Protocol #: LCI-HEM-MYE-CRD-004 (MMRC-073 CARJAK)

TITLE: Phase I/II Study of Carfilzomib, Ruxolitinib and Low-Dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma

LAY TITLE: Phase I/II Study of Carfilzomib, Ruxolitinib and Low-Dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma

Coordinating Center:
Levine Cancer Institute
Research and Academic Headquarters
1021 Morehead Medical Drive
Charlotte, NC 28204

Sponsor-Investigator:
Shebli Atrash, MD, MS
Levine Cancer Institute
Research and Academic Headquarters
1021 Morehead Medical Drive
Charlotte, NC 28204
Telephone: (980) 442-4363
Email: shebli.atrash@atriumhealth.org

Statistician:
James Symanowski, PhD
Department of Biostatistics
Levine Cancer Institute
1021 Morehead Medical Drive
Charlotte, NC 28204
Telephone: (980) 442-2348
Email: james.symanowski@atriumhealth.org

Investigational New Drug (IND) # 141696

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

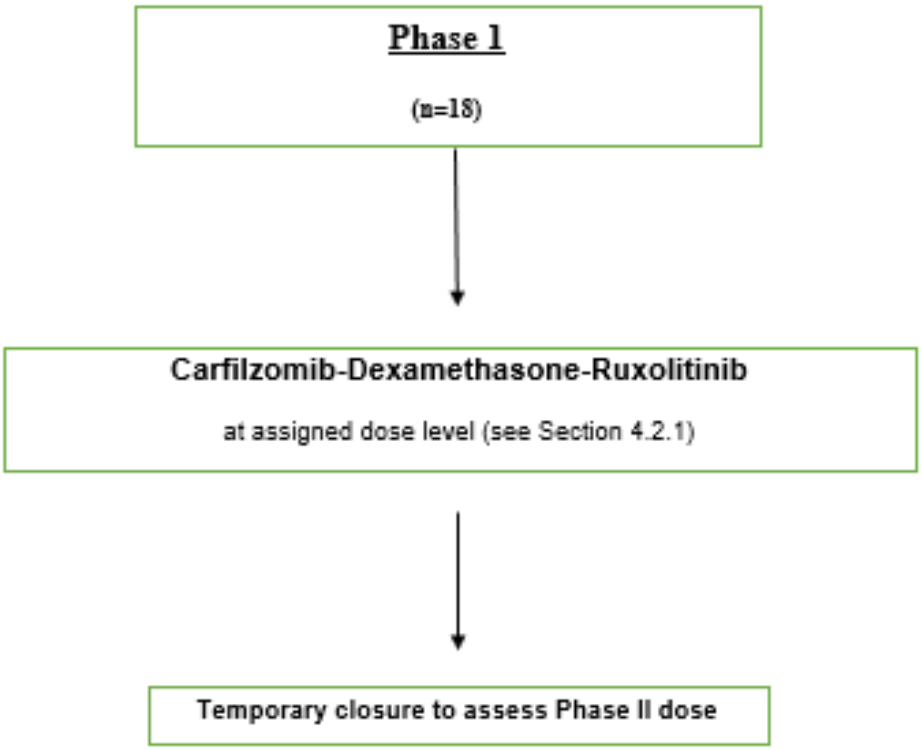
Throughout this document, symbols indicating proprietary names (®, TM) are not displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

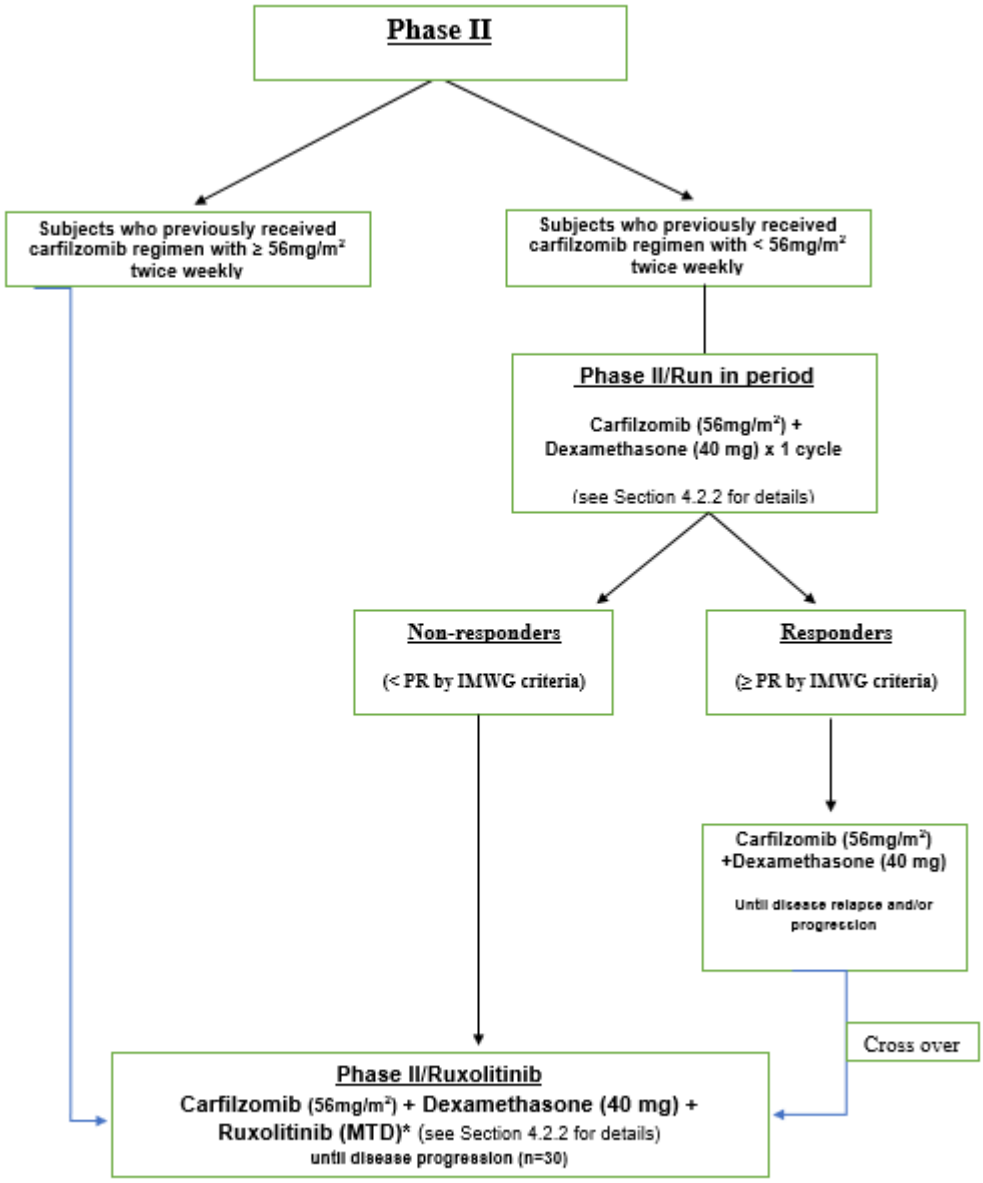
Original Phase I/II / Version 6 / September 27, 2022

PROTOCOL SUMMARY	
Study Title	Pilot Phase I/II Study of Carfilzomib, Ruxolitinib and low-dose Dexamethasone for Carfilzomib-Refractory Multiple Myeloma
Indication	Multiple Myeloma (MM)
Clinical Phase	I/II
Summary of Rationale	Despite major advances in therapy, MM is still considered an incurable malignancy. While the introduction of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), and advances in high dose therapy (HDT) administration have made an impact on progression free survival (PFS) and overall survival (OS) for MM patients in general, the majority of patients suffer relapses with progressively shorter disease-free intervals with each relapse. Therefore, it is imperative to identify the patients at high-risk of disease relapse and develop novel therapeutic regimens that extend PFS and OS in this group of MM patients.
Study Objectives	The **primary objective of Phase I** is to establish the maximum tolerated dose (MTD) of ruxolitinib in combination with carfilzomib and dexamethasone. The **primary objective of Phase II** is to evaluate PFS at 4 months in multiple myeloma subjects who receive the combination treatment carfilzomib, dexamethasone and ruxolitinib. Secondary objectives include evaluation of objective response rate, clinical benefit rate, disease control rate, time to best response, PFS, overall survival, time to progression, duration of response (DOR), any occurrence of adverse events or serious adverse events while on study. Exploratory objectives include exploring the correlation of peripheral blood mononuclear cell (PBMC) SNPs and JAK inhibition with toxicities and treatment response, exploring the correlation of PBMC proteasome inhibition with toxicities and treatment response, and examining changes in biology of BM and BM plasma cells before and after treatment with global gene expression profiling/RNA seq/whole genome sequence/proteomics.
Sample	Up to 18 subjects in Phase I and an additional 30 subjects in Phase II
Inclusion/ Exclusion	**(See protocol for complete inclusion/exclusion criteria)** **Inclusion criteria:** • Age $\geq$ 18 years • Documented history of relapsed and or refractory multiple myeloma with > 2 lines of therapy and evidence of relapse or progression within 60 days of a carfilzomib containing regimen at dose $\geq$ 27 mg/m^2 • Measurable disease • Evidence of adequate bone marrow reserves • Evidence of adequate hepatic, renal, and cardiac function **Exclusion Criteria:**

	• Non-secretory multiple myeloma • Known amyloidosis • Known POEMS syndrome • Clinically significant illness that, in the opinion of the Investigator, places the subject at unacceptable risk for adverse outcome if he/she were to participate in the study • Pregnant or breastfeeding • Known human immunodeficiency virus (HIV) infection • Active hepatitis B and/or hepatitis C infection • "Currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix
Dosage/ Dosage Form, Route, And Dose Regimen	**Phase I**: Carfilzomib will be administered at 56 mg/m2 Days 1, 2, 8, 9, 15, 16 of a 28-day cycle. Dexamethasone will be administered at 40 mg Days 1, 8 and 15 of every cycle. Ruxolitinib to determine maximum tolerated dose (MTD) will be administered orally at 5, 10 or 15 mg twice daily on Days 1-28. Cycles last for 28 days. **Phase II/Run-in Period**: Carfilzomib at a twice weekly dose of 56mg/m2 and dexamethasone will be administered following the Phase I schedule for all subjects who had received a carfilzomib dose less than the twice weekly dose of 56mg/m^2 prior to study enrollment to assess non-response. Note: Subjects who previously received carfilzomib regimen with ≥ 56mg/m2 will proceed directly to Phase II/Ruxolitinib. Non-responders (after Cycle 1): proceed to Phase II/Ruxolitinib. Responders (after Cycle 1): carfilzomib-dexamethasone will be administered until disease relapse/ progression, at which time they will cross over to carfilzomib-dexamethasone-ruxolitinib (Phase II/Ruxolitinib) until disease relapse/progression. **Phase II/Ruxolitinib**: Ruxolitinib will be administered orally at MTD on Days 1-28 for non-responders until disease relapse/progression. Cycles last for 28 days.
Statistical Analysis	Kaplan-Meier techniques will be used to estimate overall survival, progression-free survival, time to progression, time to best response, and duration of response. The 4-month PFS rate will be estimated based on the KM analysis with Greenwood's Formula for the 95% confidence interval. The 4-month response rate will be estimated using all enrolled patients as the denominator with the associated 95% confidence interval by the Clopper-Pearson method. Safety and toxicity will also be assessed using frequencies and proportions. Logistic regression and Cox proportional hazards models will be used to assess the correlation between biomarkers and efficacy and toxicity outcomes.

SCHEMA


Phase 1
(n=18)
Carfilzomib-Dexamethasone-Ruxolitinib
at assigned dose level (see Section 4.2.1)
Temporary closure to assess Phase II dose



*MTD= Maximum tolerated Dose (Determined in Phase I)

LIST OF ABBREVIATIONS

Abbreviation	*Spelled out abbreviation*
ADL	Activities of daily living
ADRs	Adverse drug reaction
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
AUC	Area under the curve
BID	Twice a day
BM	Bone marrow
BSA	Body surface area
BNP	Brain Natriuretic Peptide
BTZ	Bortezomib
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
Cmax	Maximum concentration
CMP	Good manufacturing practices
CR	Complete response
CrCl	Creatinine clearance
CRd	Carfilzomib, revlimid, dexamethasone
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical Trial Management System
DCSI	Development core safety information
DLT	Dose limiting toxicity

DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data and Safety Monitoring Committee
EBMT	European group for blood and bone marrow criteria
EC	Ethics committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FDA	Food and Drug Administration
FLC	Free light chain
FOCBP	Females of child bearing potential
GCP	Good clinical practice
GMP	Good manufacturing practice
HA	Health authority
HBV	Hepatitis B Virus
HDT	High dose therapy
HIV	Human immunodeficiency virus
IMiD	Immunomodulatory agent
INR	International normalized ratio
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IV	Intravenously
JAK	Janus kinase

LCI	Levine Cancer Institute
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MM	Multiple myeloma
MR	Minimum response
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PET/CT	Positron emission tomography/computed tomography
PFS	Progression free survival
PI	Protease inhibitor
PO	By mouth
POEMS	Polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin changes
RNA	Ribonucleic acid
RRMM	Relapsed refractory multiple myeloma
SAE	Serious adverse event
SCLC	Small cell lung cancer
SGOT	Serum glutamatic oxaloacetic transaminase
SGPT	Serum glutamatic pyruvic transaminase

SIFE	Serum immunofixation electrophoresis
SNP	Single nucleotide polymorphism
STATs	Signal transducers and activator of transcription
TLS	Tumor lysis syndrome
TTP	Time to progression
UIFE	Urine immunofixation electrophoresis
UPEP	Urine protein electrophoresis
UPP	Ubiquitin-proteasome pathway

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase I

The primary objective of Phase I is to establish the maximum tolerated dose (MTD) of ruxolitinib in combination with carfilzomib and dexamethasone in relapsed refractory multiple myeloma.

