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A Response-Adapted Clinical Trial of Weekly Carfilzomib with or without Rituximab for Waldenström's Macroglobulinemia and Marginal Zone Lymphoma

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SCHEMA

Registration: WM and MZL, N=24. (At least 5 Rituximab-refractory)

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Carfilzomib (CFZ) for two, 28 day-cycles as follows:

CFZ 20 mg/m2 as a 30-min IV infusion on Day 1 of cycle 1

If tolerated, CFZ 56 mg/m2 as a 30-min IV infusion on Days 8 and 15 of cycle 1

If tolerated, CFZ 70 mg/m2 as a 30-min IV infusion on Days 1, 8, and 15 of cycle 2

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Assess paraprotein and/or nodal response; BM Bx (research)

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If minimal response (MR: 25% or greater m-protein reduction) for WM, or PR for MZL: continue CFZ x 4 more cycles at 70 mg/m2 dose level (days 1, 8, and 15) as tolerated.

If not: Continue CFZ x 4 more cycles at 70 mg/m2 dose level if tolerated, and add rituximab 375 mg/m2 weekly x 4 doses (cycle 3) then monthly (cycles 4-6)

Note: Study to be stopped for futility if < 3 of the first 9 subjects achieve initial response with CFZ alone

Note: Study accrual to be suspended if cardiotoxicity limits are exceeded, or rituximab cannot be delivered per protocol (see section 12)

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Stop therapy after 6 total CFZ cycles: Surveillance for up to 1 year (measured from time of study drug start)

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1.0 OBJECTIVE

1.1 Primary Objective: Determine the overall response rate of single-agent weekly CFZ, measured after 2 cycles of therapy, in WM and MZL.

1.2 Secondary Objectives:

1.2.1 Assess safety and tolerability of single agent, weekly CFZ in patients with WM and MZL, and determine the tolerability of weekly CFZ+rituximab for applicable patients. .

1.2.2 Estimate the time to best response, response duration, and survival with weekly CFZ for WM and MZL

1.2.3 Evaluate the overall response rate associated with weekly CFZ in a subset of patients with rituximabrefractory WM or MZL

2.0 BACKGROUND

2.1 Waldenström's macroglobulinemia (WM) and marginal zone lymphoma (MZL) are incurable subtypes of non-Hodgkin lymphoma (NHL) with a protracted natural history.[1, 2] Therapy for WM and MZL, extrapolated from more common NHL subtypes, has been historically characterized by increasing toxicity of alkylating agents alone or in combination, and successively shortening remissions. WM and MZL patients present with unique features including high rates of marrow compromise in WM, paraprotein-related complications in WM, and autoimmune phenomena or infections in MZL. This context points to a significant unmet need for specific therapies for patients with WM and MZL.

Recent therapeutic advances including the successful application of rituximab, proteasome inhibitors (PI), and more recently cell signaling/kinase inhibitors.[3, 4] While these agents have improved the outlook for patients, the optimal combination, sequence, and dosing strategy of novel therapies remains undefined. Following demonstration of its activity in relapsed and refractory non-Hodgkin lymphoma in 2005, bortezomib was found efficacious in Waldenström's and carries a consensus recommendation for use in relapsed or refractory disease.[5-7] Bortezomib produces response rates of 80% or higher, when co-administered with rituximab, in WM in relapsed/refractory and newly diagnosed patients.[8, 9] In extranodal marginal zone lymphoma (MALT lymphoma), single-agent bortezomib showed a response rate of 48%, and 6/11 patients when combined with rituximab in a smaller study, supporting further trials of proteasome inhibition in this histology.[10, 11] Thus, proteasome inhibition is a potentially effective strategy in both WM and MZL, justifying the study of this therapeutic class in both diseases.

Nonetheless, the prototype proteasome inhibitor bortezomib is associated with well-known neurotoxicity. The novel expoxyketone proteasome inhibitor carfilzomib (CFZ), with increased potency and selectivity compared to bortezomib, has shown favorable results with an attenuated risk of neuropathy in patients with WM and multiple myeloma.[12-14] CFZ is currently approved for treatment of relapsed/refractory multiple myeloma in patients who have received 1 or more lines of therapy as a single agent, and in combination with dexamethasone or lenalidomide plus dexamethasone, in patients who have received 1 to 3 prior lines of therapy.

The approved dose of CFZ for relapsed/refractory multiple myeloma is as follows, and employs a priming dose and if tolerated, then escalating to 27 mg/m2 (over 10 minutes) when given in combination with lenalidomide and dexamethasone, or escalating CFZ to 56 mg/m2 (given over 30 minutes) when given in combination with dexamethasone:

- CFZ in combination with lenalidomide and dexamethasone

o cycle 1: 20 mg/m2 over 10 minutes on days 1 and 2; if tolerated, increase dose to 27 mg/m2 over 10 minutes on days 8, 9, 15, and 16 of a 28-day treatment cycle
o cycles 2-12: 27 mg/m2 over 10 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle

o cycles 13-18: 27 mg/m2 over 10 minutes on days 1, 2, 15, and 16 of a 28-day treatment cycle

· CFZ in combination with dexamethasone

o cycle 1: 20 mg/m2 over 30 minutes on days 1 and 2; if tolerated, increase dose to 56 mg/m2 over 30 minutes on days 8, 9, 15, and 16 of a 28-day treatment cycle

o cycle 2 and onwards: 56 mg/m2 over 30 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle

Results of CFZ for first-line treatment of WM in combination with rituximab and dexamethasone have recently been published in abstract form. The combination produced a response in 81% of patients, and 22/31 remain on study at 8 cycles of therapy; no neuropathy of grade 2 or higher was seen.[12] However, the single-agent efficacy of CFZ in WM or other NHL is undefined, nor have response-adapted studies--reserving combination therapy with rituximab for non-responders-- been reported.

