Study Title	Phase I/II study of carfilzomib in combination with bendamustine and dexamethasone in patients with newly diagnosed multiple myeloma
Protocol Number	AAAJ2359
Institution Name	Columbia University Medical Center
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PROTOCOL SYNOPSIS

TITLE: Phase I/II study of carfilzomib in combination with bendamustine and dexamethasone in patients with newly diagnosed multiple myeloma (MM)

OBJECTIVES	**Primary Objective** • Determine the MTD of carfilzomib (CFZ) in combination with bendamustine and dexamethasone **Secondary Objectives** • Determine the overall response rate (ORR) • Determine duration of response (DOR) • Determine progression free survival (PFS) • Determine time to best response • Determine overall survival (OS) • Evaluate the safety and toxicity • Stem cell collection parameters using the regimen as induction
STUDY DESIGN	This is a phase I/II study to define dose-limiting toxicity and determine preliminary evidence for efficacy of CFZ in combination with bendamustine and dexamethasone for patients with newly diagnosed MM. This trial is an open-label, single-center, dose escalation safety study. Doses will be allocated to patients using a two-stage Up-and-Down dose escalation scheme without intra-patient dose escalation. Patients will receive CFZ on days 1, 2, 8, 9, 15, and 16 every 28 days with dose escalation from 27 to 36, then 45, then 56 mg/m^2. No matter what target dose the subject will receive, doses on days 1 and 2 in the first cycle will always be 20 mg/m^2, followed by the target dose for all subsequent dates and cycles. Bendamustine will be given IV on days 1 and 2 with dose escalation up to 90 mg/m^2. Dexamethasone 20 mg PO or IV will be given on days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle. Study treatment will be given until 8 cycles are completed or until disease progression, whichever comes first. This protocol can also be used as induction therapy for transplant.
STUDY POPULATION	Approximately 26 evaluable subjects (men and women at least 18 years of age) will participate in this study.
INCLUSION CRITERIA	Patients must have histologically or cytologically confirmed symptomatic MM, Salmon-Durie Stage II or III, or International Staging System II or III. Patients must be untreated.
EXCLUSION CRITERIA	Patients who have had systemic therapy for MM. Local radiation therapy for symptomatic bone lesions (e.g., uncontrolled pain or high risk of pathologic fracture) are permitted. Patients are also allowed up to 2 cycles of high dose steroids (maximum total dose of 320 mg dexamethasone or equivalent) if needed for symptomatic disease before study enrollment

PROCEDURES	Eligible patients will be entered on study centrally at the Columbia University Medical Center. Each patient enrolled in the study will be registered in the CUMC's Clinical Trials Management Application (CTMA) at study entry. Each patient enrolled will be assigned a sequential study identifier by CTMA. Following registration, patients should begin the research treatment within one week.
STUDY TREATMENT	Patients will receive CFZ infusion on days 1, 2, 8, 9, 15, and 16 every 28 days, with initial dose 20 mg/m^2 and dose escalation up to 56 mg/m^2. Bendamustine will be given IV on days 1 and 2 with dose escalation up to 90 mg/m^2, and dexamethasone 20 mg PO or IV on days 1, 2, 8, 9, 15, 16 and 22 of each 28-day cycle.
STATISTICAL METHODS	1. Two-stage Up-and-Down dose escalation scheme (Storer's schema D, with a one-patient-per-level run-in) without intra-patient dose escalation 2. Logistic regression model 3. Fisher's exact test 4. Kaplan-Meier estimator 5. Monte Carlo simulation

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LIST OF ABBREVIATIONS

Abbreviation	**Definition**
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BSA	body surface area
BTZ	bortezomib
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CFZ	Carfilzomib
CHF	congestive heart failure
CR	complete response
CrCl	Creatinine Clearance
CRF	case report form(s)
CTCAE	Common Terminology Criteria for Adverse Events
CTMA	Clinical Trials Management Application
dL	deciliter
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FLC	free light chain
GCP	Good Clinical Practice
h	hour(s)
ICH	International Conference on Harmonization
Ig	Immunoglobulin

IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
kg	kilogram(s)
LDH	lactate dehydrogenase
mg	milligram(s)
mL	milliliter(s)
MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PD	progressive disease
PFS	progression free survival
PO	per os (orally)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
sCR	stringent complete response
SD	stable disease
SPEP	serum protein electrophoresis
TLS	Tumor lysis syndrome
TTP	time to progression
UPEP	urine protein electrophoresis
VGPR	very good partial response

1 INTRODUCTION

1.1 DISEASE SPECIFIC BACKGROUND

Multiple myeloma (MM) is a malignant plasma cell disorder resulting in approximately 11,000 deaths in the United States each year. It is estimated that between 60,000-80,000 people are currently under treatment for refractory or relapsed MM. (1) Prognosis and survival have improved over the last 20 years, but the disease is still universally fatal despite efforts to develop new and more effective chemotherapeutic regimens. Therefore, new regimens need to be developed for patients prior to peripheral blood stem cell transplant and for those unable to tolerate the toxicity of transplant.

1.2 PROTEASOME BACKGROUND

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

1.3 CARFILZOMIB BACKGROUND

Carfilzomib (CFZ) is a novel, highly selective epoxyketone proteasome inhibitor that produces potent and sustained proteasome inhibition both in vitro and in vivo. CFZ appears to lack many of the off-target activities frequently associated with bortezomib (BTZ). This lack of off-target activity may account for observed differences in tolerability seen with CFZ including lack of significant neuropathy and minimal neutropenia and diarrhea. To date, single agent CFZ has been evaluated in Ph 1 and 2 studies in >600 patients, and the vast majority of patients treated had relapsed and/or refractory MM. In these settings, CFZ has demonstrated durable single-agent activity and was well-tolerated in patients with advanced stage disease with co-morbidities including baseline neuropathy or renal insufficiency.

In the phase II clinical trial PX-171-003-A1 with carfilzomib as a monotherapy, 266 patients had received a median of five prior treatments with a median of 13 different anti-myeloma drugs; nearly all of the patients had been previously treated with Velcade. Patients received CFZ single agent (20 mg/m^2 intravenously (IV) on days 1, 2, 8, 9, 15, and 16) every 28 days for the first cycle, with the dose then being escalated to 27 mg/m2 on the same schedule for up to 12 cycles. (2) At the time of reporting, 30% had completed at least 6 cycles of study treatment, approximately 11% had completed 12 cycles, among 257 patients evaluable for response, 0.4% (one patient) had a complete response (CR), 4.7% had a very good partial response (VGPR), and 19% had a partial response (PR), for an overall response rate of 24%; an additional 12% of patients had a minimal response, yielding an overall clinical benefit rate of 36%. Stable disease (SD) for at least 6 weeks was achieved in 32%. Among patients with a PR or better, the median DOR was 7.4 months. Among patients with a minimal response, the median DOR was 6.3 months, indicating durable minor responses. CFZ was well-tolerated. Based on these data, Carfilzomib was approved by the US Food and Drug Administration (FDA) in July2012.

Singhal et al presented the results of parallel safety analyses of patients from four Ph 1 and 2 studies with CFZ.(3) Toxicity consisted mainly of myelosuppression. Grade 3/4 hematologic toxicities consisted of thrombocytopenia in 18% of patients, lymphopenia in 11%, neutropenia in 8%, and anemia in 7%. Grade 3/4 nonhematologic toxicities included fatigue in 6% of patients; pneumonia and congestive cardiac failure in 3% each; nausea, dyspnea, increased blood creatinine levels, and increased blood uric acid levels in 1% each; and diarrhea in 0.4%. Grade 1/2 peripheral neuropathy was present in 77% of patients at baseline; new-onset neuropathy was infrequent, with grade 3 or lower neuropathy occurring in less than 1% of patients. The excellent safety/tolerability profile of CFZ has permitted prolonged administration (in some cases over 24 mos of continuous therapy including extension study) with minimal dose modifications. The low level of neuropathy seen with CFZ provides a new and promising option for patients with pre-existing neuropathy from either underlying disease or prior neuropathic anti-myeloma therapy.

Combination of CFZ with lenalidomide and dexamethasone with escalated dose of CFZ 27 mg/m^2, lenalidomide 25 mg, and dexamethasone 40 mg/day, showed acceptable tolerability in patients heavily pre-treated with bortezomib (BTZ) and immunomodulatory agents. The combination yielded a 59% overall response rate (ORR) without reaching the maximum tolerated dose (MTD).(4)

A phase I/II clinical trial investigating CFZ in combination with lenalidomide and dexamethasone for newly diagnosed MM patients also showed high response rate. CFZ dose was escalated to 36 mg/m^2, and no dose-limiting toxicities were observed (MTD was not reached). After completion of eight cycles, all patients (n=19) achieved at least a partial remission with 63% ≥VGPR, 37% CR/near CR. Side effects were mostly mild, and no significant peripheral neuropathy was observed.(5)

Dr. Sonneveld and colleagues recently reported their experience with Carfilzomib combined with thalidomide and dexamethasone (CARTHADEX) as induction therapy prior to transplantation. In their study of 34 patients, the median time to maximum response was 1 cycle and responses occurred across all cytogenetic risk groups. Furthermore, stem cell harvest was accomplished in all studied subjects showing that a Carfilzomib based regimen is feasible in preparation for ASCT. (6)

There is additional data to support the use of a CFZ based regimen in the upfront setting. Dr. Kolb and colleagues presented their study on the use of Carfilzomib, Melphalan, and Prednisone (CMP) in Elderly patients with de-novo Myeloma (ASCO Abstract 8009, 2012). The maximum tolerated dose of CFZ in the phase 1 portion of the study was 36 mg/m^2. Of the 26 patients evaluable for response, the overall response rate was 92% including 42% with a VGPR or better. These results compared favorably to those achieved with other melphalan/novel compound based regimens including MPV, MPT and MPR.(7)

Finally, there is evidence that combining a proteasome inhibitor with Bendamustine is safe and well tolerated. Dr. Berdeja and colleagues at the Sarah Cannon Research Institute presented their study on the use of Bendamustine, Bortezomib, and Dexamethasone (BBD) as first line therapy for patients with MM who are not eligible for transplantation. Bendamustine was given at a dose of 80 mg/m^2 at two different dosing schedules for up to 8 cycles of therapy. There were no grade

4 hematologic adverse events and only 33-40% Grade 3 hematologic events. The response rate was similar in both groups with an overall response rate varying between 78-90%.(8)

1.4 BENDAMUSTINE BACKGROUND

Bendamustine, a bifunctional alkylating agent, which has little cross-resistance with other alkylating agents, was approved by the US Food and Drug Administration (FDA) for the treatment of CLL and rituximab-refractory, indolent B-cell non-Hodgkin' lymphoma (NHL). Bendamustine has also been approved in Europe for the treatment of MM.(9) A dose escalation study of bendamustine in patients with relapsed MM determined the MTD to be 100 mg/m^2 on days 1 and 2, with a response rate of 55%. A prospective, randomized clinical trial showed superiority of combined bendamustine and prednisone when compared with the standard melphalan/prednisone in terms of response rate, time to treatment failure, and quality of life.(10) Our group performed a phase I/II trial using bendamustine combined with lenalidomide for patients with relapsed or refractory MM, and data was recently published.(11) The MTD was identified at 75 mg/m^2 bendamustine and 10 mg lenalidomide. Among the 29 patients, 24% achieved a VGPR and 52% PR, with an ORR of 76%. The estimated 1 and 2 year OS was 93% and 62% respectively. We did not observe any severe non-hematologic side effects or severe peripheral neuropathy in this trial. Despite the fact that combination therapy with bendamustine and lenalidomide is very promising, this therapy harbors an increased risk of neutropenia. In addition many patients have received lenalidomide before and develop drug resistance.

