%$ decrease in calcium $\geq 2$ -fold increase in LDH	Any	Hold <b>all</b> drugs until all abnormalities in serum chemistries have resolved to baseline, then resume treatment at full doses.
Other non-hematologic toxicity	$\geq 3$	Hold suspected study drug(s) until toxicity resolves to $<$ grade 1 or baseline, then reduce suspected drug(s) by one dose level.

### 6.3 Missed Doses

Missed doses will not be replaced during a cycle. Doses can be adjusted by +/- 2 days to allow for holidays, travel issues, etc. Additional adjustments may be granted at the PI's discretion. Everything possible should be done to prevent adjustments from in the study schedule during Cycle 1.

### 6.4 Changes in Body Surface Area (BSA)

Dose adjustments do not need to be made for weight gains/losses of  $\leq 20\%$  from baseline. Participants with a Body Surface Area (BSA) of greater than 2.2 m<sup>2</sup> will receive a capped dose using 2.2 m<sup>2</sup> as the cut-off value.

## 7.0 AGENT ADMINISTRATION

### 7.1 Carfilzomib

#### 7.1.1 Accountability

Instructions for the receipt, inspection, storage, preparation, administration, and disposal of Carfilzomib for Injection are provided in the Pharmacy Manual at each clinical site.

### 7.1.2 Availability

Carfilzomib for injection is supplied as a lyophilized parenteral product in single-use vials. Before use, the lyophilized product is reconstituted with water for injection to a final concentration of 2 mg/mL.

### 7.1.3 Storage, Stability, and Preparation

Lyophilized Carfilzomib for Injection is stored in a refrigerator at 2°C to 8°C. Carfilzomib doses are based on BSA. In a typical dose of carfilzomib, 27 mg/m<sup>2</sup> in a participant with a BSA of 2.0 m<sup>2</sup>, the dose delivered would be 54 mg carfilzomib in a volume of 27 mL. Participants with a BSA of 2.2 m<sup>2</sup> or higher receive a dose based upon 2.2 m<sup>2</sup> BSA. After addition of the appropriate amount of Water for Injection and vigorous mixing, the solution is administered as an IV infusion.

### 7.1.4 Administration

The dosing schedule of carfilzomib will be on Days 1, 2, 8, 9, 15, and 16 in a 28-day cycle for 6 cycles and then weekly (Days 1, 8, 15, and 22) thereafter until disease progression or clinical relapse. Participants treated prior to approval of amendment 1, will have carfilzomib administered on Days 1, 2, 8, 9, 15, and 16 during Cycles 1 and 2 and on Days 1, 8, 15, and 22 beginning on Cycle 3. Carfilzomib dose levels being investigated are: 20mg/m<sup>2</sup>, 20/27mg/m<sup>2</sup>, 20/36mg/m<sup>2</sup>, 20/45mg/m<sup>2</sup>, and 20/56mg/m<sup>2</sup>.

Current clinical experience indicates that carfilzomib can be safely administered as an IV push at rates of approximately 10 mL/minute for doses of 20-27mg/m<sup>2</sup>. Higher doses (> 27 mg/m<sup>2</sup>) should be administered as a 30-minute infusion. For IV infusion over 30 minutes, carfilzomib should be diluted into 50cc of 5% Dextrose Injection, USP (D5W). Based on preclinical studies, these adjustments in infusion rate and time should not affect the PDn effects in humans.

Each dose will consist of carfilzomib for injection administered on a mg/m<sup>2</sup> basis, and should be based on the participant's actual calculated body surface area (BSA) at baseline. Participants with a BSA > 2.2 m<sup>2</sup> will receive a dose based on a 2.2 m<sup>2</sup> BSA.

IV hydration will be given immediately before carfilzomib dose during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Participants should be monitored periodically during this period for evidence of fluid overload.

Patients not receiving dexamethasone as part of the regimen (those treated in part

1 of phase 1) should receive 4mg dexamethasone premedication >30 minutes prior to all carfilzomib doses in cycle 1. Dexamethasone premedication can continue beyond cycle 1 at the discretion of the treating physician. Patients being treated with 10 or 20 mg dexamethasone as part of their regimen should not receive an additional 4mg as premedication.

Complete blood counts (CBC) with platelet count should be obtained and reviewed prior to carfilzomib dosing. See section 6.2.2 for guidelines for dose reductions, adjustments and delays for hematologic toxicities.