The dosing of carfilzomib has recently undergone evolution, with implications for patient convenience and the practical administration of therapy. CFZ was historically administered twice weekly, but recent data from multiple myeloma (MM) identified acceptable safety and promising efficacy once weekly administration at the so-called 20/70 dose (CFZ 20 mg/m2 over 30 minutes on Cycle 1 Day 1,then 70 mg/m2 on D8 and D15 of cycle 1 and all days of future cycles; cycles are repeated every 28 days).[15] In that study, only 12% of patient discontinued therapy due to adverse events. Despite limitations of cross-trial comparisons, adverse event rates were similar or lower than prior twice-weekly studies. This data, in addition to providing the basis for a large upcoming study using weekly carfilzomib in myeloma (NCT#02412878), support the proposed weekly dosing in this trial.

CFZ has been associated with cardiac toxicity in clinical trials, possibly related to co-administration of routine IV fluids, cardiac myocyte protein accumulation and oxidative damage, or combined reasons[16]. The rate of any-grade cardiac failure approaches 6-8% with CFZ, higher than after bortezomib although one study found no change in prospectively monitored ventricular function between these agents.[14, 17, 18] Serial monitoring of the cardiac marker brain natriuretic peptide (BNP) has been evaluated as an early biomarker of cardiac risk, particularly in MM patients. Available data show variable sensitivity of BNP in predicting cardiac failure, and suggest further prospective study of this marker is warranted. [16, 19] This trial requires baseline evaluation of ejection fraction and will exclude patients with inadequate cardiac function, will suspend accrual for excess cardiotoxicity as in section 12, and will hold therapy for uncontrolled systolic hypertension and include blood pressure monitoring at home for selected patients.

Overall, this will address the substantial unmet need of defining a disease-specific therapy for WM and MZL patients, clarify the efficacy and safety of single-agent carfilzomib, and employ a response-adapted strategy adding rituximab added for initial non-responders as described in section 2.2.

2.2 Response adapted therapy for WM and MZL: Rationale for the Addition of Rituximab for Initial Carfilzomib Non-responders

This approach offers promise to define the single-agent activity of CFZ, and reduce unneeded exposure to combination CFZ+ R therapy in a proportion of WM and MZL patients. In addition, this provides an opportunity to perform correlative studies which may help optimize sequencing of therapy in future studies. The addition of rituximab is supported by its known significant single agent activity in WM and MZL, with over 50% of patients responding; it is also well tolerated, and does not appear to cause additive toxicity in combination with bortezomib.[20-22]

In this trial, rituximab will be administered for subjects who fail to achieve a minimal response in WM or at least a PR in MZL, after 2 cycles of CFZ single-agent therapy. A stopping rule is included to minimize unnecessary exposure to single-agent CFZ (see section 12.0, Statistical Methods). We will assess the efficacy and safety of this approach, while simultaneously evaluating secondary endpoints (such as modulation of the risk of tumor flare in WM) and correlative hypotheses (carfilzomib may upregulate CD20 expression to prime for rituximab response). Thus study is best regarded as a phase II study, with stopping for futility, powered to evaluate the response rate of single-agent weekly CFZ in WM and MZL.

3.0 DRUG INFORMATION: Carfilzomib (CFZ) and Rituximab

3.1 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 C40H57N5O7 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.

3.1.1 FORMULATION: Carfilzomib 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 □ CD, Captisol®).

3.1.2 STORAGE Lyophilized Carfilzomib for Injection must be stored at 2–8°C in a securely locked area to which access is limited to appropriate study personnel. Additional drug information, in particular the Identified Risks of Carfilzomib, is contained in Appendix 20.1. Further information can be found in the product labelling.

3.2 Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes, approved for treatment of CD20-positive Non-Hodgkin Lymphomas (NHL). Rituximab will be obtained from a commercial source.

4.0 STAGING CRITERIA

Staging and response assessment will follow the guidelines of the VIth International Workshop for WM (Appendix 20.2 and 20.4), the Lugano criteria for nodal lymphoma[23] and for spleen-only disease will follow guidelines of Matutes and colleagues.[24]

5.0 ELIGIBILITY CRITERIA

Patients with Waldenström Macroglobulinemia or Marginal Zone lymphoma who meet inclusion/exclusion criteria below are eligible.

At least 5 patients with rituximab-refractory disease will be enrolled (best response of stable disease or progression while on treatment with, or progression within 6 months of, rituximab-containing therapy). Accrual will be modified to ensure 5 rituximab-refractory patients are enrolled, without enrolling more than 24 total patients.

5.1 Inclusion Criteria

- Waldenström's macroglobulinemia (WM) or marginal zone lymphoma (MZL) based on institutional pathology review; see Appendix 20.3 for WM criteria. Patients may have either previously untreated or relapsed/refractory disease.
- Measurable disease: for WM presence of monoclonal IgM immunoglobulin concentration on serum electrophoresis, with lymphoplasmacytic marrow infiltrate; for MZL: measurable nodal disease measuring at least 1.5 cm in longest dimension, or splenomegaly.

- Indication for initiation of therapy, as defined in protocol section 5.3
- Age greater than or equal to 18 years old
- Adequate hematopoiesis, including ANC >1,000/μL and platelet count >75,000/μL unless disease-related (due to marrow infiltration or splenomegaly).
- Serum creatinine <2.5 mg/dL or creatinine clearance >30 cc/min.
- Bilirubin <2 x ULN and AST and ALT <3 x ULN.
- All patients must be informed of the investigational nature of this study and have given written consent in accordance with institutional and federal guidelines.
- Expected survival of >90 days.
- Females of childbearing potential (FCBP) must agree to pregnancy testing and to practice contraception.
- Male subjects must agree to practice contraception.