The pharmacokinetics of Bendamustine excretion has been studied with results recently published.(12) After a single 60minute intravenous dose of radioactive Bendamustine was administered, patients had blood, urine and feces samples collected for analysis. Approximately half the administered dose was recovered in the urine and a quarter in the feces with less than 5% of the administered dose recovered in the urine as unchanged Bendamustine. Clearance of Bendamustine from the plasma was rapid with a $t_{1/2}$ of ~40 minutes. The conclusion of the study was that Bendamustine is extensively metabolized with subsequent excretion in both the feces and urine. Accumulation of Bendamustine was not anticipated in cancer patients with renal or hepatic impairment because of the short half-life.

1.5 STUDY RATIONALE

Results of phase I/II trials using CFZ or bendamustine indicate that both drugs are very potent for the treatment of MM. The drugs have different intracellular targets and the combination may result in additive/synergistic anti-myeloma effects without showing cross-resistance. Lack of significant toxicities of CFZ suggests that this drug is favorable for use in combination therapies especially in patients who are suffering from pre-existing neuropathy. In the proposed phase I/II clinical trial, we will investigate the safety and efficacy of CFZ in combination with bendamustine and dexamethasone for newly diagnosed MM. The combination is very promising in order to overcome drug resistance combined with a favorable toxicity profile and might be very effective.

One study that has particular relevance to our proposed work was published in Leukemia and Lymphoma by Dr. Fenk and Colleagues (13). In this study, the investigators enrolled 50 patients with relapsed/refractory multiple myeloma and offered treatment with escalating doses of Bendamustine with Bortezomib and dexamethasone. The overall response rate was 84% with manageable toxicity. Median time to progression was 8 months and median overall survival was 20 months.

At the annual ASCO meeting in June 2013, a phase 1/2 study was presented by Dr. Bereneson and colleagues (ASCO Abstract 8599) showing that CFZ is a suitable replacement for bortezomib in many different regimens. Their study included patients receiving bendamustine. The authors concluded that replacement of bortezomib with CFZ in a bortezomib-containing combination regimen often leads to responses and is well tolerated.

1.6 DOSE RATIONALE

A phase 1b/2 dose escalation study (PX-171-007) of single agent CFZ administered is ongoing and as of 23 April 2010, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m^2 (bolus administration). A review of the tolerability of 36 mg/m^2 CFZ in these patients indicates that this regimen was very well tolerated with only one DLT (Grade 3 fatigue) and an overall adverse event (AE) profile similar to that seen with the 27mg/m^2 CFZ experience with bolus dosing (see investigator brochure for details). There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease (PD). Because of the long-term tolerability CFZ, the Phase 1b portion of this study was reopened, and a separate arm for MM was added. In the same trial, more recently patients have been treated with CFZ given as a 30-minute infusion in order to potentially minimize Cmax-related infusion events. The protocol was amended and doses of 20/36 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m^2 for all subsequent doses), 20/45, 20/56 mg/m^2 and so forth are being investigated. Papadopoulos, et al presented the result of PX-171-007 trial at the 2010 ASH showing that in patients with R/R MM, single-agent CFZ as 30-minute IV infusion was well-tolerated at doses 20/36, 20/45 and 20/56 mg/m^2 with near complete proteasome inhibition. A dose level of 56 mg/m^2 is being expanded as the recommended phase 2 dose on 30-minute IV infusion schedule (14). All protocols using ≥36 mg/m^2 CFZ are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of CFZ in patients with relapsed and refractory MM was reported at the 2009 American Society of Hematology meeting. which demonstrated that CFZ can be safely administered to patients with substantial renal impairment (creatinine clearance [CrCl] < 30, including patients on dialysis) without dose adjustment. A phase I study of CFZ in patients with relapsed and refractory multiple myeloma and varying degrees of renal insufficiency has been initiated and preliminary results were reported at the 2009 American Society of Hematology meeting. (15) At the time of this preliminary analysis, 22 patients had been treated on the trial. Ten patients had CrCl ≥ 80 mL/min; 9 had CrCl 50-79 mL/min; 9 patients had creatinine clearance 30-49 mL/min; 9 patients had CrCl < 30 mL/min and 2 patients were on chronic dialysis. Adverse events in these patient groups were similar regardless of degree of renal dysfunction and included anemia, fatigue, and diarrhea as the most common adverse events observed.

These data indicate that CFZ does not exacerbate underlying renal dysfunction, and confirm the "pre-renal" etiology of the BUN/creatinine elevations observed with IV bolus CFZ.

Bendamustine is a drug which is approved and has been widely used in therapy for MM, NHL, breast cancer and other malignancies for 46 years. Based on several phase III trials, bendamustine received FDA approval for CLL (100 mg/m^2) and NHL (120 mg/m^2 d1 and d2) in the US. Due to the extensive experience and large amount of safety and toxicity data on bendamustine in hematologic malignancies, we think it is safe to use bendamustine dose

escalation up to 90 mg/m^2 in combination with CFZ for patients with newly diagnosed MM (16).

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

- Determine the MTD of CFZ in combination with bendamustine and dexamethasone

2.2 SECONDARY OBJECTIVES

- Determine the anti-tumor efficacy (ORR) of the combination of CFZ plus bendamustine and dexamethasone
- Determine DOR
- Determine progression free survival (PFS)
- Determine overall survival (OS).
- Determine time to Best Response
- Evaluate the safety and toxicity.
- Stem cell collection parameters after using the protocol as induction regimen

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a phase I/II, open label, single-center, non-randomized dose escalation study. The primary endpoint of this study is dose-limiting toxicity (DLT), to define the recommended phase II dose of CFZ in combination with bendamustine and dexamethasone in patients with newly diagnosed MM. This study defines the phase II dose as the combination at which 20% of treated patients would be predicted to experience DLT (as defined in Section 6.2).

Doses will be allocated to patients using a two-stage Up-and-Down dose escalation scheme, (17) (Storer's schema D, with a one-patient-per-level run-in) without intra-patient dose escalation. The details of this escalation are described in Section 12.6. A maximum of 28 patients will be enrolled. Using this schema, enough patients will be enrolled at a dose level near the MTD that the study will have the power of a typical stand-alone Phase 2 study.

The secondary endpoint is to determine preliminary evidence of efficacy of CFZ in combination with bendamustine and dexamethasone, including overall response rate, DOR, PFS, time to best response, , overall survival (OS) and evaluate the dose and toxicity. Patients will receive CFZ on days 1, 2, 8, 9, 15, and 16 every 28 days. Bendamustine will be given IV on days 1 and 2 with dose escalation up to 90 mg/m^2 and dexamethasone 20 mg PO or IV on 1, 2, 8, 9, 15, 16 and 22, 23 of each 28-day cycle. This regimen can also be used as induction treatment for autologous stem cell transplant.

Table 1. Dose Escalation Schema (all dose levels of Carfilzomib will start at 20mg/m^2 day 1 and 2 of cycle 1 as a lead in dose)

	Carfilzomib	**Bendamustine**	**Dexamethasone**
-1	27 mg/m^2	60 mg/m^2	20mg
1	27 mg/m^2	70 mg/m^2	20mg
2	36mg/m^2	70 mg/m^2	20mg
3	36 mg/m^2	90 mg/m^2	20mg
4	45 mg/m^2	90 mg/m^2	20mg
5	56mg/m^2	90 mg/m^2	20mg

For patients deemed to be ineligible for transplant by their treating physician, up to 8 cycles of CFZ, bendamustine and dexamethasone (CBd) will be administered. Upon completion, patients will be recommended to receive maintenance therapy off trial, with carfilzomib preferentially, or another regimen at the discretion of the treating physician. Patients who have started maintenance carfilzomib (36 mg/m^2 on days 1, 2, 15, 16) per the previous version of this protocol will be allowed to continue for up to 2 years.

For patients deemed to be eligible for transplantation by their treating physician, 4 cycles of CBd will be given followed by the collection of peripheral blood stem cells. A 4-week window is

allowed to accommodate scheduling of the stem cell collection. Peripheral blood stem cells should be mobilized with granulocyte-colony stimulating factor +/- plerixafor. Chemotherapy based mobilization techniques, (with Cytoxan for example) are not permitted in order to allow the comparison of the transplant and non-transplant arm. After stem cell collection, all patients will then receive additional 4 cycles of CBd followed by autologous stem cell transplant. In order to compare both arms, patients in the stem cell transplant arm should receive altogether 8 cycles CBd prior to transplant. After stem cell transplant, patients will be recommended to receive maintenance therapy off trial, with carfilzomib preferentially, or another regimen at the discretion of the treating physician. Patients who have started maintenance carfilzomib (36 mg/m^2 on days 1, 2, 15, 16) per the previous version of this protocol will be allowed to continue for up to 2 years.

3.2 NUMBER OF CENTERS

Columbia University Medical Center in New York, NY.

3.3 NUMBER OF SUBJECTS

26 evaluable subjects (men and women who are at least 18 years of age) will participate in this study.