Appropriate chemistries, including creatinine should be obtained and reviewed prior to carfilzomib dosing during cycles 1 and 2. Electrolyte abnormalities that are National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) > 2 or clinically significant should be corrected prior to dosing. Renal function must be monitored closely during treatment with carfilzomib. Carfilzomib must be held for participants with a creatinine clearance (by Cockcroft-Gault formula see Appendix C) < 15 mL/min at any time during study participation.

Participants with laboratory abnormalities consistent with TLS should not receive the scheduled dose. Lab abnormalities consistent with TLS is defined as  $\geq 3$  of following: serum creatinine  $\geq 50\%$  increase, uric acid  $\geq 50\%$  increase, phosphorus  $\geq 50\%$  increase, potassium  $\geq 30\%$  increase, calcium  $\geq 20\%$  decrease, LDH  $\geq 2$ -fold increase prior to dosing should not receive the scheduled dose. Participants with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

Participants should have a dedicated line for carfilzomib administration. Before and after administration, the line must be flushed with a minimum of 20 mL of normal saline. If a dedicated line is not possible, the existing line must be flushed with a minimum of 20 mL of normal saline before and after drug administration.

Participants may experience stinging, burning, or a painful sensation at the injection site during the IV push administration of carfilzomib. This generally is mild and subsides shortly following the infusion. Slowing the IV push to the maximum allowed time (10 minutes) can help with minimize such a reaction.

Carfilzomib is considered an irritant. Nonetheless, care should be taken to avoid extravasation. If any signs or symptoms of extravasation occur, the infusion should be terminated and restarted in another vein. Apply ice immediately for 30-60 minutes, subsequently alternating on and off every 15 minutes for 24 hours. The extremity should be monitored for 24-48 hours, then the participant may resume normal activity as tolerated. Do not apply heat or sodium bicarbonate. If pain, erythema or swelling persists beyond 48 hours the participant should be referred to a plastic surgeon for possible debridement at the treating physician's discretion.



The dose will be administered at a facility capable of managing hypersensitivity reactions. Medications to treat infusion-related reactions, as well as emergency equipment should be available for immediate use. If a patient develops a grade  $\geq 2$  infusion-related reaction, the infusion should be stopped and appropriate symptomatic treatment per institutional guidelines should be started immediately. The participant should be observed for at least 30 to 60 minutes depending on the severity of the reaction. At the discretion of the treating physician, treatment may be resumed. Discontinue treatment if subsequent infusion-related reaction occurs.

In the event of  $\geq$  grade 2 infusion-related or hypersensitivity reaction during carfilzomib infusion, discontinue the carfilzomib injection. Begin appropriate symptomatic treatment immediately per institutional guidelines. The participant should be observed for at least 30 to 60 minutes depending on the severity of the reaction. At the discretion of the treating physician, treatment may be resumed. Discontinue treatment if subsequent infusion-related reaction occurs.

Procedures for dose reductions, adjustments and delays are summarized in Section 6.0.

### **7.1.5 Guidelines for Monitoring and Treatment of Tumor Lysis Syndrome**

Tumor Lysis Syndrome (TLS), which may be associated with multiorgan failure, has been observed in treatment Cycles 1 and 2 in some participants with MM who have been treated with carfilzomib.

#### **7.1.5.1 Laboratory Monitoring**

Participants with laboratory abnormalities consistent with TLS should not receive the scheduled dose. Lab abnormalities consistent with TLS is defined as  $\geq 3$  of following: serum creatinine  $\geq 50\%$  increase, uric acid  $\geq 50\%$  increase, phosphorus  $\geq 50\%$  increase, potassium  $\geq 30\%$  increase, calcium  $\geq 20\%$  decrease, LDH  $\geq 2$ -fold increase prior to dosing should not receive the scheduled dose. Participants with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

#### **7.1.5.2 Clinical Monitoring**

Inform participants of signs and symptoms that may be indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Advise participants to report such symptoms immediately and seek medical attention.

#### **7.1.5.3 Treatment of Tumor Lysis Syndrome**

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

A “first-dose effect” has been seen, which is notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a “first dose” effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.

## **7.2 Pegylated Liposomal Doxorubicin (Doxil® or Lipodox)**

### **7.2.1 Accountability**

Instructions for the receipt, inspection, storage, preparation, administration, and disposal of pegylated liposomal doxorubicin (PLD) are provided in the Pharmacy Manual at each clinical site.

### **7.2.2 Availability**

Pegylated liposomal doxorubicin (PLD) is supplied in 20mg and 50mg vials as a liposomal dispersion at a concentration of 2mg/ml. Vials are intended for single use.