5.2 Exclusion Criteria

- Known HIV, Hepatitis C, or Hepatitis B positivity (subjects with hepatitis B surface antigen [SAg] or core antibody positivity, who are receiving and responding to antiviral therapy directed at hepatitis B or are negative for HBV DNA, are allowed)
- Candidate for potentially curative antibiotic therapy for gastric MALT. (Gastric MALT lymphoma patients with stage I/II H. pylori positive lymphoma must fail therapy with H.-pylori directed therapy before being considered for this study.)
- ECOG performance status 3 or higher.
- Known active CNS involvement.
- Pregnant or lactating females
- Inadequate cardiac function, as measured by left ventricular ejection fraction (LVEF)that is less than or equal to 40%, or the presence of New York Heart Association (NYHA) classification of greater than stage II congestive heart failure.
- Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to screening
- Uncontrolled inter-current illness including, but not limited to, unstable angina, recent myocardial infarction within 6 months of screening and uncontrolled cardiac arrhythmias, psychiatric illness, or psychosocial difficulty that would limit compliance with study requirements.
- Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study

5.3 An indication for therapy initiation is required of all patients included on this trial. These listed below separately, for WM and MZL:

5.3.1 WM: Symptoms related to WM including: fever, night sweats, weight loss, fatigue; evidence of hyperviscosity; symptomatic lymphadenopathy or lymphadenopathy measuring 5 cm or larger; symptomatic hepatomegaly and/or splenomegaly; other symptomatic organ or tissue infiltration; peripheral neuropathy due to Waldenström's macroglobulinemia; or laboratory indications including symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic anemia or thrombocytopenia, nephropathy related to Waldenström's, amyloidosis related to Waldenström's, hemoglobin less than or equal to 10g/dL, platelet count less than or equal to 100,000/uL

5.3.2 MZL: Symptoms related to splenomegaly or lymphadenopathy; evidence of rapid disease progression; high tumor bulk (presence of 3 lymph node groups measuring 3 cm or more, or one node or conglomerate measuring 7 cm or more), cytopenias due to bone marrow infiltration or hypersplenism (hemoglobin less than or equal to 10 g/dL, platelet count less than or equal to 100,000/uL);

autoimmune hemolytic anemia or thrombocytopenia. Advanced stage disease, disease-related effusions, end organ compromise (iron deficiency anemia, organ infiltration), are also permissible criteria for initiation of therapy on this study.

6.0 REGISTRATION

Subjects will be registered by institutional research staff prior to the start of protocol therapy. A complete, signed study consent and HIPAA consent are required for registration.

7.0 TREATMENT PLAN

7.1 Each cycle of CFZ therapy is given every 28 days. Up to 6 cycles of CFZ therapy will be administered on protocol. Four weekly doses of weekly rituximab, then 3 additional doses of monthly rituximab, will be administered to select patients who do not respond to CFZ following the first 2 cycles. (Total 7 doses of rituximab).

We anticipate accrual of 24 patients over 18 - 24 months. Accrual will be limited to the first 9 patients initially then paused -- if needed-- to ensure the stopping rule (section 12.2 and 12.3) has not been reached before additional patients are accrued.

Plasmapheresis may be undertaken at any point in the study when clinically indicated. If protocol therapy is discontinued for disease progression requiring other treatment, patients may go on to receive other therapy at the discretion of their physician, but will be removed from this study.

7.1.1 Dose and Administration
Subjects with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2.

Carfilzomib will be administered 20 mg/m2 over 30 minutes on Cycle 1 Day 1. If tolerated, the dose will be increased to 56 mg/m2 on D8 and D15 of cycle 1. Escalation to 70 mg/m2 starting with cycle 2 and beyond is allowed for all patients who have met criteria for ongoing therapy without delay due to toxicity, or need for dose modification as described in section 8.0.Cycles are repeated every 28 days. Do not administer as an IV bolus.

A maximum of 6 total cycles may be given.

7.1.1.1. If 20 mg/m2 is not tolerated, it may be repeated with additional supportive care at clinical discretion for up to 4 weekly doses (C1 D1, C1 D8, C1 D15, and C2 D1) while reconsidering dose escalation. CFZ must then be escalated to 56 mg/m2 for at least 2 doses, prior to increasing to 70 mg/m2 as tolerated.

Carfilzomib Therapy: Day 1, 8, and 15 of 28-day cycles	
Carfilzomib	Cycle 1-6 (actual dates may vary +/- 3 days)
Carfilzomib 20 mg/m2 over 30 minutes *with dexamethasone pre-medication	Cycle 1 Day 1
Carfilzomib 56 mg/m2 over 30 minutes *with dexamethasone pre-medication for cycle 1	cycle 1 Day 8 and 15
Carfilzomib 70 mg/m2 over 30 minutes	All future days starting with Cycle 2 Day 1.

Dose modification in response to toxicity is described under section 8.0 below.

7.1.2 Required Premedication and Post-medication for Cycle 1, All Doses

For cycle 1: dexamethasone 8 mg orally or IV will be administered. Pre-medicate 30 minutes to 4 hours prior to all doses in cycle 1, and as needed with future cycles to reduce the incidence and severity of infusion reaction.

In addition, for cycle 1, 250 ml hydration using normal saline will be given pre-dose on day 1, 8, and 15 unless contraindicated due to clinician judgment. This hydration is optional for future cycles.