3.4 ESTIMATED STUDY DURATION

The anticipated accrual duration is 2 years. The study duration is approximately 4 years.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

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

Disease-related:

- Patients must have histologically or cytologically confirmed symptomatic MM, Salmon-Durie Stage II or III, or International Staging System II or III or fulfill the CRAB criteria (see Appendix A, B). Patients should not have previously been treated. Finally, patients must meet at least one of the following parameters of measurable disease:
  - Bone marrow plasmacytosis with> 10% plasma cells, or sheets of plasma cells, or biopsy proven plasmacytoma which must be obtained within 6 weeks prior to registration.
  - Measurable levels of monoclonal protein (M-protein): ≥1 g/dL on serum protein electrophoresis (SPEP) or ≥200 mg of monoclonal light chain on a 24 hour urine protein electrophoresis (UPEP) or involved free light chain (FLC) ≥ 10 mg/dL (≥ 100 mg/L) which must be obtained within 4 weeks prior to registration.
    Serum and urine M-protein levels should be determined by electrophoresis rather than by quantitative immunoglobulin (Ig) measurement. Exceptions are made in cases in which the M-spike value may be deemed to be unreliable (e.g. co-migrating M-spike). In these cases, quantitative Ig should be used. To assess response and progression, however, SPEP values should only be compared to SPEP values and quantitative Ig values only to quantitative Ig values.
- Prior kyphoplasty, vertebroplasty, local radiation therapy for symptomatic bone lesions (e.g., uncontrolled pain or high risk of pathologic fracture) are permitted
- Patients are allowed up to two cycles of high dose steroids (maximum total dose of 320mg Dexamethasone or equivalent) if needed for symptomatic disease before study enrollment

Demographic:

1. Age ≥ 18 years
2. Life expectancy ≥ 3 months
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
4. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 μmol/L)
5. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
6. Hemoglobin ≥ 8 g/dL (80 g/L) (subjects may be receiving red blood cell [RBC] transfusions in accordance with institutional guidelines)
7. Platelet count ≥ 75×10^9/L (≥ 30×10^9/L if myeloma involvement in the bone marrow is > 50%)
8. CrCl ≥ 30 mL/minute, either measured or calculated using a standard formula (e.g., Cockcroft and Gault)
9. LVEF ≥ 40%. 2-D transthoracic ECHO is the preferred method of evaluation. MUGA is acceptable if ECHO is not available.

Ethical/Other

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception.
3. Male subjects must agree to practice contraception.

4.2 EXCLUSION CRITERIA

Disease-related

1. Patients who have had chemotherapy for MM. Exception: local radiation therapy for symptomatic bone lesions (e.g., uncontrolled pain or high risk of pathologic fracture).
2. Patients currently receiving high dose systemic steroids for treatment of MM in excess of 320mg total dose of dexamethasone or equivalent, patients who received an investigational agent within 5 half-lives of the agent.
3. Patients with non-measurable MM or primary plasma cell leukemia ($> 2.0 \times 10^9$/L circulating plasma cells by standard differential)

Concurrent Conditions

1. Pregnant or lactating females
2. Major surgery within 21 days prior to enrollment
3. Acute active infection requiring treatment should be under control
4. Known human immunodeficiency virus (HIV) infection
5. Known active hepatitis B or C infection
6. Unstable angina or myocardial infarction within 4 months prior to enrollment, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
7. Uncontrolled hypertension or uncontrolled diabetes
8. Uncontrolled, non-hematologic malignancy requiring active treatment.
9. Patients with known brain metastases (treated or not) will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs.
10. Significant neuropathy (Grades 3–4, or Grade 2 with pain)
11. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize CFZ), or similar chemical or biologic composition to Bendamustine or other agents used in the study.
12. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
13. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to enrollment
14. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

5 SUBJECT ENROLLMENT

Following registration, patients should begin the research treatment within one week. Issues that would cause research treatment delays should be discussed with the Investigator. If a patient does not receive study treatment following registration, the Study Coordinator should be contacted for required data submissions. Patients that do not receive any study treatment will not be evaluable for toxicity or response.

Each patient enrolled in the study will be registered in the CUMC's Clinical Trials Management Application (CTMA) at study entry. Each patient enrolled will be assigned a sequential study identifier by CTMA.

CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (i.e., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAJ2359 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (i.e. tissue, DNA, etc.) as applicable

- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (i.e., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (i.e., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc)
    - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "AAAJ2359 Complete Subject Registration Request (PHI)".

Upon Receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6 TREATMENT PROCEDURES

6.1 DRUG PREPARATION AND ADMINISTRATION

6.1.1 CARFILZOMIB

- CFZ for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with D5W for Injection to a final CFZ concentration of 2.0 mg/mL prior to administration. The dose will be calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.
- IV hydration will be given immediately prior to CFZ during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload (e.g. clinical examination).
- The infusion will be performed as per institutional guidelines.
- CFZ will be given as an IV infusion over 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of CFZ in Cycle 1 and following the dose on Cycle 2 Day 1. During these observation times, post dose IV hydration (up to 500 mL normal saline or other appropriate IV fluid formulation) may be given at the discretion of the treating physician. Subjects should be monitored periodically during this period for evidence of fluid overload.
- In subjects considered at risk for TLS, additional oral hydration may be considered at the Investigator's discretion. Subject should be monitored for evidence of fluid overload.
- No matter what target dose the subject will receive, days 1 and 2 doses in the first cycle will always be 20 mg/m^2. For example, if subject is scheduled to receive 27 mg/m^2, 20 mg/m^2 will be given on days 1 and 2 of cycle 1 only; followed by 27 mg/m^2 for all subsequent doses, same as 20/36 and 20/45 mg/m^2 and 20/56 mg/m^2 for the entire protocol.

6.1.2 BENDAMUSTINE

- Bendamustine is an FDA approved drug which will be provided by Teva Pharmaceuticals Industries Ltd (Petach Tikva, Israel)

Patients will receive Bendamustine 70 or 90 mg/m^2 IV on day 1 and 2 of each cycle.
Bendamustine will be administered as an infusion over 60 minutes. The infusion will be performed as per institutional guidelines
Please note: the flush is not included in the total recommended infusion times.

6.1.3 DEXAMETHASONE

- Dexamethasone will be administered 20 mg PO or IV on days 1, 2, 8, 9, 15,16, 22, 23. Dexamethasone will be administered prior to CFZ doses on days 1, 2, 8, 9, 15, 16.
- Decadron, Hexadrol, Dexameth, Dexone, DXM, others. Commercially available in 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tablets.

(Comments on Sections 6.2 and 6.3: in considering DLT definitions and dose modification guidelines for combination studies, we suggest using a rationally based approach when possible that takes into consideration the unique toxicities of each agent)

6.2 DEFINITION OF DOSE-LIMITING TOXICITY

Subjects will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute version 4.0 (Appendix C).

A DLT is defined as any of the below treatment emergent toxicities with attribution to one or more of the study drugs that occur during Cycle 1. If a DLT occurs during Cycle 1 the patient does not need to be removed from study. Toxicities that occur in subsequent cycles will be handled through dose modifications (Section 6.3) but will not affect the definition of MTD.

Non-hematologic:

- New onset of ≥ Grade 2 neuropathy with pain
- ≥ Any Grade 3 toxicity (excluding nausea, vomiting, diarrhea). Grade 3 Non-Hematologic AEs will be critically assessed by the Principal Investigator to determine attribution to study drugs. Attribution to study drug will define the DLT.
- ≥ Grade 3 nausea, vomiting, or diarrhea despite maximal antiemetic/antidiarrheal therapy and related to study drug
- ≥ Grade 4 fatigue lasting for ≥ 7 days
- 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.

Hematologic:

- Grade 4 neutropenia (ANC < 0.5 x 109/L) lasting for ≥ 7 days
- Febrile neutropenia (ANC < 0.50 x 109/L with a fever ≥ 38.3ºC)
- Grade 4 thrombocytopenia (platelets < 25.0 x 109/L) lasting ≥ 7 days despite dose delay
- Grade 3-4 thrombocytopenia associated with bleeding
- Any 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.

6.3 DOSE REDUCTIONS/ADJUSTMENTS

The dose of CFZ and bendamustine should be held and/or reduced according to the following guidelines:

6.3.1 DOSE REDUCTIONS FOR HEMATOLOGIC TOXICITIES:

Study drug will be withheld from subjects with: Grade 4 thrombocytopenia

Grade 4 anemia does not require the CFZ dose to be withheld. However, subjects should receive supportive measures in accordance with institutional guidelines.

The following table outlines the dose reduction guidelines for CFZ and bendamustine for thrombocytopenia and neutropenia:

Table 2. Dose Reduction Guidelines for Thrombocytopenia	
	Recommended Action
When Platelets:	**Carfilzomib and bendamustine**
Fall to $< 50 \times 10^9$/L	Interrupt both drugs, follow CBC weekly
Return to $\geq 75 \times 10^9$/L	Resume at full dose
Subsequently drop to $< 50 \times 10^9$/L	Interrupt both drugs, follow CBC weekly
Return to $\geq 75 \times 10^9$/L	Resume at 1 dose decrement on both drugs

Table 3. Dose Reduction Guidelines for Neutropenia	
	Recommended Action
When ANC	**Carfilzomib and bendamustine**
Falls to $< 0.5 \times 10^9$/L	Interrupt both drugs
	add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly
Returns to $> 1.0 \times 10^9$/L (if neutropenia was the only toxicity noted)	Resume at full dose on both drugs
Returns to $> 1.0 \times 10^9$/L (if other toxicity noted)	Resume at 1 dose decrement on both drugs
Subsequently drops to $< 0.5 \times 10^9$/L	Interrupt both drugs
Returns to $> 1.0 \times 10^9$/L	Resume at 1 dose decrement on both drugs

6.3.2 DOSE REDUCTIONS FOR NON-HEMATOLOGIC TOXICITIES

Both study drugs should be held for ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline.

6.3.2.1 CARFILZOMIB TREATMENT ADJUSTMENTS (NON-HEMATOLOGY TOXICITIES)

After resolution of the event to ≤ Grade 1 or return to baseline, if the AE was not treatment-related, subsequent treatment with CFZ may resume at full dose. If the event was treatment-related, subsequent treatment with CFZ will resume at one level dose reduction, i.e., to 27 mg/m^2 for subjects previously receiving 36 mg/m^2 and to 36 mg/m^2 for subjects previously receiving 45 mg/m^2. If toxicity continues or recurs, a second CFZ dose reduction may be permitted the discretion of the investigator. No more than two dose reductions will be permitted in an individual subject on study. If toxicity continues or recurs after two dose reductions, the subject should be removed from study.

If the subject tolerates the reduced dose for two cycles, subject may be dose escalated to the dose prior to reduction

If there is no resolution of toxicity after 4 weeks of withholding treatment (up to 3 weeks for infection treatment), the subject will be withdrawn from the study.