### **7.2.3 Storage and Stability**

Intact vials of pegylated liposomal doxorubicin (PLD) should be stored under refrigeration (2-8°C). Prolonged freezing may adversely affect liposomal drug products, but freezing for less than one month doesn't seem to do so. Pegylated liposomal doxorubicin (PLD) diluted for infusion is stable for 48 hours under refrigeration or 24 hours at room temperature.

### **7.2.4 Preparation**

The desired volume of liposomal dispersion should be withdrawn and must be added to 250ml D5W for IV infusion.

### 7.2.5 Administration

PLD will be administered on Day 8 of each 28-day cycle for a maximum of 6 cycles. PLD dose levels being investigated are: 20mg/m<sup>2</sup>, and 30mg/m<sup>2</sup>.

Pegylated liposomal doxorubicin (PLD) will be administered as an IV infusion over 1 hour beginning one hour after the beginning of the carfilzomib infusion. On days when carfilzomib is held, PLD should also be held. PLD may be administered through the same line as carfilzomib. Rapid flushing of the infusion line should be avoided post PLD administration.

Pegylated liposomal doxorubicin (PLD) is considered an irritant. This is in contrast to conventional doxorubicin which can cause severe tissue damage on extravasation. Nonetheless, care should be taken to avoid extravasation. If any signs or symptoms of extravasation occur, the infusion should be terminated and restarted in another vein. Apply ice immediately for 30-60 minutes, subsequently alternating on and off every 15 minutes for 24 hours. The extremity should be monitored for 24-48 hours, then the participant may resume normal activity as tolerated. Do not apply heat or sodium bicarbonate. If pain, erythema or swelling persists beyond 48 hours the participant should be referred to a plastic surgeon for possible debridement at the treating physician's discretion.

Infusion-related reactions have been seen in up to 10% of participants per the manufacturer. Participants who experience this reaction generally do so during the first infusion and not with subsequent dosing. Symptoms may include fever, flushing, dyspnea, facial swelling, headache, chills, back pain, tightness in the chest and throat, rash, pruritus, chest pain, hypotension, syncope, sinus tachycardia, apnea, bronchospasm/wheezing, cyanosis, and asthma. Serious and sometimes life-threatening or fatal anaphylactic shock/anaphylactoid reactions have been reported.

Rapid infusion may increase the risk of some infusion-related reactions, and it is suggested that first infusion be initiated at a rate of 1 mg/min. If no reactions are observed after 5-10 minutes, the rate can be increased to complete the infusion over 1 hour.

The dose will be administered at a facility capable of managing hypersensitivity reactions. Medications to treat infusion-related reactions, as well as emergency equipment, should be available for immediate use. If a participant develops a grade  $\geq 2$  infusion-related reaction, the infusion should be stopped and appropriate symptomatic treatment per institutional guidelines should be started immediately. The participant should be observed for at least 30 to 60 minutes depending on the severity of the reaction. At the discretion of the treating physician, treatment may be resumed with administration of H<sub>1</sub>-blockers and/or steroids. Discontinue treatment if subsequent infusion-related reaction occurs.

Procedures for dose reductions, adjustments and delays are summarized in Section 6.0.

### **7.2.6 Palmar-Plantar Erythrodysesthesia (PPE)**

The onset of PPE is often preceded by exposure of the affected area to friction and/or heat. All participants should therefore be advised to avoid contact with heated objects or bathing and washing with hot water during therapy.

Pyridoxine (vitamin B6) has been reported to decrease the severity of PPE and may decrease its incidence if used in a prophylactic setting. Participants in this study should receive pyridoxine starting on or before Day 1 of Cycle 1 [36, 37] (See section 6.3.2 for details).

Management of PPE once it has appeared is predominantly supportive, with use of treatments such as topical wound care, cold compresses, and elevation. Non-steroidal anti-inflammatory drugs are beneficial in some, and topical 99% dimethyl-sulfoxide has been reported to be of benefit as well, but none of these studies have been studied in a randomized, blinded, prospective fashion. Pyridoxine will be continued in the event that PPE develops despite prophylaxis [38].

## **7.3 Dexamethasone**

### **7.3.1 Accountability**

Dexamethasone is not provided by the study. It will be sourced from a commercial pharmacy.