1.1.2 Phase II

The primary objective of the Phase II segment of this study is to evaluate the 4-month progression free survival rate (PFS4) in subjects who receive the combination treatment carfilzomib, dexamethasone and ruxolitinib.

1.2 Secondary Objectives

Secondary objectives include evaluation of objective response rate (ORR), clinical benefit rate, disease control rate, progression-free survival, time to best response, overall survival, time to progression and duration of response in subjects that receive treatment with the triple drug combination, and further evaluation of the safety and tolerability of the combination of carfilzomib, dexamethasone and ruxolitinib (Phase I) and carfilzomib, dexamethasone +/- ruxolitinib (Phase II).

1.3 Exploratory Objectives

Exploratory objectives include the following:

- Explore the correlation of serum cytokine profile with toxicities and treatment response
- Explore the correlation of PBMC proteasome and JAK inhibition with toxicities and treatment response
- Examine changes in biology of BM and BM plasma cells before and after treatment by RNA sequencing

2 BACKGROUND AND RATIONALE

2.1 Study Disease

Multiple myeloma (MM) is a neoplasm of plasma cells that is characterized by osteolytic bone lesions and organ damage, such as hypercalcemia, anemia, and renal insufficiency. Despite major advances in therapy, MM is still considered an incurable malignancy. While the introduction of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), and advances in high dose therapy (HDT) administration have made an impact on PFS and OS for MM patients in general,

the majority of patients suffer relapses with progressively shorter disease-free intervals with each relapse. Therefore, it is imperative to identify the patients at high-risk of disease relapse and develop novel therapeutic regimens that extend progression free survival (PFS) and overall survival (OS) in this group of MM patients.

2.2 Carfilzomib

2.2.1 Carfilzomib Indication

Carfilzomib is a proteasome inhibitor indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. Carfilzomib is also indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

2.2.2 Clinical Pharmacology

Mechanism of Action

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

Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like activity when measured in blood 1 hour after the first dose. On Day 1 of Cycle 1, proteasome inhibition in peripheral blood mononuclear cells (PBMCs) ranged from 79% to 89% at 15 mg/m2, and from 82% to 83% at 20 mg/m2. In addition, carfilzomib administration resulted in inhibition of the LMP2 and MECL1 subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively, at 20 mg/m2. Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing.

Pharmacokinetics

Absorption: The Cmax and AUC following a single intravenous dose of 27 mg/m2 was 4232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1,

suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 mg/m2, there was a dose-dependent increase in exposure.

Distribution: The mean steady-state volume of distribution of a 20 mg/m2 dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

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

Elimination: Following intravenous administration of doses ≥ 15 mg/m2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. The pathways of carfilzomib elimination have not been characterized in humans.

Age: Analysis of population pharmacokinetics data after the first dose of Cycle 1 (Day 1) in 154 patients who had received an IV dose of 20 mg/m2 showed no clinically significant difference in exposure between patients < 65 years and ≥ 65 years of age.

Gender: Mean dose-normalized AUC and Cmax values were comparable between male and female patients in the population pharmacokinetics study.

Hepatic Impairment: The pharmacokinetics and safety of carfilzomib were evaluated in patients with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5 × ULN or AST > ULN), moderate (bilirubin > 1.5 to 3 × ULN), or severe (bilirubin > 3 × ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%).

Renal Impairment: A pharmacokinetic study was conducted in which 43 multiple myeloma patients who had various degrees of renal impairment and who were classified according to their creatinine clearances (CLcr) into the following groups: normal function (CLcr > 80 mL/min, n = 8), mild impairment (CLcr 50–80 mL/min, n = 12), moderate impairment (CLcr 30–49 mL/min, n = 8), severe impairment (CLcr < 30 mL/min, n = 7), and chronic dialysis (n = 8). Carfilzomib

was administered intravenously over 2 to 10 minutes, on two consecutive days, weekly for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. Patients received an initial dose of 15 mg/m2, which could be escalated to 20 mg/m2 starting in Cycle 2 if 15 mg/m2 was well tolerated in Cycle 1. In this study, renal function status had no effect on the clearance or exposure of carfilzomib following a single or repeat-dose administration.

Cytochrome P450: In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. In vitro studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration. Carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

P-gp: Carfilzomib is a P-glycoprotein (P-gp) substrate and showed marginal inhibitory effects on P-gp in a Caco-2 monolayer system. Given that carfilzomib is administrated intravenously and is extensively metabolized, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

2.2.3 Nonclinical Toxicology

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

Carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the in vitro bacterial reverse mutation (Ames) test and was not clastogenic in the in vivo mouse bone marrow micronucleus assay.

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies.

2.2.4 Clinical Studies

The carfilzomib clinical investigation program began in September 2005. Carfilzomib is currently being investigated for potential treatment of both hematologic and solid tumor malignancies, but not necessarily being developed in the solid tumor setting.

As discussed below, the clinical development of carfilzomib initially focused on patients with relapsed and refractory multiple myeloma, assessing carfilzomib as monotherapy in these patients with few therapeutic options. Subsequently, carfilzomib is being evaluated as a

component of combination therapy for treatment in earlier lines of therapy for patients with multiple myeloma, including newly diagnosed multiple myeloma patients. The clinical program has also expanded to include investigation in solid tumors (e.g., small cell lung cancer lung cancer [SCLC]) and pediatric acute lymphoblastic leukemia (ALL), but not necessarily developed in these settings.

lnitial Clinical Development – Carfilzomib as Monotherapy

Carfilzomib for Injection was originally approved in 2012 in the United States (US) (brand name Kyprolis) under the US Food and Drug Administration's (FDA) accelerated approval program for the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory drug (IMiD), and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Accelerated approval in the US, was based on the results of the single-arm Phase II study PX-171-003 – Part 2 (A1) where an ORR of 23.7%, DOR of 7.8 months, PFS of 3.7 months, and OS of 15.4 months were observed. The approved carfilzomib dose is 20 mg/m2 during Cycle 1, and if tolerated, the dose is increased to 27 mg/m2 during Cycle 2, given twice weekly for 3 of every 4 weeks (Days 1, 2, 8, 9, 15, and 16), with infusion durations of 2 to 10 minutes. In an even more advanced and refractory population, the Phase III Study PX-171-011 (FOCUS) did not meet the primary objective of demonstrating superiority of carfilzomib monotherapy over the active doublet therapy in the control arm (corticosteroids and optional cyclophosphamide) in OS (hazard ratio [HR] = 0.975 [95% confidence interval (CI): 0.760–1.249], 1-sided p-value = 0.4172). The median OS with carfilzomib monotherapy was 10.2 months versus 10.0 months for active control. The PFS was similar in both study arms of PX-171-011 (carfilzomib monotherapy 3.7 months versus active control arm 3.3 months, HR = 1.091 [95% CI: 0.843–1.410]).

Subsequent Clinical Development – Carfilzomib in Combination Therapy

The efficacy observed in the monotherapy program supported the development of carfilzomib in combination with lenalidomide and low-dose dexamethasone, based on the hypothesis that this combination may result in the ability to deliver optimized proteasome inhibition leading to improved efficacy. Results from the randomized, pivotal, Phase III Study PX-171-009 (ASPIRE) demonstrated that carfilzomib in combination with lenalidomide (Revlimid) and low-dose dexamethasone (CRd) in subjects with relapsed multiple myeloma has unprecedented efficacy with an 8.7-month improvement in median PFS when compared with (Revlimid) lenalidomide with low-dose dexamethasone (Rd) (HR = 0.69), and a median PFS of 26.3 months with CRd treatment.

Current Status of Carfilzomib Clinical Development

As of 19 July 2019, approximately 4508 individual subjects have been treated with carfilzomib as participants of Amgen-sponsored clinical studies. As of 31 July 2019, approximately 6582 subjects have received carfilzomib in investigator-sponsored trials.

A thorough and comprehensive assessment of carfilzomib safety was conducted by Amgen with safety information available from a large clinical development program. Important adverse drug reactions (ADRs) identified based on a comprehensive analysis of safety data from all relevant sources, including clinical studies and the Amgen Global Safety Database have been well-characterized. There was no evidence of cumulative or new-onset toxicity with prolonged exposure to carfilzomib. Overall, the safety and efficacy data from the clinical program support continued development of carfilzomib in subjects with multiple myeloma and expansion to the pediatric ALL population.

2.3 Dexamethasone

2.3.1 Description

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

2.3.2 Toxicology

Human Toxicology: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis.

2.3.3 Pharmacology

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. Dexamethasone may suppress the body's response to viral and bacterial infections.

2.4 Ruxolitinib

2.4.1 Mechanism of Action

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

2.4.2 Pharmacodynamics

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF patients. Ruxolitinib administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 10 hours in both healthy subjects and myelofibrosis patients.

2.4.3 Pharmacokinetics

Absorption

In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (Cmax) achieved within 1 to 2 hours post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was estimated to be at least 95%. Mean ruxolitinib Cmax and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There were no clinically relevant changes in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal, with the mean Cmax moderately decreased (24%) and the mean AUC nearly unchanged (4% increase).

Distribution
The apparent volume of distribution of ruxolitinib at steady-state is 53 to 65 L in myelofibrosis patients. Binding to plasma proteins in vitro is approximately 97%, mostly to albumin.

Metabolism
In vitro studies suggest that ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

Elimination
Following a single oral dose of [14C]-labeled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity. The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean half-life of ruxolitinib + metabolites is approximately 5.8 hours.

2.4.4 Clinical Studies in Myeloproliferative Neoplasms

Two randomized Phase III studies (Studies 1 and 2) were conducted in patients with myelofibrosis (either primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group Consensus Criteria (IWG).

The starting dose of ruxolitinib was based on platelet count. Patients with a platelet count between 100 and 200 X 109/L were started on ruxolitinib 15 mg twice daily and patients with a platelet count greater than 200 X 109/L were started on ruxolitinib 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily for patients with platelet counts between 100 to less than or equal to 125 X 109/L of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 X 109/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 X 109/L.

2.4.5 Clinical Studies in Multiple Myeloma

There is pre-clinical data[1] (Burger R et al, ASCO 2012) that demonstrates direct cytotoxic effects of ruxolitinib on JAK-STAT pathway dependent cell lines and IL-6 mediated dexamethasone resistance could be reversed by addition of ruxolitinib.

2.5 Background/Study Rationale

The ubiquitin-proteasome pathway (UPP) is responsible for the vast majority of regulated intracellular proteolysis1 and has been best validated as a target for cancer therapy in MM2-Pre-clinical[2-8] and clinical studies [9-19] have led to regulatory approvals of the PIs bortezomib and carfilzomib. Plasma cells are uniquely sensitive to PIs since the UPP capacity for protein turnover is impaired during their differentiation, creating an unfavorable match between proteasome load and capacity[20]. This balance has been proposed as a determinant of the apoptotic sensitivity to PIs, with plasma cells having a low protein load and/or high proteasome capacity showing relative resistance, while a high load and/or low capacity confers sensitivity[21]. In the clinic, the PIs are used in virtually all patients[22-26].

Despite their demonstrated benefits, response rates to bortezomib or carfilzomib in unselected patients in the relapsed and/or refractory settings are less than 50%[17-18] and 25%[21-23], respectively, and their use is associated with substantial toxicities and cost. Moreover, virtually all patients who initially respond eventually develop disease that is refractory to further PI-based therapy through poorly defined mechanisms.

The current Phase I/II study of carfilzomib, ruxolitinib and low-dose dexamethasone is to evaluate the potential to overcome PI resistance in RRMM who have previously relapsed or progressed on carfilzomib.

The primary purpose of this trial is to determine if the combination of carfilzomib, ruxolitinib and low-dose dexamethasone improves the 4-month progression free survival rate compared to historical controls.