Table 4: Carfilzomib dose adjustment guidelines summary for non-hematologic toxicities

CTCAE Category	Adverse Event	Carfilzomib Treatment Adjustment
Allergic reaction/hypersensitivity	Grade 2 – 3	Hold until ≤ Grade 1, reinstitute at full dose.
	Grade 4	Discontinue
Metabolic	Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold CFZ until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection	Infection Grade 3 or 4	Hold CFZ until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions. If there is no resolution of toxicity after 3 weeks, the

		subject will be withdrawn from the study.
	Herpes zoster or simplex of any grade	Hold CFZ until lesions are dry. Reinstitute at full dose
Neurology	Grade 2 treatment emergent neuropathy with pain or Grade 3 neuropathy	Continue to dose. If neuropathy persists for more than two weeks hold CFZ until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement
Neurology	Grade 4 neuropathy	Discontinue
Renal	CrCl ≤ 15 mL/min	Hold until CrCl > 30 mL/minute; restart at 1 dose decrement
Cardiovascular	Congestive heart failure (CHF)	Any subject with symptoms of CHF, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, with the approval of the Onyx Medical Monitor, or the subject may be withdrawn from the study. or the subject may be withdrawn from the study. If no resolution after 2 weeks, the subject will be withdrawn from the study.
Venous Thrombosis/embolism	Grade 3 (uncomplicated) or Grade 4 (life-threatening)	Hold dose and start therapeutic anticoagulation; restart CFZ at Investigator's discretion (maintain dose level)
Others	Other non-hematologic toxicity assessed as CFZ-related ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

CFZ should be held for CrCl < 15 mL/min.

Table 5: Carfilzomib Dose Adjustment Guideline for Renal Dysfunction	
Renal Dysfunction	**Recommended Action**
Normal to mild (CrCl >50 mL/min)	Full dose
Moderate (CrCl 15–50 mL/min)	Full dose
Severe (CrCl ≤ 15 mL/min)	Hold CFZ until CrCl > 30 mL/min; restart at one level dose reduction

6.3.2.2 BENDAMUSTINE TREATMENT ADJUSTMENTS (NON-HEMATOLOGY TOXICITIES)

There are no reductions in the bendamustine dose if bendamustine is given at 70 mg/m^2. If AEs occur at 70 mg/m^2 that require holding bendamustine, the dose will remain the same once treatment resumes. If Bendamustine is held for more than 4 weeks, sites should contact the Principal Investigator to discuss the appropriateness of continuing the patient on study. If an AE occurs at 90 mg/m^2, the bendamustine dose will be reduced to 70 mg/m^2 according to the table.

Table 6. Bendamustine Dose Management based on non-hematologic toxicities	
Renal toxicity: CrCl ≤ 30 ml/minute	Hold bendamustine, if toxicity resolves to CrCl >30 ml/minute, restart the next cycle at the same dose level.
Hepatic toxicity assessed as bendamustine related: moderated hepatic impairment (AST or ALT ≥ 2.5 times ULN and total bilirubin ≥ 1.5 times ULN)	Hold bendamustine and follow. If the toxicity resolves to AST or ALT < 2.5 times ULN and total bilirubin < 1.5 times ULN, restart the next cycle at the next lower dose level. IF AE occurred under 70 mg/m2 of bendamustine and the dose is held for more than 4 weeks the patients will be off study.

6.3.2.3 Dexamethasone Treatment Adjustments

Table 7. Dexamethasone Treatment Adjustments		
CTCAE Category	**Adverse Event**	**Dexamethasone Treatment Adjustment**
Gastrointestinal (All patients will be treated with H2 Blockers, ranitidine, or omeprazole as per Section6.5.1)	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2	If symptoms persist despite prophylaxis, decrease dexamethasone dose by 50% permanently.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Restart at 50% of current dose. If

		symptoms persist, discontinue dexamethasone and do not resume
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema ≥ Grade 3	Diuretics as needed, and decrease dexamethasone dose by 25%, if edema persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Neurology	Confusion or Mood Alteration ≥ Grade 2 (interfering with function and/or ADLs)	Hold dexamethasone until symptoms resolve, restart at 50% of current dose. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Venous Thrombosis/embolism	Grade 3 (uncomplicated) or Grade 4 (life-threatening)	Hold dose and start therapeutic anticoagulation; restart CFZ at Investigator's discretion (maintain dose level)
Musculoskeletal	Muscle Weakness ≥ grade 2 (symptomatic and interfering with +/- function of ADLs)	Decrease dexamethasone dose by 25%, if weakness persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 25% decrements until levels are satisfactory.

6.3.2.4 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Study drugs do not need to be held in the following cases:

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals)
- Grade 3 fatigue (unless persisting for >14 days)
- Alopecia
- Lymphopenia

6.3.3 MISSED DOSES

Missed doses will not be replaced during a cycle. If a subject misses more than 1/3 doses of a treatment cycle for reasons other than toxicity, the subject will be discontinued.

6.3.4 CHANGES IN BODY SURFACE AREA

Dose adjustments do not need to be made for weight gains/losses of ≤ 10%. Subjects with a BSA of greater than 2.2 m^2 will receive a capped dose based upon a 2.2 m^2 BSA .

6.3.5 DOSING MODIFICATIONS

Dose modifications and delays different from those stated in the protocol, for management of toxicities, will be permitted at the discretion of the Investigator.

If the AE is not described in 6.3 and cannot be attributed to a specific drug e.g. (hyperglycemia and dexamethasone,) a dose reduction of both CFZ and bendamustine should be performed.

6.4 SAFETY CONSIDERATIONS

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

- A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.
- Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.
- Dexamethasone 20 mg PO or IV (part of treatment regimen) will be administered prior to all CFZ doses on days 1, 2, 7, 8, 15, 16.
- Acyclovir or similar should be given to all subjects with a history of herpes simplex or zoster, per institutional prophylaxis guidelines, unless contraindicated.
- CrCl changes are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with CFZ. Renal function must be monitored closely during treatment with CFZ. Serum chemistry values (basic metabolic panel including creatinine) must be obtained and reviewed prior to each dose of CFZ during Cycles 1 and 2. CFZ must be held for subjects with a CrCl < 15 mL/min at any time during study participation as outlined in Section 6.3.2.1 Table 5.
- Subjects with active or suspected infection of any kind that required systemic treatment should be treated with anti-infectives and the infection should be under control before the treatment starts.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts ≤ 50,000/mm3, treatment must be held. If platelet counts drop again to ≤ 50,000/mm3 on the subsequent cycle, the dose of CFZ and bendamustine must be reduced or held according to the Dose Reductions / Adjustments rules outlined in Section 6.3.1.

- Subjects should have anemia corrected in accordance with the Institutional guidelines.
- CFZ treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.
- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with CFZ. Prophylactic anticoagulation or antiplatelet therapy should be prescribed in conjunction with CFZ and dexamethasone . The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks. Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with CFZ in combination with dexamethasone
- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving CFZ. Monitor for signs and symptoms of TTP/HUS. Discontinue CFZ if diagnosis is suspected. If the diagnosis of TTP/HUS is confirmed, then discontinue CFZ permanently.
- Cases of posterior reversible encephalopathy (PRES) have occurred in patients receiving CFZ. Consider a neuroradiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue CFZ if PRES is confirmed.

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

TLS, which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with CFZ and bendamustine respectively.

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

6.4.1.1 HYDRATION AND FLUID MONITORING FOR CFZ

Oral and IV fluid hydration see section 6.1.1

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

6.4.1.2 BENDAMUSTINE ADMINISTRATION

Bendamustine should be administered intravenously over 60 minutes on day 1 and day 2 after CFZ infusion of each cycle, additional hydration will be decided per physician discretion.

6.4.1.3 LABORATORY MONITORING FOR TLS

Appropriate chemistries, including creatinine, and complete blood counts (CBC) with platelet count should be obtained and reviewed at day 1 on each cycle prior to study drug dosing. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the CFZ and bendamustine dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive **both** CFZ and bendamustine doses. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

6.4.1.4 CLINICAL MONITORING FOR TLS

Inform subjects 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 subjects to report such symptoms immediately and seek medical attention.

6.4.1.5 MANAGEMENT OF TUMOR LYSIS SYNDROME

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

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

6.5 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before Day 1 through the end of the subject's study participation. Any change in concomitant medications must be recorded.

If clinically indicated subjects should receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone (or trimethroprim/sulfamethoxazole if fluoroquinoles are contraindicated). In addition, subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis.

6.5.1 REQUIRED CONCOMITANT MEDICATIONS

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

Patients should be treated with H2 blockers, ranitidine, or omeprazole.

All patients need anti-emetics either IV or PO prior to the infusion of Bendamustine. It is recommended that patients have anti-emetics as PRN medication available.

6.5.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO twice daily (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

Subjects may receive RBC or platelet transfusions if clinically indicated in accordance with institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed with the Lead Principal Investigator

Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically during cycle 1.

Subjects may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed. Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines.

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

6.5.3 EXCLUDED CONCOMITANT MEDICATIONS

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

7 STUDY EVALUATION

If a cycle is missed or a subject's study treatment and/or testing days need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business and vacation travel plans, illness, transportation issues, holidays, family emergencies, etc.), a window of two (2) weeks is available for rescheduling the start of a cycle and procedures per the discretion of the investigator. A window of +/- 1 day is allowed for rescheduling study visits other than day 1 visits, at the discretion of the principal investigator. For cycle 1 day 1, labs (except for CBC with differential, BMP, HFP) do not need to be repeated if they were drawn within 8 days of day of treatment.

7.1 SCREENING (WITHIN ≤ 28 DAYS OF REGISTRATION UNLESS OTHERWISE NOTED)

- History & physical examination
- Vital signs, AE assessment
- Physical exam
- ECOG Performance status
- Baseline EKG and transthoracic Echocardiogram
- CBC (with differential and platelets): should be performed < 48 hours prior to day 1. These labs should be resulted prior to the start of the subsequent cycle.
- Optional correlative studies: 1 tube of blood
- Calcium, phosphorus, sodium, potassium, serum creatinine, BUN, uric acid, LDH
- Fasting glucose
- TSH
- Direct bilirubin
- AST/ALT
- Alkaline phosphatase
- Protein, Albumin
- Partial thromboplastin time (PTT)/PT/International Normalized Ratio (INR)
- SPEP including M-spike, FLC
- UPEP
- 24 hour urine collection for total protein
- Immunofixation of serum and urine
- Bone marrow aspirate/biopsy, cytogenetics (may be done within 6 weeks)
- Beta 2 microglobulin
- Quantitative Immunoglobulins (IgG, IgA, IgM)
- Skeletal Survey (can be done within 8 weeks)
- CXR
- DEXA Scan hip and spine
- Pregnancy test: Women of childbearing potential must have a negative serum or urine pregnancy test within 10-14 days and 24 hours of starting study drug.
- Urinary collagen type 1 cross-linked N-telopeptide (NTX)
- Serum Collagen type 1 cross-linked C-telopeptide (CTX)

7.2 DURING STUDY TREATMENT

Day 1 of each cycle (q4 weeks)

- History & physical examination
- Vital signs, AE assessment

- Physical exam
- ECOG Performance status
- CBC (with differential and platelets): Results of day 1, 8, 15 of each cycle should be evaluated prior to start of drug treatment.
- Optional correlative studies: 1 tube of blood
- Calcium, phosphorus, sodium, potassium, serum creatinine, BUN, uric acid, LDH: Results of day 1, 8, 15 of each cycle should be evaluated prior to start of drug treatment
- Total bilirubin
- AST/ALT
- Alkaline phosphatase
- Protein, albumin
- PTT/PT/INR
- SPEP including M-spike, FLC
- UPEP
- 24 hour urine collection for total protein
- Quantitative Immunoglobulins (IgG, IgA, IgM)
- Pregnancy test: Tests must be repeated every 4 weeks while on study treatment (every 14 days for women with irregular menstrual cycles) and 4 weeks after the last dose of anti-myeloma therapy.
- Urinary collagen type 1 cross-linked N-telopeptide (NTX)
- Serum Collagen type 1 cross-linked C-telopeptide (CTX)

7.3 DISCONTINUATION OF STUDY TREATMENT

The following studies are required at the time of discontinuation of study treatment.