### **7.3.2 Availability**

Dexamethasone is commercially available in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5mg, 4 mg, and 6 mg tablets. It is also available as a 0.5 mg/5mL elixir, and as 4 mg/mL, 10 mg/mL, and 20 mg/mL solution for injection. Please refer to the FDA approved package insert for dexamethasone for product information, extensive preparation instructions, and a comprehensive list of adverse events.

### **7.3.3 Storage and Stability**

Dexamethasone tablets should be stored at room temperature. Solution for injection may be administered diluted in IV fluids over 10-20 minutes.

### **7.3.4 Administration**

Dexamethasone will be administered on the same dosing schedule as carfilzomib

(Days 1, 2, 8, 9, 15, and 16 for 6 cycles and then Days 1, 8, 15, and 22 thereafter until disease progression or clinical relapse). Dexamethasone dose levels being investigated are: 10 mg and 20mg.

Dexamethasone should be taken IV or PO  $\geq$  30 minutes prior to Carfilzomib injection.

After cycle 2, participants enrolled into part 1 of phase 1 (those not receiving dexamethasone) can have dexamethasone 20mg added at the discretion of the treating physician. If dexamethasone is added, the dose modification guidelines (section 6.2) should be followed.

## **7.4 General Concomitant Medication and Supportive Care Guidelines**

### **7.4.1 HSV Prophylaxis**

Acyclovir, or valacyclovir, should be given to all participants, per institutional prophylaxis guidelines, unless contraindicated.

### **7.4.2 Pyridoxine**

It is recommended that all participants be initiated on pyridoxine (vitamin B6) at 200 mg PO QD for prophylaxis against palmar plantar erythrodysesthesia (PPE) starting on or before Day 1 of Cycle 1. Pyridoxine will be continued in the event that PPE develops despite prophylaxis

Vitamin B6 has been reported to cause neuropathy[39]. Therefore any participants who develop a neuropathy more severe than grade 1 while on study should first have this agent discontinued.

### **7.4.3 Glucocorticoids**

Glucocorticoids (other than those required per protocol) are permitted for non-malignant conditions (i.e. asthma, IBD, etc.) but should not be used unless completely necessary. Glucocorticoids have anti-myeloma effect that may lead to confusion of the response data for this study. Glucocorticoid use while on study should be kept minimal.

### **7.4.4 Bisphosphonates**

Participants should receive therapy with bisphosphonates as per institutional guidelines. The choice of agents in this category will be left to the discretion of the treating physicians.

#### **7.4.5 Erythropoietins**

Participants may develop new or worsening anemia and may require either initiation of an erythropoietin preparation or an increased dose of the agent they are already receiving. The choice of preparations to be used will be left to the discretion of the treating physicians.

#### **7.4.6 Filgrastim (G-CSF), Peg-Filgrastim, and Sargramostim (GM-CSF)**

Participants may develop neutropenia and may benefit from initiation of some type of colony stimulating factor, but they should not be given prophylactically. The choice of preparations to be used will be left to the discretion of the treating physicians.

#### **7.4.7 Platelet, RBC, Whole blood, or FFP Transfusions**

Participants may receive platelet, red blood cell (RBC), whole blood, or fresh frozen plasma (FFP) transfusions if clinically indicated.

#### **7.4.8 Antiemetics and Antidiarrheals**

Carfilzomib and PLD treatment can cause nausea, vomiting, or diarrhea, sometimes requiring the use of antiemetics or antidiarrheals, but these agents should not be started prophylactically. If needed, the choice of preparations to be used will be left to the discretion of the treating physicians.

Participants with severe nausea, vomiting, or diarrhea should have fluid and electrolyte replacement administered to prevent dehydration per institutional guidelines.

#### **7.4.9 Palliative Radiation**

Palliative radiation while on study is allowed at the discretion of the treating physician as long as the definition of progressive disease is not met (see section 9.8). Participants meeting the definition of progressive disease should be discontinued from study.

#### **7.4.10 Anti-Myeloma Therapy**

The concurrent use of any approved or investigative drug with known or suspected anti-myeloma effect outside the scope of this trial is prohibited, with exception to those specifically permitted in section 7.4.

#### **7.4.11 Investigational Agents**

Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

### **8.0 DURATION OF THERAPY**

#### **8.1 Criteria for Removal from Study**

Treatment may continue until disease progression or clinical relapse, as defined in Sections 9.8 and 9.9 respectively, or until one or more of the following criterion applies:

- Participant withdraws consent
- Holding study drug(s) > 2 continuous weeks for adverse event(s)
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator
- Suspected or confirmed pregnancy
- Major violation of the study protocol
- Participant lost to follow-up
- The PI decides to remove the participant from study for any reason
- Death
- The treating center decides to close the study

#### **8.2 Duration of Follow-Up**

Participants will be followed for 18 months after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, even if the follow-up exceeds 18 months.