7.1.3 Supportive Care
Consider antiviral prophylaxis for patients who have a history of herpes zoster infection, using Acyclovir 800 mg PO daily. Additional prophylaxis or monitoring for infections may be used for subjects deemed at high risk of bacterial, viral, or fungal infections.

Premedication for rituximab will be administered according to standard, institutional guidelines.

7.1.4 Blood pressure monitoring at least twice per week during cycle 1 will be conducted for patients with pre-existing systolic hypertension on medical therapy, or any who develop grade 3 hypertension or require the addition of antihypertensive therapy during cycle 1.

7.2 Administration of Rituximab to CFZ Non-responders
Subjects who fail to achieve at least a 25% M-protein reduction based on SPEP m-protein quantification for WM, or partial response for MZL based on imaging, following 2 cycles of CFZ therapy will receive rituximab concurrent with CFZ.

7.2.1 Note: the bone marrow aspirate / biopsy after cycle 2 is exploratory and not to be used for response assessment or determination regarding rituximab.

7.2.2 IV Rituximab, pre-medications, and hypersensitivity management will be administered according to standard institutional or pharmacy guidelines.

RITUXIMAB weekly x 4 doses (cycle 3) then monthly (cycles 4-6)				
Treatment	Cycle 3-6 for patients not responding to CFZ (actual dates may vary +/- 3 days; cycle timing refers to CFZ)			
	C3 D1,8,15,22	C4D1	C5D1	C6D1
Rituximab 375 mg/m2	X, X, X, X	X	X	X

7.2.3 Following rituximab administration for WM, weekly laboratory evaluation of IgM levels (to evaluate for Ig M flare for clinical and study data purposes) is required. (See section 10, study calendar). As clinically indicated, viscosity measurement and other evaluation or management of hyper-viscosity syndrome, including plasmapheresis, should be undertaken. Weekly evaluation will continue until no longer clinically indicated.

7.3 Criteria for removal from protocol treatment: (Note: Subjects discontinued from CFZ will not receive rituximab on study.)

7.3.1 Symptomatic progression of disease after completion of at least 4 total cycles of CFZ therapy (with or without rituximab). IgM flare following rituximab (even if requiring plasmapheresis), or biochemical progression alone do not require removal from protocol treatment.

7.3.2 Inability to tolerate more than 20 mg/m2 of CFZ during the first 4 doses of therapy, despite maximal supportive care.
7.3.3 Development of excess hematologic toxicity not responding to supportive care or persisting despite dose reductions—as outlined in Section 8.0
7.3.4 Development of any other unacceptable toxicities unless prophylactic measures can be taken for subsequent cycles.
7.3.5 Missed doses will not be replaced during a cycle. If a subject misses more than 2 doses of any cycle for reasons other than toxicity, the subject will be discontinued.
7.3.6 Delay of a treatment cycle for more than 4 weeks due to adverse events
7.3.7 Completion of protocol treatment (maximum of 6 cycles, or 18 doses of CFZ).
7.3.8 The patient may withdraw from the treatment at any time for any reason.
7.3.9 Subjects may be removed from treatment in the event of study termination for any reason, as described under section 18.0.

7.4 Early Termination for Futility
As in section 12.2, the study will be stopped if two or fewer of the first 9 patients respond after cycle two. Previously enrolled subjects will continue on study as per the treatment plan (Section 7).

8.0 REQUIREMENTS TO BEGIN A NEW CYCLE AND DOSE ADJUSTMENT GUIDELINES

Parameters for retreatment and treatment modifications are as follows. Patients may be reduced to dose level -1 or 2, without impact on future enrolled patients (who will initiate the Starting Dose.)

Dose levels are as follows:

- Starting Dose: CFZ 20 mg m2 (C1D1) then 56 mg/m2 (cycle 1 day 8 and 15), then 70 mg/m2 (all future weekly doses)
- Dose level -1: CFZ 56 mg/m2
- Dose level -2: CFZ 27 mg/m2

8.1 Requirements to Begin a New Cycle
Subsequent cycles of CFZ therapy will not begin until the ANC is ≥500/μL and the platelet count is ≥50,000/μL unless related to disease infiltration. For patients with cytopenias related to marrow infiltration, return to the subject's baseline ANC and platelet count is adequate to resume a subsequent cycle.

Treatments will also be delayed for reasons described in Section 8.2, or for clinically significant Grade 2 or 3 adverse events and unrelated Grade 4 adverse events at the discretion of the treating physician, or Principal Investigator.

Therapy may be delayed a maximum of 4 weeks until these values are achieved for Day 1 of each cycle. Hematopoietic growth factors and blood product support are allowed. There are no study parameters required for initiation of rituximab. Rituximab and CFZ should be started simultaneously during Cycle 3 for subjects who qualify (section 7.2), and are deemed fit for rituximab therapy by the investigator.

Subjects who undergo dose reduction to dose level -2 may not undergo further dose changes.

8.2 Specific management of toxicities are as follows:
8.2.1 Neutropenia
- For the first instance of ANC ≤1000/uL with complications, or ANC ≤500/uL unless related to disease infiltration, GCSF support will be initiated.
- For the second such instance despite GCSF support, CFZ will be reduced to dose level -1.

- For the third instance or failure to achieve ANC 500/uL in 4 weeks, despite GCSF support, the subject will be reduced to dose level -2. If severe neutropenia persists, patients will be removed from study.
- For subjects with disease infiltration, GCSF support may be used at the discretion of the investigator. For ANC ≤500/uL without complications and attributable to disease infiltration, return to a subject's baseline is required and adequate, to start a new cycle.