- History & physical examination
- Vital signs, AE assessment
- Physical exam
- Performance status
- CBC (with differential and platelets)
- Optional correlative studies: 1 tube of blood
- Calcium, phosphorus, sodium, potassium, serum creatinine, BUN, uric acid, LDH
- Total bilirubin
- AST/ALT
- Alkaline phosphatase
- Protein, albumin
- PTT/PT/INR
- SPEP including M-spike, FLC
- UPEP
- 24 hour urine collection for total protein
- Quantitative Immunoglobulins (IgG, IgA, IgM)
- Pregnancy test: Tests must be repeated every 4 weeks while on study treatment (every 14 days for women with irregular menstrual cycles) and 4 weeks after the last dose of anti-myeloma therapy.
- Urinary collagen type 1 cross-linked N-telopeptide (NTX)
- Serum Collagen type 1 cross-linked C-telopeptide (CTX)
- Bone Marrow Aspiration and Biopsy with cytogenetic assessment
- Assessment of minimal residual disease by Multiparameter Flow Cytometry

7.4 FOLLOW-UP

- History & physical examination
- Physical exam
- ECOG Performance status
- CBC (with differential and platelets)
- Calcium, phosphorus, sodium, potassium, serum creatinine, BUN
- SPEP including M-spike, FLC
- UPEP
- 24 hour urine collection for total protein
- Immunofixation of serum and urine
- Quantitative Immunoglobulins (IgG, IgA, IgM)

7.5 DURATION OF STUDY TREATMENT

Study treatment will be given until progression of disease. This will consist of 8 cycles of induction therapy with CBd followed by stem cell transplant in those eligible. After stem cell transplant or completion of CBd in those not eligible for transplant, carfilzomib maintenance is recommended but will be given outside the trial at the discretion of the treating physician. Patients who progress at any time will end protocol treatment. Patients will come off study treatment for unacceptable toxicity, patient refusal, pregnancy, non-compliance or any Grade 3/4 toxicity that is severe and in the opinion of the sub-investigator dangerous to the patient.

Only patients that completed at least 2 cycles of treatment will be considered evaluable and included in the analysis.

7.6 DURATION OF FOLLOW–UP

Patient will be followed until death. Patients removed from study for unacceptable AEs will be monitored until resolution or stabilization of the AE.

8 STUDY CALENDAR

All pre-study scans, x-rays, biopsy, CBC (with differential and platelet count) and all required pre-study chemistries to be done up to 4 weeks before registration. If a cycle needs to be delayed due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business and vacation travel plans, illness, transportation issues, holidays, family emergencies, etc.), a two week delay is available for rescheduling of day 1 treatment and procedures per the discretion of the treating physician investigator. A 4-week window is allowed between cycles 4 and 5 for transplant eligible subjects in order to accommodate for scheduling of stem cell harvest. After discontinuation of therapy, subjects should be followed every 3 months (± 1 month) for the first two years, every 6 months (± 1 month) for years 2-5, and annually thereafter until death. See footnote 17 for study visit windows. Laboratory results (day 1, 8, 15 of each cycle) should be evaluated prior to start of drug treatment.

Study parameters	**Baseline**	**Cycle 1-8[2,17]**			**Discontinuation of therapy[12]**	**Follow-up[13]**
	D-28 to D-1	**D1[18]**	**D8**	**D15**		
History & Physical Examination, Height & Weight[1]	X	X			X	X
VS, AE assessment		X			X	
Performance Status (ECOG)	X	X			X	X
CBC (with differential and platelets)[16]	X	X	X	X	X	X
Basic Metabolic Panel (with creatinine)[16]	X	X	X	X	X	X
Phosphorus	X	X	X	X	X	X
Baseline EKG and TTE	X					
Glucose	X[19]					
Total Bilirubin[16]	X[18]	X	X	X	X	
AST/ALT[16]	X	X	X	X		
Alkaline Phosphatase[16]	X	X	X	X		
Albumin[16]	X	X				

Study parameters	Baseline	Cycle 1-8[2,17]			Discontinuation of therapy[12]	Follow-up[13]
	D-28 to D-1	D1[18]	D8	D15		
TSH	X					
PT, PTT, INR	X	X				
Uric Acid	X	X	X	X	X	
LDH	X	X	X	X	X	
SPEP[3,7]	X	X			X	X
Serum FLCs[3,7]	X	X			X	X
UPEP[3,7]	X	X			X	X
24 hour urine collection for total protein[7]	X	X			X	X
Immunofixation of serum and urine[7]	X	X			X	X
Bone Marrow Aspirate/Biopsy[4] May also be used for research purposes	X[7]				X[4]	
Cytogenetics (bone marrow)	X				X	
Beta 2 Microglobulin	X	X			X	
Quantitative Immunoglobulins[5]	X	X			X	
Pregnancy test[6]	X	X				
DEXA Scan Hip and Spine[14]	X				X	
C-telopeptide, beta cross-linked, serum (CTX)	X	X			X	

Study parameters	Baseline	Cycle 1-8[2,17]			Discontinuation of therapy[12]	Follow-up[13]
	D-28 to D-1	D1[18]	D8	D15		
Collagen cross-linked, urine (NTX)	X	X			X	
Correlative serum sample[20] (optional;1 gold top tube with at least 5ml)	X	X			X	
Minimal Residual Disease Assessment by Flow Cytometry[15]					X	
For Stem Cell Transplantation Candidates ONLY: Mobilization will occur after cycle 4						
X-ray: skeletal survey with CXR[8]	X				X	
Carfilzomib		X[9]	X[9]	X[9]		
Bendamustine		X[10]				
Dexamethasone		X[11]	X[11]	X[11]		

1. Physical exam including graded neuropathy, Height is obtained at baseline only; weight is measured at baseline, day 1 of each treatment cycle, at discontinuation of therapy, and at follow-up assessment visits.
2. Results for VS, performance status, CBC with differential, chemistry with phosphorus should be evaluated prior to start of drug treatment.
3. After baseline testing, the appropriate marker should be followed to assess response. This might be either SPEP, FLCs and/or UPEP. Serum immunofixation should be performed in patients in which the M-protein spike became undetectable.
4. Bone marrow aspirate/biopsy is obtained at the beginning and at the end of treatment, and at the following events: achievement of CR, relapse, PD. One additional green top tube (5mL) of aspirate and/or leftover biopsy material will be used by Dr. Lentzsch's lab and will require opt-in consent as part of the ICF process
5. Includes lgG, IgA, IgM.
6. All FCBP should complete a serum pregnancy test within 7 days prior to day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1). Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential."
7. Required to document CR or PD
8. Skeletal surveys in general are poor tools for following disease on a short term basis. Therefore, a skeletal survey should be performed at discontinuation of study treatment, for symptoms that would suggest new bony lesions, and if deemed necessary by the sub-investigator, to be used as a tool for response assessment.

9. CFZ is administered IV on day1, 2, 8 ,9,15, and 16 of cycles 1-8.
10. Bendamustine is administered IV on days 1 and 2 of cycles 1-8.
11. Dexamethasone is administered IV or PO on days 1, 2, 8, 9, 15, 16, 22, 23 of cycles 1-8.
12. To be performed within 4 weeks after completion of the last cycle.
13. After discontinuation of therapy, subjects should be followed every 3 months (± 1 month) for the first two years, every 6 months (± 1 month) for years 2-5, and annually thereafter.
14. To be performed at baseline or within one year before C1D1; and at the end of treatment or after 1 year, whichever comes first.
15. Please note that MRD will be tested at best response.
16. CBC and serum chemistry (BMP & HFP) need to be drawn on days 1, 8, and 15 of cycles 1-8 and days 1 and 15 of maintenance cycles; all other study labs do not need to be drawn if they were drawn within 8 days of C1 D1.
17. A window of +/- 1 day is allowed for rescheduling study visits other than day 1 visits (labs should be drawn on day of chemo as indicated), at the discretion of the principal investigator.
18. At baseline, order direct bilirubin for eligibility.
19. At baseline, this is a fasting glucose
20. Correlative sample should be taken with subject fasting and in the morning at screening, on day 1 of each cycle, and at discontinuation.
21. Maintenance phase begins at Cycle 9 and subjects may receive maintenance treatments for a maximum of 2 years.
22. CFZ is administered IV on days 1, 2, 15, and 16 of maintenance cycles
23. Dexamethasone is administered IV or PO on days 1, 2, 15, and 16 of maintenance cycles.

9 STUDY DISCOTINUATION

9.1 DISCONTINUATION OF STUDY TREATMENT

The studies are required at the time of discontinuation of study treatment are listed on the study calendar.

9.2 FOLLOWUP AFTER DISCONTINUATION OF STUDY TREATMENT

After discontinuation of study treatment, patients should be followed for disease progression and death every three months (± 1 month) for the first 2 years. Follow-up can be performed by a local physician/oncologist. Data will be collected by the research team from the treating physician.

10 MEASUREMENT OF EFFECT

Definitions of response are based on the latest International Myeloma Working Group (IMWG) uniform response criteria as published in Blood in May 2011. (18)

10.1 DEFINITIONS

10.1.1 M-protein

Synonyms include M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, and M-component.

10.1.2 Response Terms

The following response terms will be used: CR, sCR, VGPR, PR, SD or NR, plateau, and progression or relapse. See section 10.3 for Response Criteria.

10.1.3 Measurable Disease

Patients who have a measurable serum or urine M-protein. A “measurable” serum M-protein is >1 g/dL and a ‘measurable” urine M-spike is >200 mg/24 hours or involved FLC ≥ 10 mg/dL (≥ 100 mg/L).