3 SUBJECT SELECTION

3.1 Accrual

This trial will enroll subjects with a diagnosis of relapsed or relapsed-refractory MM. Up to 18 DLT evaluable subjects will be enrolled in Phase I with 3 dose levels of ruxolitinib to be tested. Up to an additional 30 PFS4 evaluable subjects may be enrolled in the Phase II part at the MTD determined in Phase I.

All races and ethnic groups are eligible for this study.

3.1.1 Inclusion Criteria

Subjects must meet all the following criteria:

1. Documented history of relapsed and/or refractory multiple myeloma with > 2 lines of therapy. One of the prior lines of therapy must have been a carfilzomib containing regimen with evidence of relapse or progression within the last 60 days of the carfilzomib containing regimen with a carfilzomib dose of at least 27 mg/m^2. Carfilzomib containing regimen at the standard dose of 20/27 mg/m2 is acceptable.
2. Measurable disease, as defined by at least one of the following:
    a. Serum monoclonal protein level ≥0.5 g/dL for IgG, IgA, or IgM disease
    b. Urinary M-protein excretion of ≥200 mg over a 24-hour period
    c. Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio
3. Adequate bone marrow reserves, as defined by the following:
    a. Absolute neutrophil count (ANC) ≥ 1000 cells/mm3 within 1 week of the initiation of treatment. G-CSF may not have been administered within 7 days of Cycle 1 Day.

   b. Platelet count of ≥75 ,000 cells/mm3 for subjects who have bone marrow plasmacytosis of <50%, or ≥50,000 cells/mm3 for subjects who have bone marrow plasmacytosis of ≥50%
4. Adequate hepatic function, as defined by the following:
   a. Total bilirubin ≤2 times the upper limit of the institutional normal values
   b. Total AST and ALT ≤3 times the upper limit of the institutional normal values
5. Adequate renal function, as defined by the following: creatinine clearance (CrCl) ≥30 mL/min., as measured by a 24-hour urine collection, or estimated by the Cockcroft and Gault formula.
6. Adequate cardiac function defined as LVEF ≥ 40% by MUGA, echocardiogram or cardiac MRI.
7. Be 18-75 years of age
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
9. FOCBP and male subjects who are sexually active with FOCBP must agree to use two highly effective (as determined per the Investigator) methods of contraception during the study and for 30 days (female subjects) or for 90 days (male subjects) following the last dose of study treatment including a male condom.
10. Written informed consent and HIPAA authorization for release of personal health information signed by the subject or his/her legally authorized representative.
11. Recovered from all reversible acute toxic effects of prior therapy (other than alopecia) to ≤ Grade 1 or baseline.

3.1.2 Exclusion Criteria

Subjects must not meet any of the following criteria:

1. Non-secretory multiple myeloma
2. Known amyloidosis
3. Known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Clinically significant illness including, but not limited to the following: active systemic infection, uncontrolled hypertension (as defined by BP > 160/90), New York Heart Association Class III and IV heart failure, unstable angina pectoris, myocardial infarction within the past 6 months of consent, uncontrolled cardiac arrhythmia, or any other condition (including laboratory abnormalities) that, in the opinion of the Investigator, places the subject at unacceptable risk for adverse outcome if he/she were to participate in the study
5. Prior cerebrovascular accident with persistent neurologic deficit.
6. Psychiatric illness/social situations that would limit compliance with study treatment and requirements

7. Pregnant or breast feeding. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test within the 7 days prior to study drug administration and a negative urine pregnancy test within the 3 days prior to the first study drug administration.
8. Known human immunodeficiency virus (HIV) infection
9. Active hepatitis B and/or hepatitis C infection
    - Subjects with resolved HBV infection (i.e. subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Subjects who are PCR positive will be excluded. Exception: subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
10. "Currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Subjects are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for >5 years and are considered by their physician to be at less than 30% risk of relapse. In addition, subjects with basal cell carcinoma of the skin, superficial carcinoma of the bladder, carcinoma of the prostate with a current PSA value of <0.5 ng/mL, or cervical intraepithelial neoplasia will be eligible. Finally, subjects who are on hormonal therapy for a history of either prostate cancer or breast cancer may enroll, provided that there has been no evidence of disease progression during the previous three years.
11. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
12. Contraindication to any of the required concomitant drugs or supportive treatments or intolerance to hydration due to preexisting pulmonary or cardiac impairment including pleural effusion requiring thoracentesis or ascites requiring paracentesis.
13. Known intolerance to carfilzomib.
14. Co-administration with strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) as well as fluconazole (a dual inhibitor of CYP3A4 and CYP2C9).

4 INVESTIGATIONAL PLAN

4.1 Milestone Date Definitions

Registration date: the date the subject signs the informed consent form.

Enrollment date: the date of initiation of study treatment on Cycle 1, Day 1. For the Phase I part of the study, this will be the date of initiation of treatment with carfilzomib, dexamethasone and ruxolitinib. For the Phase II part of the study, this is the date of initiation of treatment with carfilzomib and dexamethasone +/- ruxolitinib.

Treatment discontinuation date: the date the Investigator decides to discontinue the subject from study treatment.

4.2 Overall Study Design

This is an open label, Phase I/II protocol. This study will open as a multi-center study being conducted at Levine Cancer Institute (LCI) and additional investigational sites. Potentially, a total of 18 DLT evaluable subjects will be enrolled on the Phase I portion and up to 30 PFS4 evaluable subjects may be enrolled on the Phase II portion of this study. The study accrual period will be an estimated 36 months.

4.2.1 Phase I Design

Phase I will follow the standard 3 + 3 design with 3 to 6 subjects, depending on dose limiting toxicity (DLT) observed, at each dose level to be tested. Up to 3 dose levels will be tested. The overall duration of the Phase I portion of the study is expected to be no longer than 12 months.

Subjects will receive carfilzomib 56 mg/m^2/day* IV over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of a 28 day cycle. *Note: Subjects who have received CFZ < 56mg/m^2 more than 60 days prior to informed consent should receive CFZ 20mg/m2 on Days 1 and 2 of the first cycle of protocol therapy with subsequent doses of 56mg/m^2.

Dexamethasone is administered orally prior to carfilzomib at 40 mg on Days 1, 8, and 15 of a 28 day cycle. Note: a 20 mg dose may be considered for subjects ≥ 75 years of age and for diabetic subjects.

Ruxolitinib is administered orally with or without food twice daily for 28 days of a 28 day cycle

Table 1: Dose Levels to be Tested

Cohort **Each cycle is 28 days**	**Carfilzomib** **IV over 30 min**	**Dexamethasone** **PO**	**Ruxolitinib** **PO**

	Days 1, 2, 8, 9, 15, 16	Days 1, 8 and 15	Twice Daily Days 1-28
Cohort 1	56 mg/m^{2}[a]	40 mg PO[b]	5 mg
Cohort 2	56 mg/m^{2}[a]	40 mg PO[b]	10 mg
Cohort 3	56 mg/m^{2}[a]	40 mg PO[b]	15 mg

a. Subjects who have received CFZ < 56mg/m^2 more than 60 days prior to informed consent should receive CFZ 20mg/m2 on Days 1 and 2 of the first cycle with subsequent doses of 56mg/m^2. See section 4.2.1.1 for MTD guidance
b. A 20 mg dose may be considered for subjects ≥ 75 years of age and for diabetic subjects.

4.2.1.1 Phase I Dose Escalation Guidelines

The first cohort of subjects enrolled in the Phase I portion of the study will receive dose level 1. A full safety evaluation will be conducted when these subjects have completed one cycle of combination therapy. Based on the evaluation after the first cycle, the dose escalation for subsequent subjects will proceed as follows:

- If no DLT is reported in the first three subjects at a dose level, that dose level will be considered safe, and three subjects will be enrolled at the next higher dose level.
- If 1 out of 3 subjects in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable subjects. If 2 or more subjects in a cohort of 6 subjects at a dose level has a DLT, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*.
- If there is at most 1 subject with a DLT among an expanded cohort of six evaluable subjects, that dose level will be considered safe and a cohort of three subjects will be enrolled in the next higher dose level.

When the MTD has been exceeded:

If less than 6 subjects have been treated in the next lower dose level (the possible MTD level), additional subjects will be entered into this dose level until there are 6 subjects treated. If at most 1 of these 6 subjects encountered DLT, then this dose level will be declared to be the MTD. If 2 or more of the 6 subjects encounter DLT, then the MTD has been exceeded.

NOTE: If a subject discontinues treatment for reasons unrelated to adverse events such that safety in cycle one cannot be fully evaluated, an additional subject may be enrolled; this will be reviewed on a case by case basis.

4.2.1.2 Definition of Maximum Tolerated Dose

The MTD of the combination of carfilzomib, dexamethasone and ruxolitinib in multiple myeloma subjects shall be defined as the highest dose level resulting in at most 1 out of 6 subjects experiencing DLT in Cycle 1. The dose will be escalated in a new cohort until an MTD is identified or the maximum planned dose is achieved.

4.2.1.3 Definition of DLT

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as related or possibly related to the study regimen that occurs within the first cycle of treatment and meets any of the criteria outlined below. National Cancer Institute CTCAE version 4.03 will be used for all adverse event grading.

- Grade 3 or greater non-hematologic toxicity possible/probable/definitely related to treatment. The following exceptions will apply:
  - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
  - Grade 3 fatigue for less than 1 week
  - Grade 3 or higher isolated electrolyte abnormalities that last up to 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions
  - Grade 3 or higher amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis
  - Grade 3 tumor lysis syndrome (TLS) that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3-4 thrombocytopenia (platelet count < 50,000/ mm3) with clinically significant bleeding.
- Grade 4 neutropenia must occur for more than 5 days to be considered a DLT. A grade 4 neutropenia with duration of less than or equal to 5 days or grade 3 neutropenia must result in neutropenic fever with elevated temperature (defined as

ANC < 1000/mm3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for more than one hour) to be considered dose-limiting.

- Other grade 4 hematological toxicity (other than thrombocytopenia, neutropenia, leukocytopenia and lymphopenia)

The prophylactic use of G-CSF and platelet transfusions in cycle one of the dose escalation cohorts in Phase I is not permitted.

Once the MTD has been determined in Phase I, an additional 30 evaluable subjects will be enrolled and treated at the MTD. The evaluation of the MTD will be based on the toxicity observed during Cycle 1 of Phase I.

4.2.2 Phase II Design

Subjects in the Phase II/Run-in period will receive an initial cycle with carfilzomib at the twice weekly dose of 56mg/m2 and dexamethasone. Following Cycle 1, a response assessment will be done. Subjects with a response of PR or better ("Responders") will continue therapy with carfilzomib and dexamethasone. After these responding subjects subsequently progress, they will be treated with ruxolitinib (at the dose established in Phase 1) in combination with carfilzomib and dexamethasone. Subjects with a response of less than PR ("Non-responders") will add ruxolitinib at the dose established in Phase I to carfilzomib and dexamethasone for all subsequent cycles. The cycle when ruxolitinib is added will be considered Cycle 1 (cycle numbers will start over). Disease evaluation assessment results should be available prior to dosing on Day 1 of each cycle of Phase II until initiation of ruxolitinib treatment (to ensure initiation of ruxolitinib occurs on Day 1 of a cycle).

Enrollment in the Phase II part of the study will be carried out in two stages. During the first stage, 10 PFS evaluable subjects (Section 13.3) will be enrolled. Enrollment and Stage 1 analysis of the first ten subjects on the three drugs (carfilzomib-ruxolitinib-dexamethasone) will be completed to determine if at least 3 of 10 subjects are alive and progression free at 4 months. If so, an additional 20 subjects will be enrolled (a total of 30 subjects) during the second stage. If at least 11 of 30 subjects are alive and progression free at 4 months, the null hypothesis will be rejected (based on binomial probabilities, see Section 13.1.2). The overall duration of the Phase II portion of the study is expected to be no longer than 24 months. For both Phase I and Phase II, subjects will be assessed for response after each cycle with confirmation of response according to IMWG response criteria regardless of dose level treated. Doses of each study drug may be interrupted or reduced in an attempt to manage toxicity.

Table 2: Phase II/Run-In Dosing[a]

Drug	Dose	Route	Schedule	Cycle Length

Dexamethasone	40 mg[b]	PO	D1, 8, and 15 (Prior to carfilzomib)	28 days
Carfilzomib	56 mg/m^2[c]	Intravenously (IV) over 30 minutes	D1, 2, 8, 9, 15, and 16	

[a] All subjects enrolled in Phase II will initiate treatment in the Run-in Phase with the exception of subjects who previously received a carfilzomib regimen (prior to study enrollment) of ≥ 56 mg/m^2. These subjects will proceed directly to Phase II/Ruxolitinib (see Table 3). Subjects will have a disease response assessment prior to Cycle 2 (results must be available prior to Day 1 dosing) and will continue treatment in the Run-In until one of the following:

- Determined to be a "Non-responder" after Cycle 1 (defined as < PR per IMWG criteria) OR
- Determined to be a "Responder" after Cycle 1 (defined as ≥ PR per IMWG criteria) with subsequent disease progression

After one of the above criteria are met, subjects will move into the Phase II/Ruxolitinib Phase (see Table 3)

[b] A 20 mg dose may be considered for subjects ≥ 75 years of age or for diabetic subjects.