8.2.2 Thrombocytopenia

- For the first instance of platelets ≤25,000/uL, or at the discretion of the investigator for patients deemed at risk of bleeding complications, CFZ will be reduced to dose level -1.
- For the second instance of platelets ≤25,000/uL or failure to achieve platelet count of 25,000/uL or greater after 4 weeks, CFZ will be reduced to dose level -2. If further decreases are required, the patient will be removed from study therapy.

8.2.3 Anemia

There is no pre-specified dose reduction requirement for anemia, but growth factors or transfusion (where appropriate) may be used and CFZ may be dose reduced as clinically indicated.

8.2.4 Dose Reductions for Non-Hematologic Toxicities

- Study drug should be held for ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline, unless otherwise noted in the table below.
- All cases of grade 3 or greater systolic HTN (SBP >160) will require action per protocol including holding study drug and management /dosing only once BP is controlled.
- After resolution of the event to ≤ Grade 1 or return to baseline, if the adverse event 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 dose level -1. If toxicity continues or recurs, a 2nd CFZ dose reduction to dose level -2 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.
- Dose adjustment guidelines for non-hematologic toxicities are summarized in the following table:

Symptom	**Recommended Action Carfilzomib**
Allergic reaction/hypersensitivity	
Grade 2 – 3	Hold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue
Grade 3 or higher systolic HTN	Hold until grade 2 or less, initiate medical management if clinically indicated, dose only when resolves or improves to Grade 2 or less.
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 Grade 3 or 4	Hold CFZ until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex of any grade	Hold CFZ until lesions are dry. Reinstitute at full dose
Gr 2 treatment emergent neuropathy with pain	Continue to dose. If neuropathy persists for more than two weeks hold CFZ until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement
Grade 3 neuropathy	Withhold CFZ until resolved or returned to baseline. Subsequent treatment with carfilzomib should resume at a lower dose level.
Grade 4 neuropathy	Discontinue
Renal Dysfunction CrCl ≤ 15 mL/min	Hold until CrCl > 30 mL/minute; restart at 1 dose decrement
Congestive heart failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be withdrawn from the study. If this results in a delay of treatment for more than 4 weeks, the subject will be withdrawn from the study.
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.

8.2.5 Missed Doses

Missed doses will not be replaced during a cycle. If a subject misses more than 2 doses of any cycle for reasons other than toxicity, the subject will be discontinued.

8.2.6 Changes in Body Surface Area (BSA)

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. Subjects with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2.

8.2.7 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.

8.2.8 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, 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 8 mg PO/IV will be administered prior to all CFZ doses during the 1st cycle.
- If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of CFZ after dexamethasone has been discontinued, dexamethasone should be re-started and administered prior to subsequent doses.
- 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, including creatinine, must be obtained and reviewed prior to each dose of CFZ during Cycles 1 and 2. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.
- Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with CFZ until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been completed.
- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of anti-emetics or anti-diarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

9.0 CONCOMITANT THERAPY

Medications used during the course of the study should be documented.

9.1 Prohibited Concomitant Therapy

- The administration of concurrent medications intended to treat WM or MZL are not allowed during protocol therapy, except plasmapheresis when clinically indicated. Concurrent radiation therapy is prohibited.
- Topical and inhaled corticosteroids to treat other medical conditions are allowed. Intermittent oral or IV corticosteroid administration is allowed as premedication prior to rituximab therapy or carfilzomib in cycle 1 or future cycles if clinically indicated; for management of nausea or vomiting; or for treatment of infusion reactions.

9.2 Patients should be strongly discouraged from taking any "alternative" or "naturopathic" medications since these agents may interact with CFZ. Any use of these medications should be at the judgment of the treating physician and should be documented in the patient's medical record

10.0 STUDY PROCEDURES AND CALENDAR

Pre-entry assessments other than laboratory tests may be done within 6 weeks of enrollment, and need not be repeated within that timeframe. Pre-entry laboratory studies must be done within 14 days of cycle 1.

Required Studies	Pre-Entry[1] (within 6 wks of enrollment unless indicated)	Day 1 of Each Cycle, +/- 3 days	Days 8 and 15 of each Cycle, +/- 3 days	Between Cycle 2 Day 15 and Cycle 3 day 1	Weekly for Cycles 3-6 *for all WM Rituximab –treated subjects*	End of Treatment (EOT)	Follow -Up
Physical							
Medical history	X	X[11]					
Physical exam	X	X[11]				X[7]	X[8]
Vital signs including blood pressure (BP, HR, Temp, Respiratory rate)	X	X	X				
Performance status	X						
Response assessment	X			X		X[7]	
Adverse event assessment	X	X[11]				X[7]	
Patient home blood pressure monitoring		Cycle 1[12]					
Lab							
CBC with differential	X	X[11]	X			X[7]	X[8]
Comprehensive metabolic panel	X	X[11]	X				
Serum LDH	X	X[11]				X[7]	
Serum phosphorus	X	X[11]					
for WM: SPEP with m-protein quantification, identification[1]	X	X [11]		X			X[8]
for WM: IgM (quantitative)	X	X [11]		X	X[6]	X[7]	X[8]
for WM: Serum viscosity	X						
B2 Microglobulin	X					X[7]	
Bone marrow studies	X[2]			X (for WM)[5]		X[2, 7]	
Pregnancy test	X[3]						
Hepatitis B testing	X[9]					X[7]	
Peripheral blood for flow cytometry	X			X[5]		X[7]	

BNP	X	X[11]- cycles 2,4,6 only					
Radiology							
CT chest, abdomen and pelvis	X[4]			X		X[7]	X[8]
MUGA or echocardiogram[10]	X[10]						