### **9.0 CRITERIA FOR RESPONSE**

#### **9.1 Complete Response**

Complete response (CR) requires all of the following:

- Disappearance monoclonal protein by both protein electrophoresis and immunofixation studies from the blood and urine on at least two determinations, performed a minimum of six weeks apart
- <5% plasma cells in the bone marrow

- Disappearance of soft tissue plasmacytomas for at least six weeks

## 9.2 Stringent Complete Response

Stringent complete response (sCR) requires all of the following:

- CR as defined above
- Normal free light chain ratio
- Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence

## 9.3 Near-Complete Response

Near-complete response (nCR) requires all of the following:

- The presence of a residual monoclonal protein that is visible only on immunofixation studies, and not on serum or urine protein electrophoresis
- All other criteria are met for complete response.

## 9.4 Very Good Partial Response

Very good partial response (VGPR) requires all of the following:

- Serum and urine monoclonal protein detectable by immunofixation but not on electrophoresis for at least two determinations, performed a minimum of six weeks apart
- OR
- $\geq 90\%$  reduction in serum monoclonal protein with urine monoclonal protein  $< 100$  mg per 24 hours for at least two determinations, performed a minimum of six weeks apart.
  - If present,  $\geq 50\%$  reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations) for at least six weeks.

## 9.5 Partial Response

Partial response (PR) requires all of the following:

- $\geq 50\%$  reduction in the level of the serum monoclonal protein for at least two determinations performed a minimum of six weeks apart.
- Reduction in urine monoclonal protein by either  $\geq 90\%$  or to  $\leq 200$  mg for at least two determinations performed a minimum of six weeks apart.
- If present,  $\geq 50\%$  reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations) for at least six weeks.
- If serum and urine monoclonal protein are unmeasurable, a  $\geq 50\%$  decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must



- be  $\geq 10$  mg/dl)
- If serum and urine monoclonal protein are unmeasurable and serum free light chain is unmeasurable, a  $\geq 50\%$  reduction in plasma cells is required in place of monoclonal protein provided that baseline bone marrow plasma cell percentage was  $\geq 30\%$

## 9.6 Minimal Response

Minimal response (MR) requires all of the following:

- $\geq 25\%$  to  $< 49\%$  reduction in the level of serum monoclonal protein for at least two determinations six weeks apart.
- If present, a 50 to 89% reduction in 24-hour urine monoclonal protein which still exceeds 200 mg/24hr, for at least two determinations six weeks apart.
- 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examinations) for at least six weeks.
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

*Note:* MR includes participants in whom some but not all criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR.

## 9.7 Stable Disease

Stable disease (SD) is defined as not meeting criteria for any other response as defined in this section.

## 9.8 Progressive Disease

Progressive disease (PD) requires one or more of the following:

- $\geq 25\%$  increase in the level of serum monoclonal protein, which must also be an absolute increase of at least 0.5 g/dL, and confirmed on a repeat investigation.
- $\geq 25\%$  increase in 24-hour urine monoclonal protein, which must also be an absolute increase of at least 200 mg/24hr and confirmed on a repeat investigation.
- $\geq 25\%$  increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- $\geq 25\%$  increase in the difference between involved and uninvolved free light chain levels (The absolute increase must be  $\geq 10$  mg/dl)
- Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. A definite increase is defined as at least 50% (and at least 1 cm) increase as measured serially as the sum of the products of the cross-diameters of the lesions.
- Development of new bone lesions or soft tissue plasmacytomas (not including

- compression fracture).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any cause other than progressive multiple myeloma).

*Note:* A response of progressive disease nullifies any other concurrent response. For example, at a given time point a participant meets criteria for VGPR but has development of new bone lesions the response is PD not VGPR.

## **9.9 Clinical Relapse**

Clinical relapse (i.e. progressive disease requiring alternate myeloma treatment) requires one or more of the following:

- Decrease in hemoglobin  $\geq 2$  g/dl not attributable to any cause other than progressive multiple myeloma
- Increase in creatinine by  $\geq 2$  mg/dl not attributable to any cause other than progressive multiple myeloma
- Other worsening laboratory result, or clinical condition that the treating physician determines is not attributable to any cause other than progressive multiple myeloma

## **9.10 Relapse from Complete Response**

Relapse from a complete response requires a prior CR or sCR as described above and subsequently developing one or more of the following:

- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis excluding oligoclonal immune reconstitution for at least two determinations.
- $\geq 5\%$  plasma cells in the bone marrow aspirate or biopsy.