[c] Subjects who previously received carfilzomib < 56mg/m^2 more than 60 days prior to informed consent should receive carfilzomib 20mg/m2 on Days 1 and 2 of the first cycle with subsequent doses of 56mg/m^2

Table 3: Phase II/Ruxolitinib Dosing[a]

Drug	**Dose**	**Route**	**Schedule**	**Cycle Length**
Dexamethasone	40 mg[b]	PO	D1, 8, and 15 Prior to carfilzomib	28 days *note: Cycle numbers start over at Cycle 1 once ruxolitinib is initiated
Carfilzomib	56 mg/m^2	Intravenously (IV) over 30 minutes	D1, 2, 8, 9, 15, and 16	
Ruxolitinib	MTD from Phase I	PO	Twice daily from C1D1, continuously	

a. Subjects enrolled in Phase II will initiate ruxolitinib at one of the following time-points:

- Initiated treatment in the Run-In Phase and determined to be a "Non-responder" after Cycle 1
- Initiated treatment in the Run-In Phase, determined to be a "Responder" after Cycle 1 with subsequent disease progression
- Determined to have received carfilzomib regimen (prior to study enrollment) of ≥ 56 mg/m^2. These subjects will skip the Run-In Phase and proceed directly to ruxolitinib (in combination with carfilzomib and dexamethasone).

b. A 20 mg dose may be considered for subjects ≥ 75 years of age or for diabetic subjects

4.3 Subject Enrollment

Phase I

Enrolled subjects in Phase I will be DLT evaluable if they experience a DLT during Cycle 1 of treatment with the carfilzomib, ruxolitinib and dexamethasone regimen.

Enrolled subjects in Phase I who do **not** experience a DLT must meet all of the criteria below to be DLT evaluable:

- complete Cycle 1 of ruxolitinib therapy defined as followed
  - initiate Cycle 2, or
  - discontinue ruxolitinib therapy prior to Cycle 2 if the discontinuation date (as defined in Section 4.1) is on Cycle 1 Day 25 or later
- return no more than 20% of the number of ruxolitinib pills prescribed for Cycle 1 (while taking into account the actual length of Cycle 1)
- do not receive G-CSF or platelet transfusions during Cycle 1

Subjects who discontinue study treatment without experiencing a DLT and do not meet the DLT criteria as stated above will not be included in the 3+3 MTD evaluation but will be included in the overall analyses. Enrollment of new subjects to the current cohort will only be considered if there is less than the required number of DLT evaluable subjects to determine toxicity for the cohort. For example, of 3 subjects in a cohort, one withdraws due to disease progression, but 2 others have DLT, there is no need to continue enrollment to the given cohort as the MTD has already been exceeded. Alternatively, of 3 subjects in a cohort, one withdraws due to disease progression, but 2 others have not experienced a DLT, enrollment to the cohort will continue to fully evaluate the cohort with three DLT evaluable subjects).

Phase II

All enrolled subjects will remain in the intent to treat population. Enrollment to the Phase II part of the study will continue until the sample size requirements for the PFS4 evaluable population are achieved (Section 13.3).

5 STUDY TREATMENT

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in the Investigational Brochure and Prescribing Information. Appropriate dose modifications are described in Section 6.

The study drugs must be exclusively used for the investigation specified in this protocol and will only be accessible to authorized staff.

5.1 Carfilzomib

5.1.1 Carfilzomib Dose

Subjects will receive carfilzomib 56 mg/m^2/day IV over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. Subjects who have received CFZ < 56mg/m2 more than 60 days prior to informed consent should receive CFZ 20mg/m^2 on Days 1 and 2 of the first cycle of carfilzomib with subsequent doses of 56mg/m^2.

The dose will be calculated using the subject's actual BSA at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Dose adjustments do not need to be made for weight changes of less than or equal to 20% from baseline weight.

5.1.2 Carfilzomib Administration

5.1.2.1 Hydration and Fluid Monitoring

- At least 48 hours before the first dose of carfilzomib, oral hydration should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. In subjects considered at risk for TLS, oral hydration should be continued in Cycle 2 and beyond as required by the subject's medical condition and at the Investigator's discretion.
- IV hydration will be given immediately prior to carfilzomib during the first cycle of carfilzomib. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Co-morbidities should be considered when determining the appropriate volume of fluid to administer (e.g. consider 250 ml for subjects with increased cardiac risk). If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at the completion of the first cycle of carfilzomib (Cycle 2 Day 1), then the recommended IV hydration should be given additionally before each dose in the second cycle. 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.

- If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.

5.1.2.2 Carfilzomib Infusion

- Carfilzomib will be given as an IV infusion over approximately 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 carfilzomib in the first cycle of carfilzomib. During these observation times, post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) is recommended but will be administered per the investigator's discretion . Subjects should be monitored periodically during this period for evidence of fluid overload.

5.1.3 SAFETY CONSIDERATIONS

- 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 the first or second cycle of carfilzomib, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available and instituted, as medically indicated.
- Acyclovir or similar should be given to all subjects, per institutional prophylaxis guidelines, unless contraindicated.
- For subjects who are carriers of HBV, prophylaxis with antivirals should be considered.
- CrCl changes are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib on Day 1, 8, and 15 of all cycles. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation as outlined in Section 6.3.
- Subjects with active or suspected infection of any kind that required IV systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been completed.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts ≤ 25,000/mm3, carfilzomib dosing must be held. If

platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions / Adjustments rules outlined in Section 6.3.

- Subjects should have anemia treated in accordance with the Institutional guidelines.
- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered as clinically indicated to prevent dehydration.
- Subjects with a history of HBV should be closely monitored for signs and symptoms of active HBV infection throughout treatment with carfilzomib, including the 30-day safety monitoring follow-up period.
- Subjects receiving carfilzomib should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms that may be suggestive of Progressive Multifocal Leukoencephalopathy (PML) as part of the differential diagnosis of central nervous system disorders. If PML is suspected, subjects should be referred to a specialist and appropriate diagnostic testing should be initiated. If a PML diagnosis is confirmed, carfilzomib should be permanently discontinued.
- Contraception/Female: Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females of childbearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

  Based on its mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in subjects receiving the recommended dose. Carfilzomib administered to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits. If carfilzomib is used during pregnancy, or if the subject becomes pregnant while taking this drug, she should inform the investigator or study staff immediately. The investigator should notify Amgen of the pregnancy and discuss follow-up with the subject. It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using oral contraceptives, or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception.

- Breastfeeding: No studies of carfilzomib have been conducted in breastfeeding women. Carfilzomib should not be used during breastfeeding. Breastfeeding women and women planning on breastfeeding may not participate in clinical trials with carfilzomib.

If a woman breastfeeds during the study, she must inform the investigator or study staff immediately. The investigator should notify Amgen that the subject has breastfed the infant and discuss follow-up with the subject.

- Contraception/Male: Males of reproductive potential should be advised to avoid fathering a child while being treated with carfilzomib. The potential for carfilzomib to be transferred via semen and its effect on sperm are unknown. Male subjects should refrain from donating sperm for at least 90 days after the last dose of carfilzomib. Male subjects treated with carfilzomib and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib and for 90 days after treatment. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

  Male subjects should be advised to inform the investigator or study staff immediately in the event that their female partner becomes pregnant during the study. Upon receipt of this information, the investigator should notify Amgen of the pregnancy and discuss follow-up regarding the pregnancy outcome with the subject.

5.1.4 Carfilzomib Drug Supply

Vials of carfilzomib contain 60 mg of sterile white to off-white lyophilized cake or powder. The vial amount may exceed the required dose; however vials are for single use only. Mixing carfilzomib with or administering as an infusion with other medicinal products is not allowed. Unopened vials will be stored in the original package to protect from light exposure at 2ºC to 8ºC (36ºF to 46ºF). Carfilzomib will be supplied by Amgen.

5.2 Dexamethasone Dosage and Administration

Formulation: Dexamethasone is available in seven potencies (0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) in tablet form.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: **For this study, dexamethasone is administered orally.** Dexamethasone is administered prior to carfilzomib at 40 mg on Days 1, 8, and 15 of each 28 day cycle for all cycles. A 20 mg dose may be considered for subjects ≥ 75 years of age and for diabetic subjects.

Supplier: Dexamethasone will be commercially supplied. Please refer to the package insert for complete information.

5.3 Ruxolitinib Dosage and Administration

Ruxolitinib is administered orally with or without food at the assigned cohort dose (5, 10 or 15 mg) during Phase I or the MTD twice daily continuously for 28 days during Phase II (see Section 4.2.1 for dosing cohorts). If a dose is missed, the subject should not take an additional dose, but should take the next usual prescribed dose.

5.3.1 Safety Considerations

- Treatment with ruxolitinib can cause thrombocytopenia, anemia and neutropenia. Manage thrombocytopenia by reducing the dose or temporarily interrupting ruxolitinib. Platelet transfusions may be necessary. Subjects developing anemia may require blood transfusions and/or dose modifications of ruxolitinib. Severe neutropenia (ANC less than 0.5 X 109/L) was generally reversible by withholding ruxolitinib until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until counts are stabilized, and then as clinically indicated.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with ruxolitinib until active serious infections have resolved. Observe subject receiving ruxolitinib for signs and symptoms of infection and manage promptly.
- Tuberculosis infection has been reported in patients receiving ruxolitinib. Observe subjects receiving ruxolitinib for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating ruxolitinib, subjects should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. For subjects with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting ruxolitinib. The decision to continue ruxolitinib during treatment of active tuberculosis should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment. If PML is suspected, stop ruxolitinib and evaluate.
- Advise subjects about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected.
- Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking ruxolitinib. The effect of ruxolitinib on viral replication in patients with chronic HBV infection is unknown. Subjects with chronic HBV infection should be treated and monitored according to clinical guidelines.
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with ruxolitinib. Perform periodic skin examinations.

- Treatment with ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with ruxolitinib. Assess lipid parameters approximately 8-12 weeks following initiation of ruxolitinib therapy at investigator discretion. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

5.3.2 Ruxolitinib Drug Supply

Ruxolitinib 5 mg tablets are round and white to off-white in color.

Ruxolitinib will be supplied as 5 mg tablets packaged in 60-count high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs.

Ruxolitinib will be supplied by Incyte. All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use." Bottles of ruxolitinib tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.4 Treatment Compliance

Subject compliance with the treatment and protocol includes ability and willingness to comply with all aspects of the protocol. At the discretion of the Sponsor-Investigator, a subject may be discontinued from the protocol for non-compliance with follow-up visits or study drug.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue until one of the following criteria applies**:**

- Disease progression (after ruxolitinib is initiated)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw consent for treatment
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.

5.6 Drug Accountability

Ruxolitinib and carfilzomib will be stored at the investigational sites in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and will be inaccessible to unauthorized personnel.

An adequate record of receipt, distribution, and destruction of all study drugs must be kept in the form of a drug accountability log per investigational site, Amgen, and Incyte requirements. The site Principal Investigator, or responsible party designated by the site Principal Investigator, will maintain a careful record of the inventory. Drug accountability logs will be subject to monitoring by the Sponsor.

Study drug will be dispensed to subjects from the site investigational pharmacy. Unused drug will be returned to the investigational pharmacy from which it was dispensed. Upon termination or completion of the study, all unused Amgen study drug should be returned to Amgen and all unused Incyte study drug should be returned to Incyte. If Amgen and/or Incyte directs that study drug should be destroyed upon termination or completion of the study, appropriate documentation will be provided by the site investigational pharmacy.

6 DOSE MODIFICATIONS

6.1 Phase I and Phase II Dose Modification and Dose Delay

Dose reductions are not permitted during Cycle 1 of Phase I unless the subject experiences a DLT. The subject may continue protocol therapy if the toxicity resolves, and the subject can be managed by a dose modification as detailed in this section. However, the occurrence of the DLT will be counted toward the assessment of the MTD. Dose reductions are permitted in subsequent cycles of Phase I and during all cycles of Phase II for clinically significant hematologic and non-hematologic toxicities. Held doses are not made up.

The prophylactic use of G-CSF and platelet transfusions in Cycle 1 of the dose escalation cohorts in Phase I is not permitted. Dose adjustments are permitted according to rules described in this section. Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor-Investigator; unless required for immediate subject safety.

Administration of the study drugs will be discontinued in the event of a treatment-related toxicity that persists despite appropriate dose reductions or any other toxicity that, in the opinion of the Investigator, warrants discontinuation.