10.1.4 Evaluable Disease

Patients who do not have a “measurable” serum or urine M-spike.

10.1.5 Oligosecretory Myeloma

Patients with MM who have NEVER had “measurable” disease, but have had a detectable monoclonal protein in their serum and/or urine.

10.2 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

10.2.1 Bone Radiographs

Not required to document response. If bone radiographs are obtained, their findings must be consistent with the bone response criteria.

10.2.2 Bone Progression

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

10.2.3 Clarification of Test Indications

The percentage reductions and/or increments of the M-protein in the serum and urine required for sCR, VGPR, PR, plateau, and progression (see section 10.3) apply to only those patients with "measurable" values of the serum and the urine. Immunofixation studies of both serum and urine are to document CR regardless of registration values.

10.2.4 Monoclonal Protein Considerations

Serum and urine M-protein levels should be determined by electrophoresis rather than by quantitative Ig measurement. Exceptions are made in cases in which the M-spike value may be deemed to be unreliable. In these cases, quantitative Ig should be used. To assess response and progression, however, SPEP values should only be compared to SPEP values and quantitative Ig values only to quantitative Ig values. Small migrating M-proteins (usually IgA M-proteins) are contaminated by normal γ-globulins that are often greater in quantity than the M-spike itself. In cases in which the M-spike is large and narrow on agarose (some specimens >4 g/dL) the actual Ig level (by greater than 1500 mg/dL) can be underestimated due to technical staining properties of the agarose gel.

10.3 RESPONSE CRITERIA

10.3.1 Complete Response (CR)

Patients who have complete disappearance of an M-protein and no evidence of MM in the bone marrow are considered to have CR. To be considered CR, patients must meet all of the following criteria:

- Complete disappearance of M-protein from serum: There must be no detectable serum M-protein on immunofixation.
- Complete disappearance of M-protein from urine: There must be no detectable M-protein on immunofixation.
- Bone marrow biopsy demonstrating <5% plasma cells. No increase in size or number of lytic bone lesions.
- Disappearance of soft tissue plasmacytomas.
- There must be no evidence of PD, including no increase in the number/size of lytic bone lesions, or by other parameters.

10.3.2 Stringent Complete Response (sCR)

In addition to CR criteria (defined above), these patients have a normal FLC ratio and have no

clonal cells by bone marrow immunohistochemistry or immunofluorescence. Clonal cells detected in the bone marrow by immunohistochemistry or immunofluorescence are considered abnormal if there is a kappa/lambda ratio of >4:1 or <1:2 after examination of a minimum of 100 cells.

10.3.3 VGPR

Serum and urine M-protein detectable by immunofixation but not on electrophoresis or at least a 90% reduction in serum M-protein with a urine M-protein <100 mg/24 hours.

10.3.4 Partial Response (PR)

PR requires all of the following:

- ≥50% reduction in the level of the serum monoclonal paraprotein.
- Reduction in 24-hour M-protein either by ≥90% or to <200 mg.
- If the serum and urine M-protein are not measurable (i.e., <1.0 g/dL at registration), a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of M-protein criteria.
- If serum and urine M-protein are not measurable and serum FLC are also not measurable, a ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy must be documented provided that baseline bone marrow percentage was ≥ to 30%.
- ≥50% reduction in size of soft tissue plasmacytoma (by radiography or clinical examination).
- No increase in the number or size of lytic bone lesions (development of a compression fracture does not exclude response).
- As above, there must be no evidence of PD by other parameters. Patients who meet some, but not all, of the criteria for PR are classified as MR, providing the remaining criteria satisfy the requirements for MR.

10.3.5 Minor Response (MR)

Adopted from the EBMT criteria[19] requires **all** of the following:

- 25% but <49% reduction of serum M protein and reduction in 24-hour urine M-protein by 50 to 89% which still exceeds 200 mg per 24-hour.
- In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required.
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

10.3.6 Stable Disease (SD)

Failure to meet response criteria outlined above. This is considered SD or no response.

10.3.7 Disease Plateau

(Note: plateau is not a distinct response category)
This category will not be applied to patients with non-secretory or oligosecretory myeloma. A patient in CR, PR, or MR (see Sections above) will be further classified as being in plateau if the following criteria are met:

- Serum and/or urine M-protein values must be stable for a period of at least 12 weeks. Stable values are defined as a continued CR or in the case of patients with residual M-protein, absence of progression.
- Any patient with measurable disease who is continuing to have "improvement" in serum or urine response criteria would not be considered in plateau. "Improvement" is defined as a decrease in the serum or urine M spike by >25% in a 4 week interval, with absolute decrements of at least 0.5 g/dL for serum and 200 mg/24 hours for urine. He or she might be approaching a better level of response, and therefore, should not yet be deemed in plateau until the improvement has leveled off.
- DATE of plateau will be the first date of suspected plateau. Date cannot be assigned until CONFIRMATION that the patient is in plateau (that is at least 12 weeks later).

10.3.8 Relapse or Progression

Patients will be considered to have relapse or progression if one of the following criteria is met. The investigation that qualified as progression should be repeated and verified on a subsequent occasion only if treating physician deems it clinically necessary. It is strongly recommended that the immunofixation be repeated on patients who are being considered as "relapsed" from CR status. PD should be used for calculation of time to progression and PFS end points for all patients including those in CR (including primary PD and disease progression on or off study treatment).

Requires any or more of the following:
Increase of >25% from lowest response value in any of the following:

- Serum M-component and/or (the absolute increase must be >0.5 g/dL)
- Urine M-component and/or (the absolute increased must be >200mg/24hr)
- Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL.
- Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage: the absolute % must be at least 10%.
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

Patients with a global deterioration of health status requiring discontinuation of study treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of study treatment.

10.3.9 Clinical Relapse

Requires one or more of the following:

- Direct indicators of increasing disease and/or end organ dysfunction. It is not used in calculation of TTP or PFS, but is listed here as something that can be reported optionally for use in clinical practice.
- Development of new soft tissue plasmacytomas or bone lesions.

- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion.
- Hypercalcemia (11.5 mg/dL) [2.65 mmol/L].
- Decrease in hemoglobin >2g/dL [1.25 mmol/L].
- Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more].

10.4 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

10.4.1 Confirmed Response

In order to be classified as a response, confirmation of serum M-protein results must be made by verification on two consecutive determinations 4-6 weeks apart.

- In patients whose M-protein is not measurable, serum FLCs will be followed to access response as noted above. If serum FLCs are not measurable, bone marrow biopsy will be performed to document response after every two cycle per study calendar.
- Bone marrow aspirate and biopsy are not required to document or confirm PR or, MR. Bone Marrow biopsy and aspiration will be required to confirm CR, PD, or relapse. Exception: for patients with non-secretory and oligosecretory myeloma only, a bone marrow is required to document all response categories including progression.

10.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the study treatment started).

10.4.3 Duration of Disease Free Survival

The duration from the start of CR to the time of relapse from CR. DFS applies only to patients in complete CR.

10.4.4 Duration of Stable Disease (SD)

SD is measured from the start of study treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the study treatment started.

10.4.5 Progression Free Survival (PFS)

PFS is defined as the duration of time from start of study treatment to time of progression or death, whichever occurs first.

10.4.6 Time to Progression (TTP)

Duration from start of treatment to disease progression, with deaths from causes other than progression censored.

10.5 RESPONSE REVIEW

The CUMC Data Safety and Monitoring Plan includes provisions for independent review and confirmation of responding patients on clinical trials. All reported responders on this trial will be subject to independent review and confirmation.

11 ADVERSE EVENTS

11.1 ADVERSE EVENT DEFINITIONS

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

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

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

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

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

Table 8: Severity table of Adverse Events additional to CTCAE

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

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

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

- Yes: The event is suspected to be related if:
  - there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
  - there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
  - the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
  - the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures
- No:
  - the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
  - the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
  - the event is unlikely to be related to the investigational product(s)

11.2 ADVERSE EVENTS REPORTING PROCEDURES

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

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

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

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

All Grade 3 and 4 laboratory abnormalities must be recorded as AEs on the CRF. Grade 1 and 2 abnormalities should only be recorded if they require treatment or are otherwise considered clinically significant by the Investigator.

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

11.3 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is one that meets the following criteria:

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

An **Unanticipated Problem (UP)** is any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such 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

A **Suspected Adverse Reaction (SAR)** is any AE for which there is a reasonable possibility that it was caused by the drug.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The S-I must report the following SARs:

- To the FDA, as soon as possible, but no later than 7 calendar days after the S-I's initial receipt of the information, any unexpected fatal or life-threatening SAR.
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that information qualifies for reporting, in an IND safety report, any SAR that is both serious and unexpected.
- To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies, whether or not conducted under an IND or by the S-I, that suggest a significant risk in humans exposed to the drug.
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any findings from animal or *in vitro* testing, whether or not conducted by the S-I, that suggest a significant risk in humans exposed to the drug.
- To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting, any clinically important increase in the rate of a Serious SAR over that listed in the protocol or Investigator Brochure.
- Expected SAEs and AEs should be included in the IND Annual Reports.

  Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

To the CUMC IRB:

1. Unanticipated Problems (UPs) must be reported promptly, but not later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP.
2. Expected AEs must be reported at the time of continuing review of a protocol.

11.4 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study, must be reported to the sponsor as an SAE. All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. SAEs for screen failures should not be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

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

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

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

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

Expedited Reporting by Investigator to Teva

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

The initial report must be as complete as possible, at a minimum including the SAE term(s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up MEDWATCH or CIOMS I form, and submitted to Teva in the same timelines as outlined above.

All other SAE's will be sent to Teva. on a biannual basis in the form of a line listing in English. The line listing must include the following information; patient initials, date of birth, sex, SAE onset date, SAE stop date, event name (term), outcome, date of first dose of study drug(s), date of last dose of study drug(s) prior to the event, action taken with study drug(s)the Investigator's assessment of causality (relationship to Bendamustine), and the Investigator's assessment of expectedness to Bendamustine. The sponsor reserves the right to review the CRFs or source documents in response to any inquires by regulatory agencies that the sponsor may receive.

Teva Drug Safety and Pharmacovigilance Contact Information:

Teva Fax: (215) 619-3825
e-mail: us.clinops.sae@tevapharm.com

Expedited Reporting by Investigator to Onyx

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

The initial report must be as complete as possible, at a minimum including the SAE term(s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up MEDWATCH or CIOMS I form, and submitted to Onyx in the same timelines as outlined above. The Onyx protocol number (IST-CAR-579) and the institutional protocol number should be included on all reports to Onyx.