## 10.0 STUDY CALENDAR

Assessment *	Screening <sup>a</sup>	Cycles 1 through 6						Cycles 7 and beyond				End of Study <sup>b</sup>	Follow-up <sup>c</sup>	
		D1	D2	D8	D9	D15	D16	D1	D8	D15	D22			
Sign informed consent	X													
Medical & treatment history	X													
Vital signs <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X		
Physical exam <sup>e</sup>	X	X <sup>1</sup>						X						
Toxicity assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/ differential	X	X		X		X		X	X	X	X	X	X	
Chemistries <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT/INR & PTT	X	X <sup>1</sup>												
SPEP & IFIX <sup>g</sup>	X	X <sup>1</sup>				X <sup>2</sup>		X					X	
24-hour urine total protein, UPEP, & IFIX <sup>gh</sup>	X	X <sup>1</sup>				X <sup>2</sup>		X					X	
Serum free light chains	X	X <sup>1</sup>				X <sup>2</sup>		X					X	
Quantitative immunoglobulins (IgA, IgG, IgM)	X	X <sup>1</sup>				X <sup>2</sup>		X					X	
Beta-2 microglobulin	X	X <sup>1</sup>						X					X	
Serum $\beta$ HCG <sup>j</sup>	X	X						X					X	
EKG & Chest x-ray	X													
MUGA or Echo <sup>m</sup>	X													
Imaging for plasmacytoma assessment <sup>km</sup>	X												X <sup>3</sup>	
Skeletal survey <sup>m</sup>	X												X <sup>3</sup>	
Bone marrow biopsy & aspirate <sup>n</sup>	X												X <sup>3</sup>	
Correlative samples <sup>o</sup>	X												X <sup>3</sup>	
Carfilzomib administration		X	X	X	X	X	X	X	X	X	X	X		
PLD administration				X										
Dexamethasone administration <sup>p</sup>		X	X	X	X	X	X	X	X	X	X	X		
Follow-up for survival														X

\* All assessments allowed a window of +/- 2 days for scheduling issues (such as holidays)

a: Screening period is D-21 though D1 prior to Carfilzomib dose

b: End of study must be within 30 days of last dose of study drug

c: Follow-up takes place every 3 months for up to 18 months or until resolution or stabilization of adverse events, whichever is longer

d: To be done within 1 hour prior to carfilzomib administration.

e: Physical exam includes height, weight, BSA, performance status, neurological assessment and plasmacytoma assessment if indicated .

f: Chemistries include Complete Metabolic Panel with Renal and Hepatic Panels, LDH, Magnesium, Phosphorous, Uric Acid.

g: SPEP = serum protein electrophoresis, IFIX=immunofixation, UPEP= urine protein electrophoresis.

h: All participants must complete 24 hour urine at screening and for confirmation of CR or VGPR if necessary. Additional serial 24-hour urines only required for participants with  $\geq 0.2g/24$  hours of monoclonal protein at screening.

j: Required only in women of childbearing potential; 2 negative test results required before study drug dosing on Cycle 1 Day 1.

k: Only required if clinically indicated. Imaging can include X-ray, CT, MRI, PET, etc.

m: To be repeated on study when clinically indicated.

n: Bone marrow aspirate and core biopsy for differential, cytogenetics, and fluorescent *in situ* hybridization (FISH) studies. To be repeated on study for confirmation of CR or sCR.

o: To be repeated on study whenever a bone marrow biopsy and aspirate is performed.

p: Only for patients treated in part 2 of phase 1 or phase 2.

1: Not required to be repeated in Cycle 1 if screening assessment was within 7 days of Day 1.

2: Only during Cycle 1.

3: Optional. If patient is willing and able.