Toxicity will be assessed using the CTCAE version 4.03 (Appendix 18.2).

All dose modifications should be based on the worst preceding toxicity

6.2 Dose Reduction Steps

6.2.1 Carfilzomib Dose Reduction Steps

Carfilzomib Dose Reduction Steps			
Starting Dose	**Dose reduction step - 1**	**Dose reduction step - 2**	**Dose reduction step - 3**
56 mg/m2	45 mg/m2	36 mg/m2	27 mg/m2

6.2.2 Dexamethasone Dose Reduction Steps

If a subject is unable to tolerate dexamethasone due to dexamethasone related toxicity despite dose reduction to 12 mg, dexamethasone may be discontinued. However, the subject may continue on study treatment after discussing with the Sponsor-Investigator.

Dexamethasone Dose Reduction Steps		
Starting Dose	**Dose reduction step - 1**	**Dose reduction step - 2**
40 mg	20 mg	12 mg

6.2.3 Ruxolitinib Dose Reduction Steps

Ruxolitinib Dose Reduction Steps		
Starting Dose	**Dose reduction step - 1**	**Dose reduction step -2**
15 mg bid	10 mg bid	5 mg bid
10 mg bid	5 mg bid	5 mg qd (consider)
5 mg bid	5 mg qd (consider)	-

6.3 Dose Modification Guidelines for Carfilzomib and Ruxolitinib during a Cycle of Therapy

Hematologic Toxicity	Recommended Action

• Grade 3[a] or 4 Neutropenia (ANC < 1000 mm3) • Grade 4 Thrombocytopenia (Platelets < 25,000 mm3) or any grade with bleeding.	• Withhold ruxolitinib and carfilzomib and re-evaluate in one week • If recovered to Grade 1 or better before next scheduled dose, continue ruxolitinib and carfilzomib at same dose level. • If recovered to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce ruxolitinib and carfilzomib dose by one dose level. Reductions in one drug and not the other may be considered with alternating dose reductions for subsequent occurrence. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Non-Hematologic Toxicity	**Recommended Action**
Cardiac Toxicity Grade 3 or 4, new onset or worsening of: • congestive heart failure; • decreased left ventricular function; • or myocardial ischemia	• Withhold carfilzomib until resolved or returned to baseline. • After resolution, consider restarting carfilzomib at a reduced next dose level if appropriate. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Hypertension	• Withhold carfilzomib until resolved or returned to baseline. • Restart at the dose used prior to the event or next dose level at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Complications • Grade 3 or 4	• For drug related Grade 3 or 4 pulmonary toxicity, permanently discontinue carfilzomib.
Hepatic Toxicity • Grade 3 or 4 elevation of transaminases, bilirubin or other liver abnormalities	• Withhold carfilzomib and ruxolitinib until resolved or returned to baseline. • After resolution, consider if restarting carfilzomib and ruxolitinib is appropriate; may be reinitiated at a reduced dose with frequent monitoring of liver function. • 25% dose reduction of carfilzomib in case of baseline or treatment emergent mild or moderate hepatic impairment. • Restart ruxolitinib with one dose level reduction. • If tolerated, the reduced doses of both drugs may be escalated to the previous doses at the discretion of the physician.

Renal Toxicity • Serum creatinine equal to or greater than 2 × baseline	• Withhold carfilzomib and ruxolitinib until renal function has recovered to Grade 1 or to baseline and monitor renal function. • Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation. • If attributable to carfilzomib, restart at the next scheduled treatment at a reduced dose • If not attributable to carfilzomib, restart at the dose used prior to the event. If attributable to ruxolitinib, restart with one dose level reduction. • If not attributable to ruxolitinib, restart at the dose used prior to the event • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Posterior Reversible Encephalopathy Syndrome (PRES)	• If PRES is suspected, hold carfilzomib. Consider evaluation with MRI for onset of symptoms suggestive of PRES. • If PRES is confirmed, permanently discontinue carfilzomib. • If PRES is excluded, may resume carfilzomib at same dose if clinically appropriate. • If PRES recurs, permanently discontinue carfilzomib.
Thrombotic Microangiopathy (TMA)	• If TMA is suspected, hold carfilzomib and manage per standard of care. • If TMS is confirmed and related to carfilzomib, permanently discontinue carfilzomib. • If TMA is excluded, may restart carfilzomib.
If Progressive Multifocal Leukoencephalopathy (PML) is suspected	• Hold carfilzomib • Refer to a specialist; appropriate diagnostic testing should be initiated • If a diagnosis of PML is confirmed, permanently discontinue carfilzomib
Active HBV reactivation	• Withhold carfilzomib until the infection is adequately controlled. If the benefits outweigh the risks, carfilzomib may be resumed with concomitant prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.
Active or suspected infection of any kind that requires systemic treatment	• Hold carfilzomib until the infection has resolved and the course of antibiotics has been completed, if being treated with an anti-infective(s)
Other Grade 3 or 4 non-hematologic toxicity	• Evaluate attribution and withhold the appropriate therapy. If resolved to ≤ Grade 1 or baseline, restart the withheld therapy with one level dose reduction of suspected drug. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

6.4 Dose Modification Guidelines for Dexamethasone

Dose Modifications for Toxicity Related to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above

		measures, decrease dose by one dose level until levels are satisfactory.

6.5 Criteria for Initiation of a New Cycle of Therapy

For a new cycle of treatment to begin, the subject must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be greater than or equal to 25,000/mm3
- All other non-hematologic treatment-related toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the subject's baseline condition, with the exception of fatigue which must have resolved to ≤ Grade 2.

If the subject fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the subject should be re-evaluated to determine whether the criteria have been met. If the subject continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Investigator. Phase II/Run-In only: beginning with Cycle 1, disease evaluation results should be available prior to dosing on Day 1 of each cycle until initiation of ruxolitinib (Phase II/Ruxolitinib).

7 CONCOMITANT MEDICATIONS

All baseline medications that the subject is taking within 14 days prior to the initiation of therapy must be recorded in the subject medical record. All additional medications (other than study drug or changes in baseline medications) administered during the study must be listed in the subject's medical record.

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the Investigator.

7.1 Required Concomitant Therapy

- Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study and for 30 days following the last dose of study treatment. Male subjects must agree to use a barrier method of contraception for the duration of the study and for 90 days following the last dose of study treatment if sexually active with a female of child-bearing potential.
- In addition, subjects must receive acyclovir or similar (famciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis. All subjects must receive prophylaxis with hydration as per Section 5.1.2.1.

- Thromboprophylaxis is recommended for subjects being treated with the combination of carfilzomib with dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the subject's underlying risks.

7.2 Recommended/Allowed Concomitant Therapy

- Prophylactic treatment with anti-emetic(s) prior to carfilzomib administration is recommended. Subsequent anti-emetic drugs against delayed emesis will be administered at the discretion of the investigator.
- Full supportive care is recommended, including transfusions of blood and blood products (including platelets), antibiotics, anti-diarrheals, analgesics, etc. and prophylactic treatment for tumor lysis syndrome when appropriate.
- Bisphosphonate therapy IV or PO is recommended to be administered if indicated in accordance with institutional guidelines.
- Prophylaxis with antivirals should be given to all subjects unless contraindicated, especially subjects who are carriers of HBV.
- The prophylactic use of G-CSF and platelet transfusions is permitted except in Cycle 1 of the dose escalation cohorts (Phase I) unless the subject has hematologic DLT. Erythropoiesis-stimulating agents are permitted throughout the duration of study treatment (any cycle).
- Palliative radiation is allowed

7.3 Contraindicated Concomitant Therapy

- Strong CYP3A4 inhibitors (such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and fluconazole are not permitted in combination with ruxolitinib.
- Concurrent therapy with any approved or investigative anticancer therapeutic drug with activity against multiple myeloma is not allowed.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) > prednisone 10 mg/day (or its equivalent) are not permitted.
- Other investigative agents for multiple myeloma or any other indication should not be used during the study.

8 STUDY PROCEDURES

Please see Table of Events (Appendix 18.5) for details regarding the timing and description of all study procedures.

8.1 Registration

Potentially eligible and interested subjects will be presented with the study informed consent. Following informed consent, subjects will be registered by the Coordinating Center and assigned a four digit number Sequence Number, where 1001 will be the Sequence Number assigned to the first registered subject.

No protocol-related assessments may be performed prior to obtaining informed consent. Men and women of child bearing potential on study will be counseled regarding the need to use contraception throughout the course of the study and for 30 days (female subjects) or 90 days (male subjects) after the last dose of study treatment.

8.2 Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all applicable IRB- approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

8.3 Screening Procedures

All screening procedures must be completed within 21 days prior to start of study treatment unless otherwise specified in the Table of Events (Appendix 18.5)

- Informed consent
- Inclusion/exclusion
- Medical and disease history
- Physical examination
- Vital signs
- ECOG performance status
- Pregnancy test for females of child bearing potential
- Electrocardiogram (ECG)
- ECHO, MUGA, or cardiac MRI
- Concomitant medications - all on-going medications and those taken within 14 days prior to first dose of study treatment
- Disease Assessments (see section 8.4.1)
- Laboratory Assessments (see section 8.4.2)

8.3.1 Disease assessments: Baseline measurements

- Bone marrow aspirate and serum for disease assessment and correlative studies: for % plasma cells, morphology, standard karyotype, cytogenetics by FISH and biomarkers
- Correlative bone marrow specimen: minimum of 12 mL of bone marrow aspirate will be collected and sent to the LCI HOT lab.
- Response assessments, including serum or urine protein electrophoresis (SPEP/UPEP), serum and Urine immunofixation (IFE), serum free light chains (SFLC)/ratio
- β2 microglobulin
- Radiologic imaging of plasmacytoma as clinically indicated (same technique to be used throughout the trial). Positron emission tomography/computed tomography (PET/CT) scan or magnetic resonance imaging (MRI) as clinically indicated
- Bone skeletal survey

Please note that for subjects in Phase II/Run-In who cross over to Phase II/Ruxolitinib, a new baseline should be established for disease assessments prior to initiating ruxolitinib. Response to treatment with ruxolitinib will be calculated using this new baseline.

8.3.2 Screening Laboratory assessments:

- Hematology - hemoglobin, WBC with differential, and platelet count
- Coagulation - PT/INR
- Blood chemistries - sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN, glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine and estimated creatinine clearance (see Appendix 18.4), calcium and lactate dehydrogenase (LDH). Viral hepatitis panel including HBsAg, HB core antibody, HB surface antibody, HepC antibody and HIV at baseline only.
    - HBV DNA testing (by PCR): only for subjects positive for Anti-HBc or Anti-HBs
- Disease specific laboratory evaluations as noted above.
- Correlative blood specimen

8.4 On Study Procedures:

- Vital signs
- Physical Exam
- Laboratory assessments
- ECOG performance status
- Concomitant medications and procedures
- Adverse event monitoring
- ECHO, MUGA, or cardiac MRI
- Correlative studies (Blood and bone marrow aspirate)

- Note: Post-baseline correlative samples should only be collected on subjects receiving ruxolitinib (Phase I and Phase II/Ruxolitinib).

8.4.1 Disease assessments:

- Response assessments, including serum or urine protein electrophoresis (SPEP/UPEP), serum and Urine immunofixation (IFE), serum free light chains (SFLC)/ratio
  - The following assessments will be performed at each urine disease evaluation:
    - Total protein
    - UPEP
    - Urine immunofixation electrophoresis (UIFE)
  - For subjects whose disease is not measurable by UPEP at Baseline, a 24-hour urine sample for UPEP and Urine immunofixation (UIFE) will be collected every 3 cycles at a minimum.
- If disease has not progressed and new anti-cancer treatment has not been started after study treatment discontinuation, response assessment samples should also be collected per standard of care during the follow-up visits.
- Radiologic imaging of plasmacytoma as clinically indicated (same technique to be used throughout the trial). Positron emission tomography/computed tomography (PET/CT) scan or magnetic resonance imaging (MRI) as clinically indicated
- Bone skeletal survey as clinically indicated and to confirm progression if needed.
- Phase II/Run-In only: Beginning with Cycle 1, disease evaluation results to assess response should be available for investigator review prior to dosing on Day 1 (up to 7 days prior) of each cycle until initiation of ruxolitinib. Cycle numbers start over with the initiation of ruxolitinib (the first cycle of ruxolitinib will be Cycle 1) and a new disease response baseline will be established (Phase II/Run-in subjects who cross over to Phase II/Ruxolitinib).

8.4.2 Laboratory assessments:

- Hematology - hemoglobin, WBC with differential, and platelet count
- Blood chemistries - sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN, glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine and estimated creatinine clearance, calcium and lactate dehydrogenase (LDH).
- Brain Natriuretic Peptide (BNP)
- Disease specific laboratory evaluations as noted above.
- Correlative studies (blood and bone marrow). Note: ruxolitinib must have been initiated in order to collect correlatives post-baseline.