All other SAE's will be sent to Onyx in real time and must be submitted on a FDA 3500A MEDWATCH or CIOMS I (for EU studies) form. This form must be completed and supplied to Onyx in English. The report must include the following information; patient initials, date of birth, sex, SAE onset date, SAE stop date, event name (term), outcome, date of first dose of study drug(s), date of last dose of study drug(s) prior to the event, action taken with study drug(s) the Investigator's assessment of causality (relationship to carfilzomib), and the Investigator's assessment of expectedness to carfilzomib. The sponsor reserves the right to review the CRFs or source documents in response to any inquires by regulatory agencies that the sponsor may receive.

Onyx Drug Safety and Pharmacovigilance Contact Information:

Onyx Drug Safety Fax: 650.266.0501 or 800-783-7954
SAE hotline: (650)-266-2501)
e-mail: AdverseEvents@onyx.com

11.5 PREGNANCY

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

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

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

12 STATISTICAL CONSIDERATIONS

12.1 STUDY DESIGN/ENDPOINTS

This is a phase I/II, open label, non-randomized dose escalation study. The primary endpoint of this study is to define the recommended phase II dose of CFZ in combination with bendamustine and dexamethasone in patients with newly diagnosed MM. This study defines the phase II dose as the combination at which 20% of treated patients would be predicted to experience DLT (as defined in Section 11.1). The study design allows for sufficient numbers of patients to be accrued at a dose level near the MTD that this present study will have the power of a typical phase 2 study.

Doses will be allocated to patients using a two-stage Up-and-Down dose escalation scheme, (17) (Storer's schema D, with a one-patient-per-level run-in) without intra-patient dose escalation. The initial protocol proposed a maximum sample size of 34 patients to be accrued. As of 18APR2017, a total of 14 evaluable (received at least 2 cycles of treatment) patients have been enrolled in the trial. Out of 14 patients, 4 patients were allocated to dose level 1 to 4 and 10 patients were allocated to dose level 5 (maximum dose level). Given that none of the patients have yet experienced a DLT, we considered a sample size re-calculation that would shorten the length of the trial. Given the current trend, it is expected to see at most 1 DLT at the maximum dose level 5. By planning to enroll 12 additional patients at level 5, we can ensure that the 90% confidence interval (CI) for the DLT rate will be below the targeted DLT rate of 20%, providing acceptable insurance that the toxicity at this dose level is at most 20%. With 22 patients enrolled at dose level 5, the 90% CIs are as follows: for 0 DLT observed: (0, 0.13); for 1 DLT observed: (0, 0.20). We re-estimated the sample size to 26 evaluable patients, with a maximum of 2 additional patients that might not complete the required 2 cycles of treatment. Therefore, the new targeted accrual is 28 patients, lower as compared to the initial 34.

12.2 STRATIFICATION FACTORS

There are no planned stratification factors.

12.3 SAMPLE SIZE

Approximately 26 evaluable subjects (men and women who are at least 18 years of age) will participate in this study.

12.4 ANALYSIS OF PRIMARY ENDPOINT

The primary endpoint of this trial is DLT, defined as a dichotomous variable in Section (11.1). The proportion of patients at each dose level tested who experience DLT will be estimated with an exact 90% binomial confidence interval. As a secondary analysis, depending on which doses are tested, a logistic regression model of DLT as a function of the doses of the two drugs, treated as continuous variables, may be fit to the data. The up-and-down dose escalation scheme presents a recommended phase II dose at the end of study.

12.5 ANALYSIS OF SECONDARY ENDPOINTS

- Determine preliminary evidence of efficacy (ORR) of the combination of CFZ in combination with bendamustine and dexamethasone: The proportion of responders (defined in Section 10.3) at each dose will be estimated along with 95% exact binomial confidence intervals. Fisher's exact test (at a significance level of 0.05) will be used to test the null hypothesis that there is no relationship between treatment combination and response. Depending on which doses are tested, a logistic regression model of response as a function of the doses of the two drugs, treated as continuous variables, may be fit to the data.
- Time to progression (TTP) will be analyzed by means of a product limit (Kaplan-Meier) estimator of the survival function at each dose. The median TTP will be estimated, along with a 95% confidence interval. If patients are enrolled primarily at higher doses, median TTP will not be estimable at lower doses. If all enrollments (after the rapid escalation phase) is at the upper two doses, TTP estimation will also be performed on all patients without regards to dose.
- Duration of response (DOR): Analysis plan is similar to that of TTP.
- Progression free survival (PFS): Analysis plan is similar to that of TTP.
- Overall survival (OS): Analysis plan is similar to that of TTP.
- Evaluate the safety and toxicity: In addition to the primary analysis of DLT, AEs will be tabulated at each dose level. SAEs will be tabulated by dose and assessed relation to treatment (not related; unlikely related; possibly related; probably related; related).
- Stem cell collection parameters after using the protocol as induction regimen

12.6 DOSE ASSIGNMENT ALGORITHM

The first patient will be enrolled at Level 1 (all levels correspond to Table 1). This is the first stage of dose escalation. If that patient does not experience a Grade 2 toxicity (at least possibly related to treatment), the second patient will be enrolled at the next higher level. The first patient at each dose level must complete the first cycle prior to enrolling the next patient at the next dose level. Once the first Grade 2 (or worse) toxicity at least possibly related to treatment is observed, the dose is decremented by one level, and five patients are treated at that dose. If 0/5 patients experience DLT (11.1), the next cohort of 5 is treated at the next higher level. If 1/5 patients experience DLT, the next cohort of 5 is treated at the same level. If >1/5 patients experience DLT, the next cohort of 5 is treated at the next lower level. If 0/5 patients in a cohort experience DLT at Level 4, the next cohort is treated at Level 4. If >1/5 patients experience DLT at Level 1, accrual to the trial will be paused so that amendments to the treatment plan can be considered. This algorithm is repeated until six cohorts are completed (for a maximum accrual of 4+6×5=34).(17) The first patient will be enrolled at Level 1.

Table 1. Dose Escalation Schema

	Carfilzomib	Bendamustine	Dexamethasone
-1	27 mg/m^2	50 mg/m^2	20 mg
1	27 mg/m^2	70 mg/m^2	20 mg
2	36 mg/m^2	70 mg/m^2	20 mg

3	36 mg/m^2	90 mg/m^2	20 mg
4	45 mg/m^2	90 mg/m^2	20 mg
5	56 mg/m^2	90 mg/m^2	20 mg

12.7 JUSTIFICATION OF DESIGN

The design of the trial is justified in terms of the primary objective. The operating characteristics of the dose-allocation algorithm were investigated by Monte Carlo simulation. It was assumed that the true probability of toxicity at each dose was described by Table 9.

Table 9. Dose-specific probabilities of DLT assumed for Monte Carlo simulation to assess the operating characteristics.

	True P(DLT)		
Dose combination	Simulation 1	Simulation 2	Simulation 3
1	0.05	0.07	0.07
2	0.10	0.14	0.14
3	0.15	0.21	0.21
4	0.20	0.28	0.35
5	0.25	0.35	0.49

The operating characteristics, assuming the probabilities of toxicity in Table 9, are presented in Figure 1. In each row, the left frame presents the percentage of simulated trial choosing a given dose level as the phase II recommended dose. In the top row (Simulation 1), it is seen that 85% of trials choose either Dose Level 3 or 4 (within 5% of the target combination, Level 4). All simulation scenarios control the median proportion of observed DLTs to less than 20%. In all three simulation sets, an average of at least 20 patients is treated within one level of the true target dose.

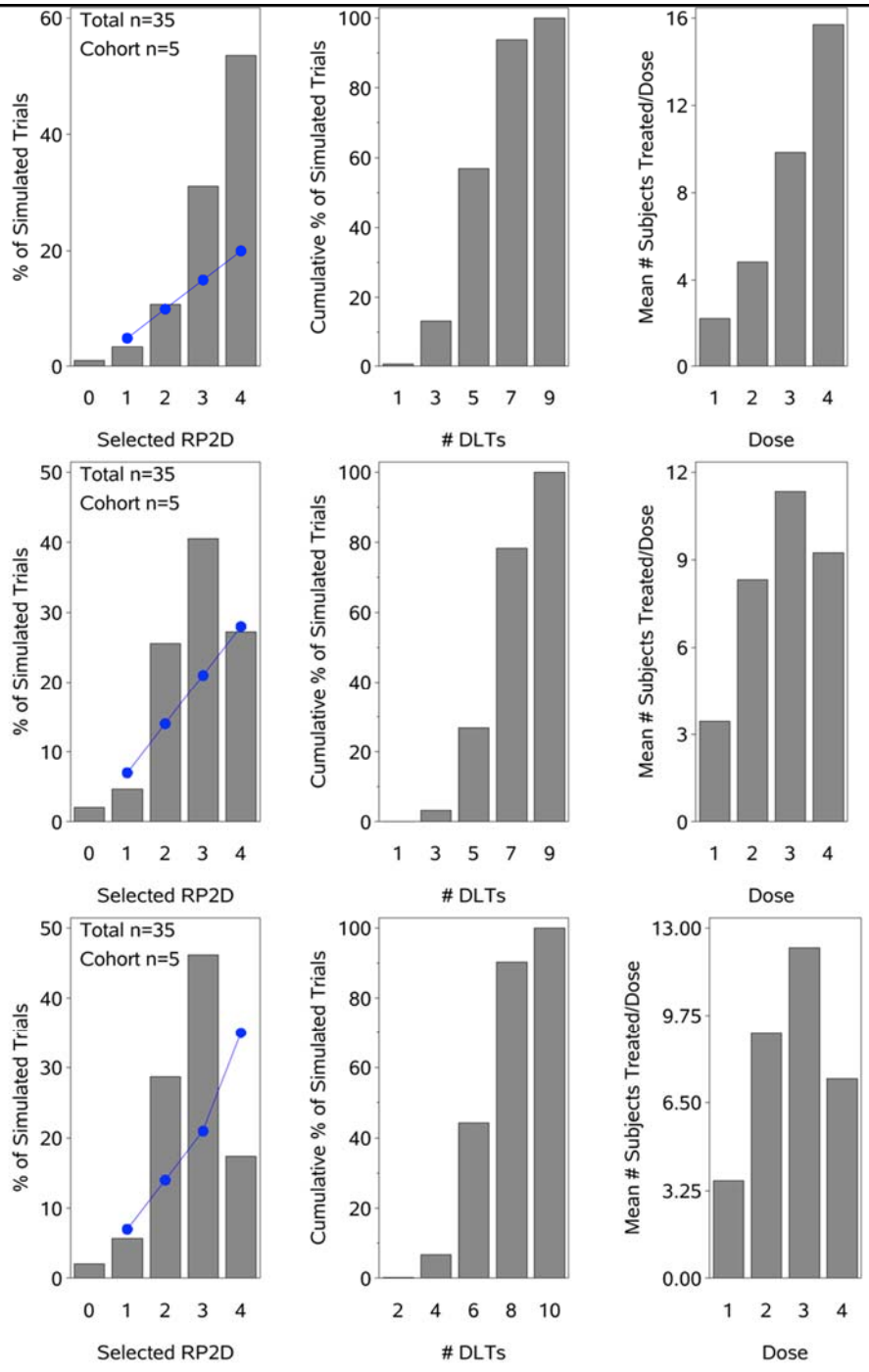

Figure 1 Operating characteristics of design estimated from Monte Carlo simulations of trial design. From left to right, histograms of the phase II doses the trial selects, expected number of observed DLTs out of 35 patients treated, and distribution of numbers of patients treated at each combination. The line in the left frame indicates the true P (DLT). From top to bottom, the frames represent Simulations 1, 2 and 3 of Table 9.

13 INVESTIGATIONAL PRODUCT

13.1 CARFILZOMIB DESCRIPTION

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

13.2 FORMULATION

CFZ for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of CFZ Free Base in 10 mm sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

13.3 STORAGE

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

13.4 ACCOUNTABILITY

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

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

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

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

14 CORRELATIVE STUDIES

Multiple Myeloma is associated with increased osteoclast activity resulting in increased bone resorption. Concurrent myeloma cells secrete factors that inhibit the activity of osteoblast resulting in pure lytic lesions. The restoration of the balance between increased bone resorption and decreased bone formation is therefore a critical goal in the treatment of MM. Bisphosphonates such as zoledronic acid (ZA) have shown to inhibit osteoclast activity. Proteasome inhibitors such as bortezomib have been shown to be osteoblast inducers resulting in increased bone formation.

We hypothesize that the more potent proteasome inhibitor carfilzomib induces osteoblast activity and subsequently bone formation. This should result in increased bone density, bone quality and increase of serum bone formation markers such as osteocalcin and P1NP in our study population. We plan to measure the bone resorption markers at baseline, day 1 of each cycle, andat treatment discontinuation.. The bone quality at the distal radius and tibia will be measured by high resolution peripheral QCT (HRpQCT) at baseline and the end of the study or after 1 year whichever comes first. The bone density at the hip and spine will be measured by DEXA scan at the same time points. This will be performed as standard of care and is well established in multiple myeloma treatment. The escalating dose of CFZ will give us information whether CFZ enhances bone formation in a dose-dependent manner. By HRpQCT, we expect to see increases in total and trabecular density and possibly in trabecular and cortical thickness, with decreases in trabecular separation. We do not anticipate that bendamustine has any effect on bone formation. Further most of the patients will receive Zoledronic Acid (ZA) that inhibits osteoclast activity and therefore only affects bone resorption markers such CTX and TRAP5b. We expect a decrease in osteoclast-mediated bone resorption and thus also decrease serum bone resorption markers.

	Baseline	**Cycle X Day 1**	**Discontinuation visit**
Osteocalcin	X	X	X
P1NP	X	X	X
TRAP5b	X	X	X

Patients will be informed of these studies during the informed consent process. All correlative studies are optional. One gold top tube of peripheral blood (at least 5mL) should be drawn fasting as indicated in the table if the subject agrees to participate in the correlative studies. Two 0.5 ml aliquots of serum will be stored at -80°C. These sample will be de-identified, collected and stored in the laboratory of Dr. Suzanne Lentzsch, Black Building, 8th Floor. After completion of the sample collection all samples will be analyzed at the Biomarker Core at CUMC under the leadership of Dr. Serge Cremers. The HRpQCT will be performed at the Metabolic Bone Diseases Program, 9th Floor of the Harkness Pavilion. We do not plan to send any samples to outside institutions.

15 REGULATORY OBLIGATIONS

15.1 INFORMED CONSENT

The investigator-sponsor will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator-sponsor, or a sub-investigator(s) designated by the investigator-sponsor, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator-sponsor will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator-sponsor will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator-sponsor will obtain the informed consent of enrolled subjects for continued participation in the clinical study

15.2 COMPLIANCE WITH LAWS AND REGULATIONS

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

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

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

Onyx Inc.

Regulatory Department

249 East Grand Ave

South San Francisco, CA 94080

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

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

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

15.3 SUBJECT CONFIDENTIALITY

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

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

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

16 ADMINISTRATIVE AND LEGAL OBLIGATIONS

16.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

The sponsor-investigator will obtain, from the CUMC IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the sponsor-investigator will promptly notify the CUMC IRB of the deviation.
The CUMC IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable ICH Guidelines on GCP.

In the event that the CUMC IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor-investigator's decision to modify the previously accepted clinical protocol, the sponsor-investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

16.2 ETHICAL AND SCIENTIFIC CONDUCT OF THE CLINICAL STUDY

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on GCP; and relevant policies, requirements, and regulations of the CUMC IRB and applicable federal agencies.

16.3 STUDY DOCUMENTATION AND ARCHIVE

16.3.1 Data Recording/Case Report Forms

Case Report Forms will be completed for each subject enrolled into the clinical study. It is the investigator/sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRFs are complete, accurate and authentic.

16.3.2 Record Maintenance and Retention

The sponsor-investigator will maintain records in accordance with GCP guidelines; to include:

- FDA correspondence related to the IND and clinical protocol, including copies of submitted Safety Reports and Annual Reports
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of AE reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed FDA Form 1572 Statements of Investigator (i.e., for the sponsor-investigator and all identified sub-investigators)
- Financial disclosure information (sponsor-investigator and clinical protocol sub-investigators)
- Curriculum vitae (sponsor-investigator and clinical protocol sub-investigators)
- Certificates of required training (e.g. human subject protections, GCP, etc.) for sponsor-investigator and listed sub-investigators
- Listing of printed names/signatures of sponsor-investigator and listed sub-investigators
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Laboratory certification information
- Instructions for on-site preparation and handling of the investigational drug(s), study treatment(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Signed informed consent forms
- Completed CRFs; signed and dated by sponsor-investigator
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of sponsor-investigator correspondence to sub-investigators, including notifications of safety information
- Subject screening and enrollment logs
- Subject identification code list
- Investigational drug accountability record, including documentation of drug disposal.
- Final clinical study report

Subject identity on study records will be indicated by a case number rather than by name, and the information linking the case numbers with the subject's identity will be kept separate from the research records. All records related to this research study will be stored in a locked file cabinet.

The sponsor-investigator will retain the specified records and reports for up to 2 years.

16.4 DATA SAFETY AND MONITORING COMMITTEE

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol and all CUMC investigator-initiated protocols will adhere to the policies of the HICCC Data and Safety Monitoring Plan (DSMP) dated July 31, 2013, which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is led by Dr. J. Gregory Mears and consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and conduct. The PI will submit data and safety

monitoring reports to the DSMC at a frequency to be determined based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB and all other designated regulatory agencies as required. All study data reviewed and discussed during these meetings will be kept confidential. Any breaches in research subject confidentiality will be immediately reported to the IRB.

16.5 QUALITY CONTROL AND QUALITY ASSURANCE

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures.

The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

1. A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

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APPENDIX A. STAGING OF MYELOMA: DURIE-SALMON SYSTEM AND INTERNATIONAL STAGING SYSTEM

The staging system most widely used since 1975 has been the Durie-Salmon system, in which clinical stage of disease (stage I, II, or III) is based on four measurements: levels of M protein, the number of lytic bone lesions, hemoglobin values, and serum calcium levels. Stages are further divided according to renal function. There is somewhat of an overlap between the various myeloma categories and stages. For example, both patients with smoldering myeloma and patients with Stage I disease do not require immediate treatment, and patients with Stage II and III disease have active, symptomatic myeloma. Increasingly, physicians are relying less on the Durie-Salmon staging system and more on biologically relevant markers as prognostic indicators when making treatment choices.

A new, simpler, more cost-effective alternative is the International Staging System (ISS). The ISS is based on the assessment of two blood test results, beta 2-microglobulin (ß$_2$-M) and albumin, which together showed the greatest prognostic power for MM. This system has only recently been developed, but has already been proven more sensitive in discriminating between three stages of the disease, which indicate different levels of projected survival and suggest increasingly more aggressive treatment strategies. The following table summarizes the staging criteria.

Stage	Durie-Salmon Criteria	ISS Criteria
I	All of the following: ❖ Hemoglobin value >10 g/dL ❖ Serum calcium value normal or =12 mg/dL ❖ Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only ❖ Low M-component production rate - IgG value <5 g/dL; IgA value <3 g/dL ❖ Bence Jones protein <4 g/24 h	β_2-M < 3.5 mg/dL and albumin ≥3.5 g/dL
II	Neither stage I nor stage III	β_2-M < 3.5 mg/dL and albumin < 3.5 g/dL; or β_2-M ≥ 3.5 and < 5.5
III	One or more of the following: ❖ Hemoglobin value <8.5 g/dL ❖ Serum calcium value >12 mg/dL ❖ Advanced lytic bone lesions (scale 3) ❖ High M-component production rate - IgG value >7 g/dL; IgA value >5 g/dL - Bence Jones protein >12 g/24 h	β_2-M ≥ 5.5 mg/dL
Durie-Salmon sub classifications (either A or B) A: Relatively normal renal function (serum creatinine value <2.0 mg/dL B: Abnormal renal function (serum creatinine value =2.0 mg/dL		

APPENDIX B. INTERNATIONAL MYELOMA WORKING GROUP DIAGNOSTIC CRITERIA

The International Myeloma Working Group developed new diagnostic criteria in 2003 for MM emphasizing clinical characteristics of PD associated with active myeloma known as "CRAB" features. The intent is to distinguish between active myeloma and smoldering (asymptomatic) myeloma that does not typically require systemic therapy.

Smoldering (Asymptomatic) Myeloma
Serum M-protein ≥3.0 g/L AND/OR Bone marrow plasma cells ≥10% No related organ tissue impairment (ROTI)
Symptomatic MM
M-protein in serum and/or urine Bone marrow clonal plasma cells or plasmacytoma ROTI C Calcium elevation in blood (>11.5 g/dL) R Renal insufficiency (serum creatinine >2mg/dL) A Anemia (Hgb <10 g/dL or 2g<normal) B Lytic bone lesions or osteoporosis OR Any one or more of the following diagnostic criteria According to new International Myeloma working group (20) 1. Clonal bone marrow plasma cell percentage ≥60% 2. Involved/uninvolved serum free light chain ratio ≥100 3. >1 focal lesions on MRI studies

APPENDIX C: NCI-CTCAE VERSION 4.0

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

Publish Date: September 15, 2009
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

APPENDIX D: PERFORMANCE STATUS CRITERIA

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