## 11.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Registration Eligibility Checklist Medical History Treatment History Radiation History Transplant History Vital Signs Labs – Hematology Labs – Chemistry Disease Assessment Skeletal Survey/Plasmacytoma Evaluation Bone Marrow Biopsy	Original Consent: Before initiation of any non-standard of care procedures  Registration and Eligibility Checklist: At time of enrollment  All others: Within 28 days of enrollment
Vital Signs Labs – Hematology Labs – Chemistry Disease Assessment Response Assessment Skeletal Survey/Plasmacytoma Evaluation Bone Marrow Biopsy Study Drug Dosing Record	Within 28 days of end of each cycle  <i>Note:</i> Some forms must be completed multiple times per cycle
Correlative Studies	Within 28 days of sample collection
Adverse Events	To be completed throughout study participation; as per guidelines in section 13.1
Off Study Vital Signs Labs – Hematology Labs – Chemistry Disease Assessment Form Response Assessment Form Skeletal Survey/Plasmacytoma Evaluation Bone Marrow Biopsy Form	Within 28 days of end of study visit
Survival Form	Within 28 days of follow-up

## 12.0 CORRELATIVE STUDIES

Bone marrow and peripheral blood samples will be taken prior to treatment, at time of complete response, and/or at end of study.

The following samples will be collected at all time points:

- Bone marrow aspirate: 6-10 mL divided between two EDTA (lavender top) tubes.
- Peripheral blood for viable PBMC: 60 mL collected in 6 large EDTA (lavender top) tubes.
- Peripheral blood for plasma: 10 mL collected in 1 EDTA (lavender top) tube.

Bone marrow aspirate samples will be pooled, and mononuclear cells will be purified over Ficoll. Resulting BM mononuclear cells will be divided into 1) viable cells cryopreserved at  $10^7$ /vial, and 2) cell pellet for nucleic acid. Plasma and from bone marrow will be divided into 2mL aliquots and frozen at  $-80^{\circ}\text{C}$ .

Peripheral blood mononuclear cells (PBMC) will similarly be isolated by Ficoll preparation from the pooled peripheral blood lavender top tubes and will be viably cryopreserved.

Plasma will be divided into 2mL aliquots and frozen at  $-80^{\circ}\text{C}$ .

Fresh PBMC or BM mononuclear cells may also be used for correlative studies at the discretion of the principal investigator.

All samples are to be delivered to the Siteman Cancer Center Tissue Procurement Core (Dr. Mark Watson, Director) during their normal operating hours. Specimens will be identified by initials and study number at the Tissue Procurement Core, and samples will be processed appropriately.

Contact information for questions regarding sample procurement only:

Mark Watson, M.D., Ph.D.  
Siteman Cancer Center Tissue Procurement Facility  
BJC Institute of Health  
5<sup>th</sup> Floor, Rooms 5120, 5113, and 5205 St Louis, MO 63110  
Phone: 314-454-7615  
Fax: 314-454-5525  
Email: [tbank@wudosis.wustl.edu](mailto:tbank@wudosis.wustl.edu)

## 13.0 SAFETY MONITORING, DATA AUDITING, AND REQUIRED REPORTING OF EVENTS

### 13.1 Adverse Events

**Definition:** any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

**Grading:** the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

**Attribution (relatedness), Expectedness, and Seriousness:** the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: (<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>).

All AEs, regardless of relationship to study drug, will be followed from first day of study treatment until 30 days following the last day of study treatment or until the start of a new chemotherapy, whichever is sooner. All AEs resulting in death within 30 days following the last day of study treatment will be recorded without regards to new chemotherapy. Thereafter, any death while off study but reasonably related to study drug(s) will be recorded, regardless of the proximity to study treatment.

All AEs should be recorded in the Case Report Forms (CRFs). The CRFs should include the duration, outcome, intensity, attribution, dose delays/dose modifications, and seriousness.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting (see Appendix D).

#### 13.1.1 Regulatory Reporting of Internal AEs

When a trend of unexpected and reasonably related non-serious AEs is identified by the PI, these events are required to be reported to Amgen, HRPO, QASMC, and the FDA in a written report (Medwatch 3500 form, see Appendix E). The events should be then added to the consent form.

All grade 3 and 4 AEs that are serious and/or unexpected and reasonably related must be reported to Amgen, HRPO, QASMC, and the FDA in a written report (Medwatch 3500 form, see Appendix E).

All grade 5 (death) AEs must be reported to Amgen, HRPO, QASMC, and the FDA in a written report (Medwatch 3500 form, see Appendix E).

### 13.1.2 Regulatory Reporting of External AEs

Any event or summary of adverse events that are provided to the investigator or study chair should be submitted to QASMC and/or HRPO for review.

## 13.2 Unanticipated Problems

### Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 13.3 Noncompliance

**Definition:** failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

## 13.4 Serious Noncompliance

**Definition:** noncompliance that materially increases risks, that results in substantial harm to participants or others, or that materially compromises the rights or welfare of participants.