8.5 End of Treatment

The end of treatment (EOT) visit is done when the subject discontinues study treatment for any reason. The decision to discontinue study treatment due to progression must be based on the

evaluation of lab assessment. If the decision to permanently discontinue the study treatment is made during a scheduled visit, then the EOT visit should be performed instead of the scheduled visit. If the decision is made between scheduled visits, an EOT visit should be performed no later than 30 days after the last treatment administration or prior to the start of new subsequent anti-cancer therapy, whichever occurs first.

8.6 Follow-Up

Subjects who received ruxolitinib on study and discontinue therapy for reasons other than disease progression should continue to have standard of care disease assessments done until progression or start of subsequent therapy. At such time, follow-up or overall survival status will take place every three months +/- 7 days until death, lost to follow up, or until the criteria defined for the final analyses (Section 13.4.1) are reached. However, in the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, subjects in follow up will continue to be followed until all subjects have discontinued study treatment and completed the required 30 day safety monitoring period (Section 9.3). Follow-up beyond the safety monitoring period is only required for subjects who received ruxolitinib.

8.7 Off-Study

Subjects will remain on study until the criteria for the final analysis have been met. Reasons a subject may be removed from the study early include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the investigator
- The subject or legal representative (such as a parent or legal guardian) withdraws study consent
- The subject is lost to follow-up
- Investigator's decision to withdraw the subject
- Subject death
- Early study termination

Subjects who do not receive ruxolitinib will be taken off study after completion of the safety monitoring period (Section 9.3)

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented.

Subjects that are Off Study will not participate in any study related procedures, including data collection. The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits.

- All subjects have discontinued from the study.
- The IRB, LCI DSMC, Sponsor-Investigator or Amgen or Incyte discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

8.7.1 Subject Withdrawal

In all cases, the reason for withdrawal must be recorded in the subject's medical record and/or research chart and CTMS.

8.7.2 Screen Failures

A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates the study before receiving first dose of the study regimen (Cycle 1, Day 1) is regarded as a "screen failure".

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the Investigator to be of clinical significance

9.2 Serious Adverse Event (SAE):

An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be participants) or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Death
- Life-threatening experience – Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity

- Congenital anomaly/birth defect in subject's offspring
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant, and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

9.2.1 Related:

An event is "related" if, in the opinion of the Investigator, it was definitely or possibly was caused by the research activity.

9.2.2 Unexpected:

An event is "unexpected" when its specificity, nature, severity or incidence is not accurately reflected in the investigator's brochure or Package Insert previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

9.3 Overlapping Toxicities

There is a possibility that hematologic toxicities and non-hematologic toxicities may overlap during study treatment. Overlapping toxicities will be monitored closely in both the Phase I and Phase II portions of the study.

9.4 Adverse Event Reporting

All Adverse Events (AE) will be recorded by the Investigator from the time of the start of study treatment through the end of the designated safety monitoring follow-up period (30 days after last dose of study treatment). AEs and study treatment administration must be recorded in the eCRF within 5 business days of awareness. All relevant historical medical conditions that are known/diagnosed prior to the administration of study drug(s) and ongoing at the time of study treatment initiation are to be recorded.

9.5 Abnormal Laboratory Values Defined as AEs

An abnormal laboratory value is considered to be an AE <u>if</u> the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Requires treatment, modification of study drug dose, or any other therapeutic intervention

- Is judged by the Investigator to be of significant clinical impact/importance
- Meets the criteria for a DLT as defined in Section 4.2.1.3

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE.

9.6 Adverse Event Grading

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting.

Grade refers to the severity (intensity) of the AE:

CTCAEv4.03 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4.03 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

CTCAEv4.03 Grade 3: severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4.03 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv4.03 Grade 5: death due to an AE

9.7 Adverse Event Attribution

The Investigator will assess the relationship of the event to the study treatment. An adverse event is considered to be associated with the use of the study regimen if the attribution is determined as possible, probable or definite. The relationship assessment of the adverse event by the Investigator should be documented as follows:

- Unrelated: The AE is clearly NOT related to the treatment.
- Unlikely Related: The AE is doubtfully related to the treatment.
- Possibly Related: The AE may be related to the treatment.

- Probably Related: The AE is likely related to the treatment
- Definitely Related: The AE is clearly related to the treatment.

9.8 Communication between Investigational Sites

Investigational sites will be required to report AEs for all grades and attributions, SAEs, study drug administration, or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. Study drug administration issues or any other problem potentially affecting the validity/integrity of the study data should be communicated to the Sponsor by email or phone as soon as possible but within *2* business days of the Investigator learning of the event.

10 SAFETY DATA COLLECTION, RECORDING AND REPORTING

Safety variables include the following: AEs and SAEs (whether related to study treatment or not), laboratory changes, changes in vital signs and, in some instances, changes in images, as evaluated at the Investigator's discretion. Adverse events will be evaluated continuously throughout the study. Safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All adverse events (Grades 1 – 5) will be determined by the Investigator and documented in subject study charts.

It is the responsibility of the Sponsor-Investigator, Investigators and the Protocol Team to ensure SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, Institutional Review Board, and FDA policy.

10.1 SAE/Pregnancy and Lactation Reporting to Sponsor-Investigator

Upon learning of an event, Investigators/Investigational Sites must notify the Sponsor-Investigator of any SAE and pregnancy/lactation exposure within 1 business day of awareness from study treatment initiation through 30 days from the last dose of study treatment. All SAEs must be followed to resolution or to stabilization if improvement or resolution is not expected. SAEs that are determined to be related to study treatment or protocol-mandated procedures are reportable for the duration of the subject's participation in the trial. Each investigational site will be responsible to report SAEs that occur at their institution to their respective IRB in accordance with the IRB reporting policy.

When new significant information becomes available, a follow-up report must be reported to the Sponsor-Investigator within 1 business day of awareness.

10.2 SAE Reporting to the FDA

The Sponsor-Investigator will be responsible for all communications with the FDA. Upon learning of the event, the Sponsor-Investigator will report to the FDA, regardless of the site of

occurrence, any serious adverse event (SAE) that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines in accordance with federal regulations.

Unexpected fatal or life-threatening experiences associated with the use of an investigational product will be reported to the FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information. All other serious, unexpected experiences associated with the use of the investigational product will be reported to the FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

The Sponsor-Investigator will notify any participating sites of SAEs reported to the FDA.

10.3 SAE Reporting by Sponsor-Investigator to Amgen and Incyte

The Sponsor-Investigator must notify Amgen regarding all SAEs occurring with carfilzomib. Subsequently, the Sponsor-Investigator must notify Incyte regarding all SAEs occurring with ruxolitinib. The MedWatch Form FDA 3500A must be completed for each event and the form must be sent to the respective funding company based on the contact information and reporting timelines listed below.

Note: Investigational sites are not responsible for submitting SAEs to funding companies as this is a sponsor responsibility.

The Sponsor-Investigator shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports from all investigational sites and will exercise reasonable due diligence to obtain follow-up information from all investigational sites on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the funding company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, the funding company will not contact non-party investigators directly, but will route all such inquiries through Sponsor-Investigator for forwarding to such investigator(s). LCI will be responsible to ensure such inquiries are completed and provided to Amgen and Incyte in a timely manner.

Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant laboratory values, scan data and autopsy reports) which are received after the initial report must be documented on a follow-up MedWatch and submitted to Amgen and Incyte. The Sponsor-Investigator will be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information from investigational sites by, among other things, maintaining written records of such attempts.

The Sponsor-Investigator will provide an annual IND report to Amgen and Incyte. Other reports containing safety data generated during the course of the study will be submitted to Amgen and

Incyte at the time the Sponsor-Investigator submits to anybody governing research conduct (i.e. regulatory authorities and IRBs). The Sponsor-Investigator will support reconciliation of all SAEs at the end of the study at a minimum.

10.3.1 Pregnancy Reporting to Amgen and Incyte

Sponsor-Investigator will report Pregnancy and potential infant exposure including Lactation to Amgen and Incyte within the timeframes listed below:

- Incyte: within 24 hours of Sponsor-Investigator awareness
- Amgen: within ten (10) calendar days of Sponsor-Investigator awareness.

10.3.2 Amgen Reporting/Contact Information

All Serious Adverse Events (SAEs) occurring with carfilzomib required to be reported pursuant to section 10.3 of the protocol shall be provided to Amgen and its representatives by LCI or the Sponsor-Investigator on a MedWatch Form FDA 3500A according to the timelines below.

- Expedited/SUSAR reports: Provide to Amgen within 24 hours after submission to the FDA.

Copies of safety reports submitted to the FDA by the Sponsor-Investigator will be shared with the contact below so that these reports can be evaluated and included in investigator brochure or Amgen IND safety submissions as required to ensure safety of other subjects who are receiving the product from Amgen for sponsored trials. Additionally, the Sponsor will provide any additional reports agreed upon by LCI or the Sponsor-Investigator and Amgen which will include a line listing of all SAEs sent to Amgen every 6-12 months.

Amgen Drug Safety and Pharmacovigilance Contact Information:

Amgen Global Safety

Toll-free #: 1-888-814-8653

Email (Only for sponsors with a secure email connection with Amgen): svc-ags-us@amgen.com

10.3.3 Incyte Reporting/Contact Information

All Serious Adverse Events (SAEs) occurring with ruxolitinib required to be reported pursuant to section 10.3 of the protocol shall be provided to Incyte and its representatives by LCI or the Sponsor-Investigator on a MedWatch Form FDA 3500A within 24 hours of the Sponsor-Investigator becoming aware of the event. Copies of IND safety reports submitted to the FDA by LCI will be shared with the contact below so that these reports can be evaluated and included in

investigator brochure or Incyte IND safety submissions as required to ensure safety of other subjects who are receiving the product from Incyte for sponsored trials.

Incyte Corporation: **SafetyReporting@incyte.com** for e-mail transmission of individual SAE reports;

Safety Contacts: Kathy Lenard Roberts, VP, Global PhV Ops & Systems Quality Management

Phone: 302-498-6727

Fax: 302-425-2780

Robert Livingston, MD, VP, Incyte PhV & Drug Safety

Phone: 302-498-7098

Fax: 302-425-2780

10.4 Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an SAE will be reported to the central IRB per IRB requirements.

Protocol deviations will be reported promptly to the central IRB per IRB requirements.

11 DATA AND SAFETY MONITORING PLAN

Data will be collected in electronic case report forms (eCRFs). Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute Investigator- Initiated Trials and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]) . It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. For the Phase I portion of the study, the Sponsor-Investigator, Statistician, and other study team members, as applicable, will conduct a teleconference after accrual of each cohort to review safety data before approving opening of subsequent cohorts for accrual. The Sponsor-Investigator, and other sponsor-level study team members, will meet to regularly to monitor subject consents, enrollment and retention, safety data and timeliness/validity/integrity of the data on a recurring basis. Documentation of recurring meetings will be kept in the study files. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the institutional LCI Data and Safety Monitoring Plan.

12 MEASUREMENT OF EFFECT

12.1 Timing of Response Evaluation

Response will be evaluated according to the schedule of evaluations listed on the Table of Events (Appendix 18.5)

12.2 Response Criteria:

The IMWG Response Criteria will be used for all evaluations of response. (Appendix 18.3)

12.3 Measurable Disease:

All subjects must have baseline assessment of disease that meet the criteria of measurable disease defined below:

- Serum M protein ≥ 0.5 g/dL (≥ 5 g/L) for IgG, IgA, or IgM disease, quantified by using densitometry on serum protein electrophoresis (SPEP).

  AND / OR

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (> 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis (UPEP see Appendix III: Notes, h.).

  OR

- Subjects who have both serum M protein levels < 0.5 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

13.1.1 Phase I

Phase I up to 18 subjects may be required to evaluate 3 dose levels of ruxolitinib in combination with carfilzomib and dexamethasone in a standard 3 + 3 design.

13.1.2 Phase II

Progression-free survival at 4 months is the primary endpoint for this study. The current study is investigating the impact of adding ruxolitinib to the combination of carfilzomib and dexamethasone in a carfilzomib refractory population. Published study results on carfilzomib plus dexamethasone in a carfilzomib refractory population (as defined in this protocol) have not

been identified. However, it is reported that the time on treatment in multiple myeloma patients receiving three or more lines of therapy had a median time on treatment of approximately 2 months[29]. Therefore, it is assumed that if multiple myeloma subjects who are carfilzomib-refractory were retreated with carfilzomib plus low-dose dexamethasone, they would experience a median PFS of 2 months. A 2-month median PFS corresponds to a 4-month progression-free survival rate of 25%. In this patient population, if subjects treated with carfilzomib, ruxolitinib, and low-dose dexamethasone achieved a median PFS of 4 months, this would be considered a significant clinical benefit. A 4-month median PFS corresponds to a 4-month progression-free survival rate of 50%. A Simon's 2-stage design will be used to test the hypothesis that the 4-month PFS rate is less than or equal to 25%. Ten subjects will be enrolled in the first stage, and if at least 3 of the 10 subjects are alive and progression free at 4 months, an additional 20 subjects will be enrolled (a total of 30 subjects). If at least 11 of 30 subjects are alive and progression free at 4 months, the null hypothesis will be rejected (based on binomial probabilities). Assuming a one-sided alpha = 0.10 significance level, this sample size will provide at least 90% power to reject the null hypothesis, assuming the true 4-month PFS rate is 50%.

13.2 Endpoint Definitions

For response and progression-related endpoints, the baseline disease assessment will be the one that occurred prior to the start of ruxolitinib therapy.

13.2.1 Primary/Phase I: Dose Limiting Toxicity (DLT)

DLTs will be determined for each subject enrolled in Phase I as a binary variable indicating whether or not the subject experienced a DLT (as described in Section 4.2.1.3) during Cycle 1 of ruxolitinib treatment administration.

13.2.2 Primary/Phase II: 4-Month Progression-Free Survival

4-month progression-free survival (PFS4) will be determined for each subject as a binary variable indicating whether or not the subject is alive and progression free at 4 months. The timing of PFS4 begins at the time subjects start treatment with ruxolitinib. The criteria for progression are described in the IMWG Criteria (Appendix 18.3).

13.2.3 Progression-Free Survival and Time to Progression

PFS is defined as the duration of time from the initiation of study treatment with ruxolitinib to first occurrence of either progressive disease or death. Disease progression as described by IMWG Criteria (Appendix 18.3). The date of progressive disease is the date of the initial assessment that identified progressive disease. If the subject dies without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not

have documented disease progression, PFS will be censored at the date of last disease assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last disease assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For subjects with only one missed assessment, the documented progressive disease status and assessment date will be used. Time to progression (TTP) will be determined in a similar fashion as PFS, with the only difference being TTP will be censored at the death date for subjects who die without progressive disease.

13.2.4 Overall Survival

Overall survival is defined as the duration from initiation of ruxolitinib treatment to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

13.2.5 Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of PR or better as per the IMWG criteria after initiating treatment with ruxolitinib.

13.2.6 Clinical Benefit

Clinical benefit will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of minimal response (MR) or better as determined by the IMWG criteria (MR adapted from EBMT) after initiating treatment with ruxolitinib.

13.2.7 Time to Best Response

This will be calculated for all subjects achieving an sCR, CR, VGPR or PR and separately for subjects achieving an MR and will be defined as the time from initiation of ruxolitinib treatment to the time of best objective status assessment of sCR/CR/VGPR/PR or of MR.

13.2.8 Disease control

Disease control will be determined for each subject as a binary variable indicating whether or not the subject achieved an sCR, CR, VGPR, PR, MR or SD $\geq$ 8 weeks in duration after initiating treatment with ruxolitinib.

13.2.9 Duration of response

Duration of response will be calculated for all subjects achieving an sCR, CR, VGPR or PR and separately for subjects achieving an MR (defined per the EBMT criteria) and will be defined as the time from first objective status assessment of sCR/CR/VGPR/PR or of MR to the time of first documented disease progression or death. The censoring mechanism for duration of response will be the same as that described for PFS.

13.2.10 Safety Endpoints

Safety endpoints will include ruxolitinib treatment administration, AEs, SAEs, deaths while on study therapy, vital signs, ejection fraction (%), and selected quantitative laboratory determinations. Treatment administration will be determined for each subject in terms of cumulative dose administration and dose intensity of ruxolitinib (adjusting for dose delays and reductions). Additionally, the relative dose intensity will be calculated for each subject in terms of the actual dose intensity as a percent of the intended dose intensity.

Phase II: Adverse Events of Special Interest (AESI)

AESIs will be continuously monitored during the Phase II part of the study in subjects receiving ruxolitinib for the purposes of the pre-specified stopping rule described in Section 13.4.3. AESIs will be determined for each subject as a binary variable indicating whether or not the subject experienced a Grade 3/4/5 adverse event related to the ruxolitinib-containing regimen. AESIs will consist of the following CTCAE terms:

- Heart failure
- Pneumonia
- Dyspnea
- Peripheral edema
- Hypertension

13.3 Analysis Populations

For the Phase I part of the study, the dose escalation and MTD evaluation will be conducted on the population who initiate Cycle 1, Day 1 treatment, and who meet the DLT evaluable criteria as described in Section 4.3. For the Phase II part of the study, the PFS4 evaluable population will include all subjects who initiate treatment with ruxolitinib, have experienced a PFS event within 4 months from the start of ruxolitinib treatment, or have at least 4 months of follow up time from the start of ruxolitinib treatment. The primary efficacy analysis will be conducted on the PFS4 evaluable population. Response-evaluable population will include all subjects (both Phase I and Phase II) who have baseline evaluation, measurable disease, and initiate study

treatment followed by at least one efficacy measurement. All response endpoints will be conducted on the response-evaluable population.

All other efficacy and ruxolitinib safety analyses will be conducted on the population of subjects (both Phase I and Phase II) who initiate treatment with ruxolitinib. Additionally, an analysis will be conducted on safety data collected from Cycle 1 through the cycle prior to initiation of ruxolitinib treatment (for all Phase II subjects initiating Cycle 1 with carfilzomib plus dexamethasone).

13.4 Analysis Methods

13.4.1 Timing of Analyses

For the Phase I part of the study, an evaluation of the data will take place after each subject completes Cycle 1. For the Phase II part of the study, AESIs will be continuously evaluated in order to assess the Bayesian stopping rules for toxicity described in Section 13.4.3. Additionally, the stage 1 analysis will occur after the first 10 PFS evaluable subjects enrolled have progressive disease, have died, or have at least 4 months of follow up time from ruxolitinib treatment start. The stage 2 analysis will occur after 30 PFS evaluable subjects have progressive disease, have died, or have at least 4 months of follow up time. For both Phase I and Phase II, a follow up analysis will occur when all enrolled subjects have progressed, have died, have become lost to follow up or withdrawn from the study, or have at least two years of follow up time after initiation of treatment with ruxolitinib. A final analysis (for both Phase I and Phase II) will occur when all subjects have died, have become lost to follow up or withdrawn from the study, or have at least 3 years of follow up time after initiation of treatment with ruxolitinib.

13.4.2 Efficacy Analyses

13.4.2.1 Primary Analysis (Phase II)

The frequency and proportion of subjects who are alive and progression free at 4 months will be calculated with a corresponding 95% confidence interval using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection regions described in Section 13.1.2 will be carried out, testing the null hypothesis that the PFS4 rate is less than or equal to 25%.

13.4.2.2 Secondary Analyses

OS, PFS, time to progression, duration of response, and time to best response will be analyzed using Kaplan Meier techniques. Medians, 25th, and 75th percentiles will be estimated. Selected landmark rates will be estimated using the product limit function. Objective response rate, disease control rate, and clinical benefit rate will be analyzed using frequencies and proportions. Ninety-five percent confidence intervals will be estimated using the Clopper-Pearson method.

13.4.3 Safety Analyses

Treatment administration will be summarized descriptively in terms of cumulative dose administration and dose intensity of ruxolitinib (adjusting for dose delays and reductions). Additionally, the relative dose intensity will be calculated in terms of the actual dose intensity as percent of the intended dose intensity. The maximum grade for each type of adverse event will be recorded for each subject and treatment-emergent adverse events (TEAEs) will be identified. TEAEs are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; or
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start.

TEAEs will be summarized using frequencies and proportions, and these will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

Clinical laboratory tests (hematology, chemistry, coagulation panel, BNP), vital signs, and ECHO/MUGA/cardiac MRI (ejection fraction (%)) will be summarized with descriptive statistics.

Phase II Stopping Rule

It is estimated that the composite rate of Grade 3/4/5 AESIs (as defined in Section 13.2.10) in relapsed or refractory multiple myeloma patients treated with carfilzomib plus dexamethasone is approximately 0.30[30]. If it becomes evident that the Grade 3/4/5 AESI rate convincingly exceeds 0.30, the study will be halted. Enrollment will be suspended if the posterior probability of the Grade 3/4/5 AESI rate exceeding 0.30 is 0.75 or higher. The prior distribution for this monitoring rule is beta (3,7). This means that our prior assumption regarding the proportion of Grade 3/4/5 AESI's is 0.30, and there is 90% probability that this proportion is between 0.098 and 0.550. The operating characteristics of the stopping rule are given in the following table and are based on 5000 simulations.

Operating Characteristics of the Stopping Rule

Number of Subjects with an AESI	Number of Treated Subjects	Posterior Probability: Pr(AESI Rate>0.30|Data)
3	5	0.781
4	8	0.779
5	11	0.761
6	14	0.777

7	17	0.767
8	20	0.768
9	23	0.772
10	26	0.770
11	29	0.761

13.4.4 Exploratory Analyses

Logistic regression and Cox proportional hazards models will be used to assess the correlation between biomarkers and efficacy and toxicity outcomes. Exploratory objectives include exploring the correlation of toxicities and disease response with:

- Baseline serum cytokine profile
- Baseline PBMC JAK inhibition
- Baseline PBMC proteasome inhibition

Genomic studies will be performed on BM aspirate samples after sorting the CD138 positive and CD138 negative cells to understand mechanisms of carfilzomib sensitivity and resistance, along with modulation of the BM micro-environment. BM aspirate samples will be collected at:

- Baseline (screening)
- After Cycle #1 (between Days 20 – 27) of ruxolitinib
- At time of disease relapse and/or progression after initiation of ruxolitinib

13.5 Interim Analyses

After 10 PFS evaluable subjects have been enrolled to the Phase II part of the study, the study will be suspended for a planned interim analysis. The interim analysis will occur 4 months from the tenth evaluable subject's enrollment (unless they have progressed or died first) and will determine if at least 3 of 10 subjects are alive and progression free at 4 months. If the answer is yes, then the study will re-open to accrual and enroll an additional 20 subjects for a total of 30 subjects**.**

14 STUDY COMPLETION

14.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits.
- All subjects have discontinued from the study.

- The IRB, LCI DSMC, Sponsor-Investigator or funding companies discontinue the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

14.2 Termination

The study will be terminated when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example:
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

15 ETHICAL AND LEGAL ISSUES

15.1 Retention of Records

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request**.**

15.2 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB, FDA) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of IRB approval must be obtained and forwarded to Amgen and Incyte.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Amgen and Incyte. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator. If a deviation occurs, the event should be reported to the Sponsor-Investigator promptly. Any IRB reportable event that occurs must be reported to the IRB per IRB requirements. All planned (intentional) deviations must be submitted to the Sponsor-Investigator for approval prior to implementation or planned occurrence. After Sponsor approval has been obtained, planned deviations must be submitted and approved by the IRB prior to the anticipated deviation occurring. Exceptions for eligibility criteria are not allowed.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for personally overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

15.3 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

16 PUBLICATION POLICY

The Sponsor-Investigator must send a draft manuscript of the publication or abstract to Amgen and Incyte prior to submission of the final version for publication or congress presentation. All relevant aspects regarding data reporting and publication will be part of the contract between Amgen, Incyte and the Sponsor-Investigator.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

17 REFERENCES

1. Burger R, Bugdahn T, Staudinger M, et al. Preclinical activity of the JAK1/2 inhibitor ruxolitinib on malignant plasma cell growth and survival. J Clin Oncol 30, 2012 (suppl; abstr e18565)
2. Orlowski RZ, Eswara JR, Lafond-Walker A, Grever MR, Orlowski M, Dang CV. Tumor growth inhibition induced in a murine model of human Burkitt's lymphoma by a proteasome inhibitor. Cancer Res. 1998;58:4342-8.
3. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res. 2001;61:3071-6.
4. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Fanourakis G, Gu X, et al. Molecular sequelae of proteasome inhibition in human multiple myeloma cells. Proc Natl Acad Sci U S A. 2002;99:14374-9.
5. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, et al. Biologic sequelae of nuclear factor-kappaB blockade in multiple myeloma: therapeutic applications. Blood. 2002;99:4079-86.
6. Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood. 2003;101:2377-80.
7. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk KD, Sun CM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007;110:3281-90.
8. Demo SD, Kirk CJ, Aujay MA, Buchholz TJ, Dajee M, Ho MN, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007;67:6383-91.
9. Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, Stahl S, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol. 2002;20:4420-7.
10. Orlowski RZ, Voorhees PM, Garcia RA, Hall MD, Kudrik FJ, Allred T, et al. Phase 1 trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood. 2005;105:3058-65.
11. O'Connor OA, Stewart AK, Vallone M, Molineaux CJ, Kunkel LA, Gerecitano JF, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009;15:7085-91.
12. Alsina M, Trudel S, Furman RR, Rosen PJ, O'Connor OA, Comenzo RL, et al. A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. Clin Cancer Res. 2012;18:4830-40.
13. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348:2609-17.

14. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487-98.
15. Orlowski RZ, Nagler A, Sonneveld P, Blade J, Hajek R, Spencer A, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25:3892-901.
16. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906-17.
17. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120:2817-25.
18. Vij R, Wang M, Kaufman JL, Lonial S, Jakubowiak AJ, Stewart AK, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012;119:5661-70.
19. Vij R, Siegel DS, Jagannath S, Jakubowiak AJ, Stewart AK, McDonagh K, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol. 2012;158:739-48.
20. Cenci S, Mezghrani A, Cascio P, Bianchi G, Cerruti F, Fra A, et al. Progressively impaired proteasomal capacity during terminal plasma cell differentiation. EMBO J. 2006;25:1104-13.
21. Bianchi G, Oliva L, Cascio P, Pengo N, Fontana F, Cerruti F, et al. The proteasome load versus capacity balance determines apoptotic sensitivity of multiple myeloma cells to proteasome inhibition. Blood. 2009;113:3040-9.
22. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516-20.
23. Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. Haematologica. 2009;94:270-5.
24. Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol. 2010;28:1209-14.
25. Usmani SZ, Crowley J, Hoering A, Mitchell A, Waheed S, Nair B, et al. Improvement in long-term outcomes with successive Total Therapy trials for multiple myeloma: are patients now being cured? Leukemia. 2013;27:226-32.
26. Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. J Clin Oncol. 2012;30:445-52.
27. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma

working group study. Leukemia. 2012 Jan;26(1):149-57.Navon A, Ciechanover A. The 26 S proteasome: from basic mechanisms to drug targeting. J Biol Chem. 2009;284:33713-8.

28. Kumar S, Paiva B, Anderson KC et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8): e328-46.
29. Kumar SK, Dimopolous MA, Kastritis E et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia (2017) 31, 2443–2448.
30. Dimopolous MA, Goldschmidt H, Niesvizky R et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 2017; 18: 1327–37.

18 APPENDICES

18.1 ECOG Performance Scale

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

18.2 NCI CTCAE VERSION 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v4.03

Publish Date: (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

18.3 Response Criteria for Multiple Myeloma

IMWG Response Criteria*

IMWG MRD Criteria (Requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG Response Criteria‖; NOTE: see [28] for additional details	
Stringent Complete Response (sCR)	• Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates. In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
Very Good Partial Response	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg

(VGPR)	per 24 h
Partial Response (PR)	• ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal Response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required.
Stable Disease (SD)	• Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates • Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive disease (PD)¶¶, ||||	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL); • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 h); • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); • Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease ŧ
Clinical Relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§of the measurable lesion; • Hypercalcaemia (>11 mg/dL);

	• Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=freelight chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=flow cytometry. SUV_{max}=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. †Sustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines.[30] The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶ Criteria used by Zamagni and colleagues,[85] and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).[81,97] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max}=2.5 within osteolytic CT areas >1 cm in size, or SUV_{max}=1.5 within osteolytic CT

areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

|| Derived from international uniform response criteria for multiple myeloma.[11] Minor response definition and clarifications derived from Raj Kumar and colleagues.[14] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§ Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

18.4 Estimated Creatinine Clearance rate (eCCr) using Cockcroft-Gault Formula

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

18.5 Table of Events

Evaluation	**Days -21 to -1 (Baseline)**	**Phase I and Phase II All Cycles[t] (cycle = 28 days)** Subjects in Phase II/Run-In period only: Please note cycle numbers will start over with 'Cycle 1' after initiation of ruxolitinib							**End of Treatment[q]**	**Follow-up[r]**
		Day 1	Day 2[x]	Day 8[x]	Day 9[x]	Day 15[x]	Day 16[x]	Day 22[x]		
Informed consent [a]	X									
Inclusion/exclusion	X									
Medical and disease history [b]	X									
Physical examination/BSA [c]	X	X[s]							X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X[s]							X	
Pregnancy test [e]	X								X	
Electrocardiogram	X									
Echocardiogram, MUGA, or cardiac MRI[f]	X	X (prior to every 2 cycles)							X	
Hematology [g]	X	X [s]	X	X	X	X	X	X	X	
Coagulation [h]	X	X [s]								
Blood chemistries [i]	X	X [s]		X		X		X	X	
BNP[w]		X[s]								
Viral hepatitis panel[v]	X									
HBV DNA testing[y]	X									
Bone marrow [j]	X	(X)							X[l]	(X)[r]
Correlative studies (Blood and bone marrow)[l]	X			X[l] (Cycle 1 of ruxolitinib only; Blood only)				X[l] (Cycle 1 of ruxolitinib only day 20 -27)	X[l]	
Response assessments (SPEP/UPEP, IFE, SFLC) [k,u]	X	X							X	(X)[r]
Serum β2-microglobulin	X									
Assessment of plasmacytoma[m]	X	(X)							(X)	(X)[r]
Bone skeletal survey[n]	X	(X)							(X)	
Carfilzomib administration[o]		X	X	X	X	X	X			

Ruxolitinib administration[o]		Twice Daily days 1 – 28 Phase I all subjects. Phase II: Subjects with < PR following Phase II/Run-In period, subjects ≥ PR following Phase II/Run-In period who then subsequently progress, and subjects who proceed directly to Phase II/Ruxolitinib								
Dexamethasone administration[o]		X		X		X				
Concomitant medications [p]	X	→							X	
Adverse event monitoring		→							X	
Follow-up										X[r]

(X) only if clinically indicated

a) All subjects must sign an IRB-approved informed consent document prior to enrollment and prior to any study related procedures.

b) Medical History including demographics, prior and current medical illness and conditions (including baseline symptoms and toxicities), prior surgical procedures. Disease history includes date of initial diagnosis, stage and extent of the disease, Prior anticancer therapy (types and response), surgery and/or radiation including documentation of sensitive or refractory status, (refractory defined as documented disease progression during or within 60 days of completing the last anti-myeloma regimen), and documentation of Proteasome Inhibitor refractory disease status.

c) A complete physical exam, including height (screening only) and weight, neurologic assessment and assessment for extramedullary myeloma will be conducted at screening, day one of each cycle and End of Treatment visit. A symptom directed physical examination will be conducted as needed during a cycle. Plasmacytomas that can be followed by physical exam are to be evaluated on day one of each cycle. Weight to be measured on day one of each cycle with calculation of BSA (Subjects with a BSA > 2.2 m^2 should receive a carfilzomib dose based on a 2.2 m^2 BSA). Dose adjustments do not need to be made for weight changes of less than or equal to 20% from baseline weight. Baseline symptoms and residual toxicity from previous therapy assessed within 14 days prior to initiation of therapy.

d) Vital signs including blood pressure, pulse, respiration rate, temperature. To be performed prior to each carfilzomib infusion and as clinically indicated.

e) For females of childbearing potential, a negative serum pregnancy test must be documented within 7 days and a negative urine pregnancy test within 3 days of C1D1. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

f) Echocardiogram, MUGA, or cardiac MRI to be performed at baseline, every 2 cycles (within5 days of Day 1), and end of therapy to calculate LVEF. Subjects who develop signs/symptoms of congestive heart failure at any point during the study are required to have an evaluation of LVEF measurements by ECHO, MUGA, or cardiac MRI, preferably by the same method used at screening. If echocardiogram, MUGA, or cardiac MRI is done within 2 months from End of Treatment visit, it does not need to be repeated.

g) Hematology: hemoglobin, WBC with differential, and platelet count.

h) Coagulation: prothrombin time (PT), international normalized ratio (INR).

i) Blood chemistry: sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN, glucose (fasting at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and estimated creatinine clearance by Cockcroft-Gault Equations (Appendix 18.4) calcium and lactate dehydrogenase (LDH). Creatinine clearance required on days of the cycle other than Day 1 may be calculated using the Day 1 weight of the current cycle.

j) Bone marrow aspirate to be collected at screening for % plasma cells, morphology, standard karyotype, cytogenetics by FISH and biomarkers. Repeat for % plasma cells at the time of CR and/or progression. Screening timepoint only: If bone marrow previously collected for pathology evaluation as previously described within 21 days prior to initiation of study therapy, the pathology evaluation does not need to be repeated as part of the screening assessments. However, a bone marrow aspirate must be performed for correlative studies (see Footnote L for information on correlative studies).

k) Serum or urine protein electrophoresis (SPEP, UPEP), serum and urine immunofixation (IFE) and serum free light chain (SFLC) assay. To be conducted prior to each cycle (within 7 days of Day 1) until documentation of initial disease progression. For cycles delayed ≤ 7 days, repeat evaluations are not required. If the start of a new cycle is delayed > 7 days a repeat disease evaluation must be performed prior to the subsequent cycle. Phase II/Run-In subjects who cross over to Phase II/Ruxolitinib only: Disease responses will be calculated from disease evaluation performed just prior to initiating ruxolitinib (a new baseline will be established).

l) Blood and bone marrow samples will be collected for correlatives prior to study treatment initiation (collection is recommended after eligibility is established; baseline samples may be collected during screening or pre-treatment on C1D1); Cycle 1 of ruxolitinib, between Day 20-27; and at disease relapse or progression after ruxolitinib has been initiated. Blood only will be collected on C1D8 of ruxolitinib. These correlative labs include serum cytokines panel, peripheral blood mononuclear cells (PBMC) for proteasome inhibition, and PBMCs for JAK inhibition. Approximately 28 mLs of blood will be collected (please refer to the Correlative Guidelines for the type of tubes required) and will be sent to the LCI HOT lab. A minimum of 12 mL (first or second pull permitted) of bone marrow aspirate will be collected and sent to the LCI HOT lab. Note: ruxolitinib must have been initiated to collect correlative samples post-baseline (do not collect post-baseline correlative samples on subjects receiving study treatment in Phase II/Run-In period). Every effort should be made to collect post-baseline correlative samples prior to carfilzomib and dexamethasone administration; after the morning ruxolitinib dose and before the afternoon dose of ruxolitinib. Correlatives collected during screening do not need to be re-collected in the event that the screening period extends beyond 21 days.

m) Known or suspected plasmacytomas are to be assessed at baseline, as clinically indicated and to confirm response and/or progression. FDG-PET is not required but suggested. The same method of evaluation should be used throughout the study (CT/MRI/PET). Phase II/Run-In subjects who cross over to Phase II/Ruxolitinb only: For subjects with plasmacytomas present at screening, imaging using the same modality utilized at screening will be repeated prior to initiating ruxolitinib (a new baseline will be established).

n) Skeletal survey includes plain X-rays of (including skull, all long bones, pelvis and chest) required if previous survey >12 weeks from study entry and at any time when clinically indicated.

o) See section 5 for complete details on study drug administration, dose modifications and start of a new cycle of therapy.

p) Concomitant medications and procedures: - all procedures and medications within 14 days prior to first dose until 30 days after the last dose.

q) End of Treatment visit should be completed within 30 days of last dose of study drug with evaluation of safety at 30 days or prior to initiation of subsequent therapy (whichever comes first)

r) Subjects who received ruxolitinib on study and discontinue therapy for reasons other than disease progression should continue to have disease assessments per standard of care done until progression or start of subsequent therapy. At such time, follow-up for overall survival status will take place every three months +/- 7 days until death, lost to follow-up, or until the criteria defined for the final analysis (Section 13.4.1) are reached. Follow-up beyond the safety follow-up period is only required for subjects who received ruxolitinib. Follow-up may be completed by phone contact. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable

s) C1D1 procedures do not need to be repeated if the screening procedure occurred within 5 days (this applies to C1D1 following screening; does not apply to C1D1 of Phase II/Ruxolitinib in subjects who cross over from Phase II/Run-In); Day 1 procedures for subsequent cycles do not need to be repeated if done within 3 days of Day 1.

t) +/- 3 day window permitted for holidays/administrative reasons

u) Phase II/Run-In period only: Beginning with Cycle 1, disease evaluation results to assess response should be available for investigator review prior to dosing on Day 1 of each cycle (within 7 days of Day 1) until initiation of ruxolitinib (after ruxolitinib has been initiated, disease evaluation assessments will continue to be collected prior to dosing on Day 1, but results will not be required to be available prior to Day 1 dosing). Cycle numbers start over with the initiation of ruxolitinib and a new disease response baseline will be established.

v) Viral hepatitis panel including HBsAg, HB core antibody, HB surface antibody, Hep C antibody and HIV at baseline only.

w) BNP to be done Day 1 (+/- 3 days) of every cycle.

x) A +/- 1 day window is allowed for study treatment on Days 2, 8, 9, 15, and 16 and procedures on Day 22, unless otherwise noted. All procedures required for Days 2, 8, 9, 15, and 16 should be performed within 1 day of study treatment, unless otherwise noted.

y) For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening. HBV DNA testing by PCR must be performed locally. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.