1 Pre-entry studies may be performed within 6 weeks of cycle 1 day 1 other than lab studies, which must be done within 14 days of Cycle 1 Day 1 of treatment. Baseline SPEP should be obtained for all patients, but repeat measurements are only required for WM patients.
2 Baseline bone marrow aspirate and biopsy should be performed within 12 weeks of enrollment. Post therapy marrow will be performed only to confirm complete response, or as clinically indicated. Bone Marrow Studies include aspirate and unilateral biopsy with immunohistochemistry, as well as flow cytometry of the aspirate at baseline and after 2 cycles (baseline and post-cycle 2 cycle marrow aspirates are required for correlative analysis for WM patients).
3 Pregnancy test in women of childbearing potential.
4 CT imaging should be performed within 8 weeks of enrollment. CT neck should also be performed, if cervical adenopathy is present on physical exam. CT scans are repeated at interim analysis or during study protocol treatment for patients with nodal/extramedullary disease at baseline. CT scan should be performed in subjects with nodal/extramedullary disease post-therapy to assess response.
5 For WM patients only, post-cycle 2 bone marrow and flow cytometry studies are required for correlative studies but will not be used for response assessment, which relies on SPEP (for WM) and CT imaging (for MZL). Post-cycle 2 studies may be performed any time after C2D15 dose of CFZ, up until Cycle 3 Day 1.
6 For subjects receiving rituximab with WM, weekly quantitative IgM level (+/- 3 days) is to be measured. Further studies (serum viscosity, CBC, chemistries; additional clinical evaluations) may be performed if hyper-viscosity is suspected. Plasmapheresis may be performed as clinically indicated.
7 Post therapy studies should be done 3 - 5 weeks post cycle 6 or after the patient's last cycle, whichever comes first.
8 Follow-up should be done as per the clinical standard of care. A typical schedule includes every 3 months (total follow-up time from start of drug is 1 year). CT imaging as a standard of care surveillance measure should be performed no more frequently than every 6 months, unless a shorter interval is clinically indicated.
9 Hepatitis B core Ab, Hepatitis B surface Ag; further testing as clinically indicated including HBV DNA
10. Measurement of cardiac ejection fraction within 12 weeks of enrollment, by MUGA, echo, or other invasive/noninvasive testing, is allowed.
11. For cycle 1 day 1 only, if history, physical exam, and labs are performed within 14 days of Cycle 1 day 1, they do not need to be repeated. BNP testing results, when associated with dyspnea or signs of cardiac disease, may be used to initiate further testing per investigator judgment.
12. Home blood pressure monitoring at least twice per week will be conducted during cycle 1 for patients with pre-existing hypertension on medical therapy, or any who develop grade 3 hypertension or require the addition of antihypertensive therapy during cycle 1. Patients should record blood pressure on a provided diary during cycle 1. Dosing of CFZ must be held for grade 3 or higher systolic hypertension as per section 8.2.4

11.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

(See Appendix 20.3, and References 25,26, and 38)
Diagnosis and response criteria are to be based on International Workshop[36], Lugano response criteria[23], and criteria of Matute et al[24] for patients with splenomegaly alone.
For WM, SPEP with m-protein quantification should be the primary means for assessing response to therapy, in addition to imaging, repeat immunofixation (to confirm CR), and marrow aspirate and biopsy when indicated. (Note that quantitative IgM by nephelometry is to be used for determining rituximab flare, as results may be available more rapidly.)

12.0 STATISTICAL CONSIDERATIONS

12.1 Accrual: We anticipate accrual of 24 patients over 18 - 24 months. Accrual will be limited to the first 9 patients initially then paused -- if needed-- to ensure the stopping rule (section 12.2 and 12.3) has not been reached before additional patients are accrued.

12.2 Sample Size: This is a Simon 2 stage (minimax) design with stopping for futility. The primary endpoint is overall response rate, measured after 2 cycles of therapy. This model requires 24 total patients to be assessable after 2 cycles.

The null hypothesis, that the true response rate of single agent CFZ is 25%, will be tested against a one-sided alternative. In the first stage, 9 subjects will be enrolled. If two or fewer patients responds, the study will be stopped for futility. If 3 or more respond, a total of 15 more subjects will be enrolled. The null hypothesis will be rejected if 10 or more responses are observed in 24 assessable subjects. This design yields a type I error rate of .05, and a power of 80%, when the true response rate after 6 cycles of CFZ is 50%.

Descriptive statistics will be used for baseline characteristics, and responses to treatment. Changes in mean fluorescence intensity pre- and post-CFZ of both CD20 and CD19 will be assessed compared using paired T testing.

Estimate time to best response, time to progression, and survival outcomes for subjects using Kaplan-Meier analysis.

12.3 Stopping Rule, and Rules for Suspending Accrual

12.3.1 Futility: The study will be stopped if two or fewer of the first 9 patients respond after cycle two, as in section 12.2 above.

12.3.2 Cardiac Toxicity: A composite endpoint of cardiotoxicity will lead to suspension of accrual, at the thresholds noted below: myocardial infarction, new onset atrial fibrillation, cerebrovascular accident, grade 4 hypertension, grade 3 left ventricular dysfunction, or grade 2 or higher heart failure. Events are counted per patient (i.e. a patient with more than one cardiac event counts only once toward this limit.)

If there is sufficient evidence to suggest that the occurrence of any of the components of this composite "toxicity" (occurrence of at least one will constitute a "toxicity") exceeds a frequency of 10% of accrued patients, study accrual will be suspended pending review by the institutional data safety monitoring committee. Further accrual may be undertaken only with approval of that committee. Sufficient evidence will be taken to be any observed ratio associated with a lower 80% one-sided confidence limit that exceeds 0.10.

Operationally, any of the following proportions of accrued patients experiencing cardiac toxicity (as defined above) would yield such a ratio: 2 of the first 8 or fewer patients, 3 of the first 15 or fewer patients, 4 of the first 23 or fewer patients.

If the true probability of toxicity is .05, the probability of stopping after 15 or 23 patients is approximately .08 and .08, respectively. If the true probability of toxicity is .25, the probability of stopping after 15 or 23 patients is approximately .81 and .90, respectively (probabilities of stopping estimated from 5,000 simulations).

12.3.3 Inability to deliver rituximab therapy as per protocol:

If per-protocol rituximab (as per protocol section 7.2) cannot be administered to at least 6 of the first eligible 12 patients for any reason, accrual will be suspended for review by the institutional data safety monitoring committee, before further accrual may proceed.

13.0 CORRELATIVE STUDIES

13.1 Assessment of CD19 and CD20 expression changes following CFZ therapy (all patients):

Bortezomib modulates CD20 expression, and affects CDC, in a time- and concentration-dependent manner.[25, 26] Increased CD20 expression is observed in bortezomib-resistant

cells, which in turn display increased sensitivity to rituximab-mediated complement-dependent cytotoxicity. Furthermore, rituximab resistance appears to depend partly on CD20 down-expression.[27-30]

Therefore, we hypothesize that 1) rituximab-resistant patients will have lower CD20 expression at baseline, and 2) that CFZ may increase CD20 expression after 2 cycles. We will explore, albeit with small sample size of WM patients, whether response to subsequent rituximab in initial CFZ nonresponders is associated with CD20 expression. We postulate that overall, it may be possible to increase CD20 expression to prime tumor cells for optimal rituximab effect, with implications for sequencing these therapies.

Methods: Peripheral blood samples from each patient before therapy and again after 2 cycles of CFZ (see Study Calendar, Section 10.0), will be submitted to UW for quantitative evaluation of CD19 and CD20 surface expression (measuring mean fluorescence intensity).

13.2 Correlating Marrow Response Using Flow Cytometry with Paraprotein Response (WM patients only): Response assessment in WM undergoes continual evolution, but still relies on magnitude of the IgM paraprotein reduction. However, discordant responses are commonly observed between paraprotein levels, node size, and marrow involvement and appear to vary based on therapy given. IgM levels have been reported to decrease rapidly with proteasome inhibitors, transiently flare following rituximab, and lag behind marrow responses after fludarabine; best paraprotein response may be delayed, occurring months following therapy.[22, 31, 32] Flow cytometry is particularly suited for quantifying the lymphoid cells in the marrow of WM patients.[33, 34] The degree of B cell lymphoid involvement at end of treatment is prognostic—WM patients with less than 5% clonal B cells as in marrow samples by flow cytometry have superior outcomes.[35]

Methods: Marrow samples from WM patients will be evaluated before treatment, after cycle 2, and at the end of study for patients with CR for flow cytometric evaluation of both lymphoid and plasma cell components, and reported descriptively alongside paraprotein responses.

13.3. Specimen Requirements: Submission for flow cytometry

- A 5-10 mL specimen of peripheral blood or BM aspirate in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.
- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.
- If no significant amount of bone marrow aspirate is obtained, a fresh bone marrow biopsy **in RPMI** (cell culture medium) may be submitted for flow cytometry.
- Formalin-fixed bone marrow biopsies or clots should be submitted for morphological evaluation and immunohistochemical studies, but they cannot be used for flow cytometry immunophenotyping.
- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry

13.4 Specimen Shipping Address
Attn: Katy Dougherty, Hematopathology Lead
Seattle Cancer Care Alliance
Hematopathology Laboratory G7800
825 Eastlake Ave E.
Seattle, WA 98109

14.0 REPORTING REQUIREMENTS FOR ADVERSE EVENTS/ADVERSE REACTIONS

14.1 Adverse Events Definitions

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

An AE therefore can be any unfavorable and unintended sign (including laboratory 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 most current version of the Common Terminology Criteria for Adverse Events (CTCAE) should be used to describe the event and for assessing the severity of AEs (see Appendix D). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form.

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

Severity	Description
GRADE 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
GRADE 2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping, using the phone, managing money, etc.).
GRADE 3 – Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing, feeding self, toileting, taking medications, not bedridden).
GRADE 4 – Life-threatening	Life –threatening consequences; urgent intervention indicated.
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.

Causality
Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:
Yes, the event is suspected to be related if:

- there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
- there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- the event responds to withdrawal of the study medication (de-challenge) and/or recurs with re-challenge (when clinically feasible); and/or

- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

No, the event is NOT suspected to be related if

- 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)

14.2 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 first dose of study drug must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate form.

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

AEs should be reported from the time the subject receives their first dose of study drug, 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 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. Adverse events will be assigned a severity grade using the most current version of the NCI-CTCAE.

Grade 3 or higher AE's will be recorded, including laboratory abnormalities. 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 reporting and AE assessment duties to Sub-investigators and must ensure that these Sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator.

14.3 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.

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

14.4 Serious Adverse Event Reporting and Documentation Requirements

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

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

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

Additionally, the Investigator is responsible for reporting adverse events to Amgen and NCCN as described below:

14.5 Expedited Reporting

The Investigator must inform Amgen and NCCN via email at the contact information listed below of all Expedited Safety Reports submitted to the relevant Regulatory Agencies within 24 hours. This must be documented on a FDA 3500A MEDWATCH or CIOMS I form and must be completed and supplied to Amgen in English.

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

All other SAE's will be sent to Amgen and NCCN on a quarterly 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 CFZ), and the Investigator's assessment of expectedness to CFZ. 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.

Amgen Pharmacovigilance Contact Information

Amgen Global Safety
Phone: 800-77-AMGEN
Fax: 1-888-814-8653 (using SAE fax cover sheet to be provided in Open Study Packet)
Email: svc-ags-in-us@amgen.com

NCCN Contact Information:
Fax: (215) 358-7699
Email: ORPReports@nccn.org

14.6 Pregnancy

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial, Amgen Drug Safety and NCCN must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Amgen Drug Safety and Pharmacovigilance and NCCN 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 Amgen Drug Safety and NCCN.

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.

15.0 DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the Principal Investigator. The Principal Investigator will review acquired data and adverse events on a regular basis. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutchinson Cancer Research Center (FHCRC) Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

16.0 RECORDS

Research staff under the supervision of the investigators will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

17.0 REGULATORY RESPONSIBILITIES

The Principal Investigator will ensure that the study is conducted in accordance with all applicable institutional, state, and federal regulatory requirements, including, but not limited to: compliance with requirements for IRB and other regulatory approvals, monitoring responsibilities, reporting obligations, and compliance with standards for written informed consent from all patients entering the study. In addition, the Principal Investigator will ensure oversight of the study via data and safety monitoring as described above.

18.0 TERMINATION OF THE STUDY

Patients may be removed from this study at any time per their discretion. Individual patients may be removed from this protocol if they develop any untoward side effects from the study treatment or for other reasons as described under section 7.7.

The study will be closed to accrual upon treatment of the total planned number of study subjects. The study will be completed following treatment of all study subjects and completion of follow-up and data analysis as described in the protocol. If the study drug becomes unavailable for any reason, the study will be suspended until drug availability resumes or terminated as appropriate. In addition, there are stopping rules in place for lack of efficacy as detailed in the statistical section. The Principal Investigator may terminate the study at any time. The IRB and FDA also have the authority to suspend or terminate the study should it be deemed necessary.

The Principal Investigator shall provide Amgen with a final study report no later than **one (1) calendar year** after study completion. The report shall include all AEs generated by the Study, irrespective of whether the AEs are serious or non-serious, and a causality assessment for each AE, regardless of whether the AE is related to the investigational drug.

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20.0 APPENDIX

20.1 Identified Risks of CFZ

A Phase 1 clinical trial, PX-171-002, testing CFZ in subjects with relapsed/refractory hematologic malignancies, is completed[7]. During the dose escalation portion of the trial, 36 subjects received CFZ on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

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

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

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

20.2 Response Assessment for WM [36]

Complete response (CR)

- Absence of serum monoclonal IgM protein by immunofixation
- Normal serum IgM level
- Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline
- Morphologically normal bone marrow aspirate and trephine biopsy

Very good partial response (VGPR)
- Monoclonal IgM protein is detectable
- ≥ 90% reduction in serum IgM level from baseline*
- Complete resolution of extramedullary disease, i.e., lymphadenopathy/ splenomegaly if present at baseline
- No new signs or symptoms of active disease

Partial response (PR)
- Monoclonal IgM protein is detectable
- ≥ 50% but <90% reduction in serum IgM level from baseline*
- Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline
- No new signs or symptoms of active disease

Minor response (MR)
- Monoclonal IgM protein is detectable
- ≥ 25% but<50% reduction in serum IgM level from baseline*
- No new signs or symptoms of active disease

Stable disease(SD)
- Monoclonal IgM protein is detectable
- <25% reduction and <25% increase in serum IgM level from baseline*
- No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly
- No new signs or symptoms of active disease

Progressive disease (PD)
- ≥ 25% increase in serum IgM level* from lowest nadir (requires confirmation) **and/or**
- progression in clinical features attributable the disease

*This study will employ M protein measurement by densitometry (SPEP) for primary measurement of response.

20.3 Diagnostic Criteria for WM (all are required)

1. IgM monoclonal gammopathy of any concentration

2. 10% or greater bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation, with a predominantly intratrabecular pattern of bone marrow infiltration

3. surface Igm+, CD5 +/-, CD10 -, CD19+, CD20+, CD23-, CD25+, CD27+, FMC 7+, CD103-, CD138- immunophenotype*. Variations from this profile can occur. However, care should be taken to satisfactorily exclude other lymphoproliferative disorders. This is most relevant in CD5+ cases, for which CLL and mantle cell lymphoma require specific exclusion before her diagnosis of WM can be made.

* The plasmacytic component will be CD138+, CD38+ and CD45- or dim.

20.4 Response criteria for Splenic MZL and Enrolled Patients with Spleen-Only /Spleen and marrow Disease[24]:

- For patients with Splenectomy: response will be considered when there is at least 50% improvement on the blood counts, non-progressive lymphocytosis and no change or improvement in the degree of BM infiltration.

- For patients solely with splenomegaly, absent CT-measurable disease:

- Partial response: 50% or greater improvement in the disease manifestations. This should include resolution or decrease in spleen size, improvement on cytopenias and resolution or decrease in lymphadenopathy if present. BM should show a decrease in the level of lymphoid infiltration and improvement of the hemopoietic reserve.
- Complete response: Resolution of organomegaly, normalization of the blood counts (Hb412 g dl1; platelets4 100 10 l1 ; neutrophils 41.5 10 l1 and no evidence of circulating clonal B cells). No evidence or minor BM infiltration detected by immunohistochemistry.
- No response and progressive disease: Less than 10% improvement on the disease manifestations or deterioration of the above, respectively.