## 13.5 Protocol Exceptions

**Definition:** A planned deviation from the approved protocol that are *under the research team's control*. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event, unless

taken to avoid or eliminate immediate harm to a participant/participants. If taken to avoid or eliminate immediate harm to a participant report within 24 hours.

### **13.6 Pregnancy**

Pregnancy of a female participant or the female partner of a male participant while enrolled on this clinical trial or up to three months following administration of study drug(s) is a reportable event (Medwatch 3500 form, See Appendix E). If the participant is on study drug(s) at the time of pregnancy it must be discontinued immediately.

The pregnant female will be followed until completion of the pregnancy. The Investigator will be required to report the results of the pregnancy (follow-up to the original Medwatch 3500 form).

If the outcome of the pregnancy meets a criterion for immediate classification as a grade 5 event—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should report the event per the guidelines below.

### **13.7 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University**

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

### **13.8 Reporting to the FDA**

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It



is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information. A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
  - Death
  - A life-threatening adverse drug experience
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
  - A congenital anomaly/birth defect
  - Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266  
FAX: 1-800-FDA-0178

### **13.9 Reporting to Amgen**

All required forms will be sent to Amgen Global Safety by Fax: (1-888) 814-8653, or at the following email address (with secure email connection with Amgen only): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com).

### 13.10 Timeframe for Reporting Required Events

<b>Deaths</b>	
Any <b>reportable</b> death while on study or within 30 days of study	Immediately, within 24 hours, to PI, FDA, Amgen, and the IRB
Any <b>reportable</b> death while off study	Immediately, within 24 hours, to PI, FDA, Amgen, and the IRB
<b>Adverse Events/Unanticipated Problems</b>	
Any <b>reportable</b> adverse events as described in Sections 12.1 and 12.2 (other than death)	Immediately, within 24 hours to PI, FDA, and within 10 working days to the IRB
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
<b>Non-Compliance and Serious Non-Compliance</b>	
All noncompliance and serious noncompliance as described in Sections 12.3 and 12.4	Immediately, within 24 hours, to PI and within 10 working days to the IRB
<b>Pregnancy</b>	
Pregnancy	Immediately, within 24 hours, to PI, FDA, Amgen, and the IRB

### 14.0 DATA AND SAFETY MONITORING PLAN

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

During the phase I dose escalation, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During the phase II, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

#### **14.1 External Data Auditing**

The study data will be audited by a member of the QASMC office on annual basis as per institutional guidelines.

### **15.0 ENDPOINTS**

#### **15.1 Primary Outcome Analyses**

The primary endpoint for each arm of the phase II portion of this trial is the proportion of confirmed tumor responses. A confirmed response is defined to be a CR, VGPR, or PR noted as the objective status. Response will be evaluated using up to 12 cycles of treatment. All participants meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

#### **15.2 Secondary Outcome Analyses**

Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier for the participants included in evaluating the decision criteria.

Progression-free survival time is defined as the time from registration to disease progression, clinical relapse, or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

Duration of overall response is defined for all participants who have achieved a confirmed response as the date at which the participant's objective status is first noted to be a CR, sCR, nCR, VGPR, or PR to the earliest date progression or clinical relapse is documented. The distribution of duration of response will be estimated using the method of Kaplan-Meier.

## **16.0 STATISTICAL ANALYSIS**

In the Phase 2 portion, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 20%, and the smallest success proportion that would warrant further treatment is 40%. The following one-stage design uses 24 participants to test the null hypothesis that the true success proportion is at most 20%.

Enter 24 participants into the phase 2 portion of the study. If 7 or fewer successes are observed, we will consider this treatment ineffective in this participant population. If 8 or more successes are observed, we may recommend further testing of the regimen in subsequent studies in this population.

Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is 0.10, 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, and the probability of stopping after the first stage can be tabulated as a function of the true success proportion.

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## APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.



## APPENDIX B: Karnofsky Performance Status Scale

DEFINITIONS	RATING (%)	CRITERIA
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

**APPENDIX C: Cockcroft-Gault Formula**

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

## **APPENDIX D: NCI Common Terminology Criteria for Adverse Events Version 4.0**

Adverse Events will be scored using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

A copy of the NCI CTCAE Version 4.0 can be downloaded from:

[http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

## **APPENDIX E: Medwatch 3500**

Reportable adverse events and pregnancies will be reported to the appropriate on a Medwatch 3500 form. The most recent Medwatch 3500 Form can be retrieved from [http://www.fda.gov/medwatch/safety/FDA-3500\\_fillable.pdf](http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf)