Clinical Protocol

A Multicenter Phase 1/2b Study of the Bruton's Tyrosine Kinase Inhibitor, Ibrutinib (PCI-32765), in Combination with Carfilzomib (Kyprolis™) in Subjects with relapsed or relapsed and refractory Multiple Myeloma

Protocol PCYC-1119-CA; Phase 1/2b

Ibrutinib (PCI-32765)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice and applicable regulatory requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

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Note: If the address or telephone number of the Investigator changes during the course of the study, written notification will be provided by the Investigator to the Sponsor, and a protocol amendment will not be required.

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STUDY SYNOPSIS

A Multicenter Phase 1/2b Study of the Bruton's Tyrosine Kinase Inhibitor, Ibrutinib (PCI-32765), in Combination with Carfilzomib (Kyprolis™) in Subjects with relapsed or relapsed and refractory Multiple Myeloma

Protocol Number: PCYC-1119-CA

Phase: 1/2b

Duration of Study: 4 years

Indication: Relapsed and/or Refractory Multiple Myeloma

Ibrutinib (PCI-32765) is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Pharmacyclics, Inc and Janssen Research & Development, LLC, for the treatment of B-cell malignancies.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

Phase 1:

- To determine the maximum tolerated doses (MTD) and the recommended Phase 2 dose (RP2D) of ibrutinib in combination with carfilzomib.
- To describe the toxicities associated with the combination of ibrutinib and carfilzomib in subjects with relapsed or relapsed and refractory multiple myeloma (MM).

Phase 2b:

- To evaluate the efficacy of carfilzomib in combination with ibrutinib compared to carfilzomib in combination with placebo on the duration of progression-free survival (PFS) in subjects with relapsed or relapsed and refractory MM.

Secondary Objectives

Phase 1:

- Overall response rate (ORR) (≥ partial response (PR); according to the International Working Group (IMWG) criteria [Rajkumar 2011])
- Duration of response (DOR).

Phase 2b:

To compare the treatment groups in terms of the following:

- ORR (≥ PR; according to the IMWG [Rajkumar 2011]).
- DOR.
- Overall survival (OS).
- Time to progression (TTP)

In addition,

- To evaluate the safety and tolerability of ibrutinib in combination with carfilzomib.

Exploratory Objectives

- To evaluate duration of the clinical benefit rate including subjects with minimal response (MR) or better according to the IMWG.
- To evaluate prognostic and predictive biomarkers and genetics relative to treatment outcomes.

Phase 1:

- To determine the pharmacokinetics (PK) and pharmacodynamics of ibrutinib (eg, BTK occupancy of drug, levels of secreted protein or bone biomarkers) in subjects with MM.

Phase 2b:

- To evaluate time-to-next treatment (TTNT).
- To evaluate patient-reported outcomes (PROs) and disease-related symptoms according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma (EORTC QLQ-MY20) and Euro QoL 5 dimension questionnaire (EQ-5D).

Hypothesis

The hypothesis of this study is that treatment of ibrutinib in combination with carfilzomib will lead to a prolonged PFS compared to carfilzomib monotherapy in subjects who have received at least two prior lines of therapy including bortezomib (BTZ) and an immunomodulatory drug (IMiD).

OVERVIEW OF STUDY DESIGN

Approximately 176 subjects, inclusive of Phase 1 and Phase 2b, will be enrolled. The Treatment Phase will extend from first dose until disease progression, unacceptable toxicity or study closure (defined as 2 years after the last subject is enrolled). During the Treatment Phase, efficacy evaluations will be performed at the beginning of each cycle and will include an overall disease assessment, complete blood count, physical examination, and assessment of PROs (Phase 2b only).

This study will be conducted in two Phases:

Phase 1 will be an open-label, national, multicenter study in subjects with MM who have received at least two prior lines of therapy, including BTZ and an IMiD to establish the RP2D. Phase 1 will be conducted at approximately 12 clinical centers in the United States, with up to 42 total subjects enrolled.

In the Dose Escalation portion of the study, up to three cohorts may be explored and dose escalation will follow the 3+3 principles. In the Dose Expansion portion of the study, a maximum of 2 cohorts will be expanded up to a total of 18 subjects per cohort in the absence of dose-limiting toxicity (DLT). The decision to expand a cohort will be made after review of the dose escalation data, and enrollment to a particular cohort(s) may be stopped at any time.

Ibrutinib will be administered orally daily at 560 or 840 mg and will be initiated on Day 8 of Cycle 1. Treatment should be continuous (without interruption) and will be self-administered. Carfilzomib will be administered intravenously (IV) over 30 (+10) minutes, on two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). The Cycle 1 carfilzomib starting dose is 20 mg/m^2 and if tolerated the dose will be increased to $\geq$27 mg/m^2/day on Day 8 Cycle 1 and stay at that level for subsequent cycles.

After enrollment completion of Phase 1, further enrollment into Phase 2b will commence after the RP2D is identified and the initial safety and efficacy data are evaluated as favorable by the Sponsor. The RP2D will be determined on the basis of PK, safety, and efficacy data obtained during Phase 1.

Phase 2b will be conducted as a randomized, double-blind, international, multicenter study in subjects with MM who have received at least two prior lines of therapy, including BTZ and an IMiD. Eligible subjects will be randomized in a 1:1 ratio to Treatment Arm A or B:

- Treatment Arm A: carfilzomib in combination with ibrutinib
- Treatment Arm B: carfilzomib in combination with matching placebo

SUBJECT SELECTION

Key Eligibility Inclusion Criteria:

- Subjects with MM who have received at least two prior lines of therapy including BTZ and an IMiD and had either no response or documented disease progression to the most recent line of therapy.
- Measurable disease of MM as defined by at least ONE of the following: serum monoclonal protein (SPEP) ≥1 g/dL, >200 mg of monoclonal protein in the urine on 24 hour electrophoresis (UPEP), or serum free light chain (SFLC): involved FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum kappa to lambda serum free light chain ratio.
- Adequate hematologic function independent of transfusions and growth factor support; absolute neutrophil count (ANC) ≥750/mm^3, platelet counts ≥75,000/mm^3 (or ≥50,000/mm^3 if bone marrow involvement is ≥50%), hemoglobin level ≥8 g/dL.
- Adequate renal and hepatic function; Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN), total bilirubin ≤1.5 x ULN, Estimated Creatinine Clearance (Cockcroft-Gault) ≥30 mL/min.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Key Eligibility Exclusion Criteria:

- Primary refractory disease defined as nonresponsive in patients who have never achieved a minimal response or better with any therapy.
- Plasma cell leukemia, primary amyloidosis, POEMS syndrome.
- Radiotherapy within 21 days prior to first administration of study treatment.
- Prior therapy with alkylators, anthracyclines, high dose corticosteroids, IMiDs, or proteasome inhibitors ≤21 days prior to first administration of study treatment or monoclonal antibody ≤6 weeks prior to first administration of study treatment.
- Peripheral neuropathy Grade ≥ 2 at screening.
- Prior treatment with ibrutinib or any other protein kinase inhibitory drug or drug targeting the BCR signal transduction pathway.
- Prior treatment with carfilzomib if subjects were considered non-responsive to carfilzomib.
- Unable to swallow capsules or disease significantly affecting gastrointestinal function.
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists.
- Requires treatment with strong CYP3A4/5 inhibitors.
- Left ventricular ejection fraction (LVEF) ≥40%.

DOSAGE AND ADMINISTRATION

Ibrutinib will be administered orally once daily on a 28-day cycle beginning on Day 8 of Cycle 1 of the Treatment Phase. Treatment will continue until disease progression or other reason for treatment discontinuation. In Phase 1, ibrutinib will be administered at 560 mg (4 capsules) or 840 mg (6 capsules) according to the designed treatment level. Subjects enrolled in the double-blind, placebo-controlled Phase 2b will receive the RP2D of ibrutinib or the matching amount of placebo capsules.

All subjects will receive carfilzomib IV over 30 minutes with carfilzomib at 20 mg/m^2 on Days 1 and 2 of Cycle 1. Thereafter, subjects will receive carfilzomib IV over 30 minutes on Days 8, 9, 15, and 16 of Cycle 1, and thereafter (Cycle ≥2) on Days 1, 2, 8, 9, 15, and 16 according to the designed treatment level in Phase 1. Subjects enrolled in the double-blind, placebo-controlled Phase 2b will receive carfilzomib according to the established RP2D of either 20/27 or 20/36 mg/m^2. Dexamethasone 4 mg premedication will be administered prior to each carfilzomib infusion during Cycle 1 only and re-initiated as clinically appropriate.

28-day dosing cycle	Ibrutinib[a]	Carfilzomib[b]
Dose Level -1	420 mg once daily	20 / 27 mg/m^2
Dose Level 1 (starting dose)	560 mg once daily	20 / 27 mg/m^2
Dose Level 2	560 mg once daily	20 / 36 mg/m^2
Dose Level 3	840 mg once daily	20 / 36 mg/m^2

a. Ibrutinib will be administered PO daily on Days 8-28 in Cycle 1 and thereafter on Days 1-28

b. Carfilzomib will be administered IV on Days 1, 2, 8, 9, 15, and 16 of each cycle. Prior to carfilzomib administration subject will be given 4 mg dexamethasone (oral or IV) during Cycle 1 only and re-initiated as clinically appropriate.

EFFICACY EVALUATIONS

Response evaluations will be performed at the beginning of each cycle until disease progression or until study closure, whichever comes first. Response evaluations will include an overall disease assessment, complete blood count, physical examination, and assessment of PROs.

If at any time complete response (CR) is suspected, all assessments including serum and urine must be performed as per the IMWG response assessment guidelines.

Radiologic skeletal survey will be performed at Screening and only be repeated as clinically indicated and/or to document response/progression status.

SAFETY EVALUATIONS

The study will be monitored in accordance with the Sponsor's pharmacovigilance procedures. Adverse events and serious adverse events will be reviewed.

A Data Monitoring Committee (DMC) will be commissioned for this study. In Phase 1, the DMC will review safety and efficacy data and advise on the RP2D. In Phase 2b, the DMC will review the unblinded safety data on an ongoing basis.

STATISTICAL METHODS

Phase 1

Designed to determine the MTD and toxicity profile of ibrutinib and carfilzomib using the standard 3+3 design. Up to 3 dose cohorts will be explored, in the absence of DLT within the initial first 3 subjects, dose escalation will continue. The MTD will be defined as the lowest dose level below which drug-related DLT is observed in ≥33% (ie, ≥2 of 3 or ≥2 of 6) subjects in a cohort. Up to 2 tested dose cohorts will be expanded up to 18 subjects per cohort to confirm initial safety/tolerability findings. Phase 1 is not powered for comparisons of treatment cohorts. The Phase 1 efficacy endpoints are the ORR according to the IMWG response criteria. The point estimate of the rate and the corresponding exact binomial 95% confidence interval will be calculated. For DOR, the distribution of DOR as assessed by Investigator will be provided using Kaplan-Meier estimates for responders.

Phase 2b

The sample size is calculated based on the primary endpoint of PFS in subjects treated with carfilzomib in combination with ibrutinib compared to subjects treated with carfilzomib and placebo. The calculation is based on the assumption that the median PFS is 4 months for carfilzomib and placebo arm and the enrollment rate will be 10 subjects per month. Approximately 134 eligible subjects will be enrolled to observe 101 PFS events in this study. Assuming 75% improvement in median PFS of the carfilzomib in combination with ibrutinib arm over carfilzomib and placebo arm (hazard ratio of 0.57), the study has at least 80% power to achieve a statistical significance level of 2.5% (1-sided) under exponential distribution for PFS.

Primary Efficacy Analysis:

PFS will be assessed by a set of written rules and formulae developed based on IMWG response criteria and will be analyzed using Kaplan-Meier estimates and two treatment arms will be compared using stratified log-rank test, stratified by the refractory status to the most recent line of therapy and the number of prior lines of therapy (2-4 versus ≥5). A sensitivity analysis of PFS will be conducted without censoring at subsequent therapy if initiated prior to documented PD.

Secondary Efficacy Analysis:

Overall response rate (ORR) will be compared using the Cochran-Mantel-Haenszel chi-square test, stratified by the two stratification factors: the refractory status to the most recent line of therapy and the number of prior lines of therapy (2-4 versus ≥5). The distribution of DOR will be estimated using the Kaplan-Meier method similar to PFS.

Exploratory Efficacy Analysis:

Descriptive statistics for change in scores from baseline to each assessment will be summarized for the PROs. Other time to event analysis will be analyzed by the same method as PFS. Categorical endpoints will be compared between two treatment arms using the Cochran-Mantel-Haenszel chi-square test, stratified by the two stratification factors used. Overall survival will be compared using stratified log rank test. Survival rate at landmark points will be summarized based on Kaplan-Meier point estimates.

Safety Analysis:

Detailed tabulations of safety data (adverse events, clinical laboratory tests and other safety endpoints) will be provided for all subjects receiving the study drug. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.

The end of the study will occur 2 years after the last subject is randomized, or the Sponsor terminates the study, whichever comes first.

ABBREVIATIONS

ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta-human chorionic gonadotropin
BCR	B-cell receptor
BM	bone marrow
BSA	body surface area
BTK	Bruton's tyrosine kinase
BTZ	Bortezemib
CBC	complete blood count
CBR	clinical benefit response rate
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CRF	case report form
CT	computed tomography
CYP	Cytochrome P
DCB	duration of clinical benefit response
DLBCL	diffuse large B cell lymphoma
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of objective response
ECG	electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMR	Electronic medical records
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma
EQ-5D	Euro QoL 5 dimension questionnaire
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IgA, IgG and IgM	monoclonal immunoglobulin A, G and M antibodies
IL-6	interleukin-6
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board

ISS	International Staging System
ITT	Intent-to-Treat (population)
IV	Intravenous
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactic acid dehydrogenase
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIP 1α	macrophage inhibitory protein-1α
MM	multiple myeloma
M- protein	monoclonal paraprotein
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate (ORR = sCR + CR + VGPR + PR)
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy or Edema, M-protein and Skin abnormalities
PR	partial response
PRO	patient-reported outcomes
PT	Prothrombin time
RANKL	receptor activator of nuclear factor κB ligand
REB	Research Ethics Board
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SFLC	Serum Free Light Chain (Freelite®)
SLL	small lymphocytic lymphoma
SPEP	serum protein electrophoresis
study drug	ibrutinib or matching ibrutinib placebo
study treatment	ibrutinib or matching ibrutinib placebo plus carfilzomib
T_{max}	time to maximum plasma concentration
$t_{1/2}$	half life
TSH	thyroid stimulating hormone
TTNT	time-to-next treatment
TTP	time-to-progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response

1. INTRODUCTION

1.1. Multiple Myeloma

Multiple myeloma (MM) is a disseminated malignant proliferation of plasma cells and plasmacytoid cells (Palumbo 2011). Its yearly United States (US) age-adjusted incidence of 5.4/100,000 is comparable to that of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 5.7/100,000), which in turn is second only to diffuse large B-cell lymphoma (DLBCL; 6.9/100,000) among lymphoid malignancy subtypes. Its most recently estimated (Surveillance Epidemiology and End Results [SEER]) population based 5-year survival of 37.7% is inferior to those of CLL/SLL (77.1%) and DLBCL (59%) (SEER 2009). MM is thus one of the most significant areas of unmet medical need, in terms of survival and incidence, among lymphoid malignancies. Myeloma cell growth occurs within bones and specifically involves the bone marrow. Its clinical hallmarks include bone destruction, which may be manifested by lytic lesions, severe osteopenia, pathologic fractures and hypercalcemia, and impaired bone marrow function, which may result in anemia, thrombocytopenia, and neutropenia. Bone destruction in particular is a major cause of severe and disabling morbidity in myeloma. Bone lesions are present in the majority of patients at presentation and nearly all patients by the time the disease runs its course. Myeloma cells typically secrete 1 (or rarely more) monoclonal paraprotein (M-protein) molecule, which may be intact immunoglobulin (usually IgG or IgA; rarely IgD, E, or M) or free (κ or λ) light chains. Examples of completely nonsecretory myeloma are rare. Myeloma M-proteins can cause numerous complications including renal insufficiency, amyloidosis, hyperviscosity, and neuropathy. The various direct and indirect destructive effects of myeloma cells render MM patients highly symptomatic and challenging to manage. In addition, these patients are subject to greater morbidity and higher mortality compared to those with the more common subtypes of lymphoma.

Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines (eg, interleukin-6 [IL-6]), chemokines, macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival. Crucial cytokines and chemokines are secreted into the microenvironment by bone marrow (BM) stromal cells, and some by the MM cells themselves. Adhesion of MM cells to BM stromal cells triggers secretion of cytokines, which augment MM cell growth and survival and confers drug resistance (Roodman 2010b). Vascular endothelial growth factor, basic fibroblast growth factor–2, and other factors secreted by MM and/or BM stromal cells promote angiogenesis, and thereby further support tumor cell growth and survival. More recently, much progress has been made in elucidating the role of osteoclasts in the development of lytic lesions and in reciprocally contributing to a microenvironment supportive of myeloma cell growth and progression. Multiple myeloma cells stimulate osteoclastogenesis by secretion of factors including receptor activator of nuclear factor κB ligand (RANKL), IL-6, and macrophage inhibitory protein-1α (MIP-1α), while osteoclasts themselves may produce IL-6, as well as interact with stromal cells. These interactions contribute to a favorable microenvironment for myeloma cell adhesion and proliferation (Kawano 1988, Roodman 2004, Aggarwal 2006, Roodman 2010a, Roodman 2010b, Roodman 2011).

Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), proteasome inhibitors (bortezomib [Velcade®], carfilzomib [Kyprolis®]), immunomodulatory drugs (IMiDs) (thalidomide [Thalomid®], lenalidomide [REVLIMID®] and pomolidomide [Pomalyst®]) with and without corticosteroids. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past five years, even with the best available approved agents, 20–40% of patients fail to respond to the primary therapy, and almost all subjects are known to eventually relapse.

Therefore, novel rationally designed therapies, based on a thorough understanding of disease mechanisms; continue to be urgently required for MM patients

1.2. Ibrutinib (PCI-32765) Background

Ibrutinib (PCI-32765) is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Pharmacyclics, Inc and Janssen Research & Development, LLC, for the treatment of B-cell malignancies including CLL, the related SLL, Mantle Cell Lymphoma (MCL), and Waldenstrom's Macroglobulinemia. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

The investigational product is formulated as a hard gelatin capsule for oral administration. At the present time there are no approved inhibitors targeting BTK.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration. For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure.

1.2.1. Ibrutinib in Multiple Myeloma

Study PCYC-1111-CA is a multicenter Phase 2 study in subjects with relapsed or relapsed and refractory MM. The primary objective of the study is to determine the efficacy of ibrutinib, both as a single agent and in combination with dexamethasone by the clinical benefit response rate (CBR). The secondary objectives are to evaluate the efficacy of ibrutinib in this population as assessed by the duration of clinical benefit response (DCB), overall response rate (ORR), duration of response (DOR). The exploratory objectives are PFS, time to progression (TTP), and OS, hematologic improvement, and the safety and drug PK.

Subjects are enrolled to one of four cohorts, with ibrutinib doses ranging from 420 mg/day (Cohort 1), 560 mg/day (Cohort 2), and 840 mg/day (Cohorts 3 and 4). Ibrutinib is given in combination with weekly dexamethasone in Cohorts 2 and 4; addition of dexamethasone is permitted upon disease progression in Cohorts 1 and 3. Cohort 1 and 2 have been fully enrolled, and accrual to cohorts 3 and 4 is ongoing. Three of 13 subjects in Cohort 1 had decreases of the monoclonal myeloma M-protein, one of whom had a partial response (PR) following the addition of dexamethasone. A total of 5 out of 13 subjects continued on treatment for more than 4 months. As of April 2013, 2 subjects were continuing on treatment for more than 12 months, one with stable disease (SD) and one with a PR (in combination with dexamethasone). There have been no new safety signals in this study. Decreases in multiple cytokines and chemokines that were elevated at baseline were noted among subjects with SD.

1.2.2. Summary of Human Pharmacokinetics

The results from extensive PK sampling and evaluation performed in approximately 250 subjects receiving ibrutinib across 3 clinical studies are summarized below.

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560 and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to

ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Based on these findings, there is no plan to conduct a study of ibrutinib in renally impaired subjects. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll on Study PCYC-1102-CA in which PK assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in subjects with severe renal impairment or subjects on dialysis. In vitro studies have indicated that ibrutinib is metabolized by cytochrome P450 (CYP) 3A4/5. The study of ibrutinib in hepatic impaired subjects (PCI-32765CLL1006) is in progress.

1.2.3. Summary of Clinical Safety of Ibrutinib

Safety data are available for 636 subjects treated in 5 monotherapy and 3 combination therapy studies, as discussed below (Investigator's Brochure Version 7, dated 31 July 2013). For a comprehensive summary of nonclinical and clinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure for ibrutinib.

Monotherapy Studies

The integrated safety profile of ibrutinib administered as monotherapy to 506 subjects across several clinical studies (PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1106-CA, PCI-32765MCL2001, PCYC-1111-CA, PCYC-1117-CA, and PCI-32765-JPN-101) has been evaluated. The most common treatment-emergent adverse events as of 06 April 2013 were diarrhea (42.1%), fatigue (33.8%), nausea (26.1%), cough (20.2%), and peripheral edema (18.6%). Grade 3 or 4 adverse events were experienced by 60.7% of subjects, the most common (>2%) of which were hematologic in nature: neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Pneumonia (7.7%) was the most frequent nonhematologic Grade 3/4 adverse event. Serious adverse events were experienced by 46.4% of treated subjects.

The only serious events occurring in more than 1% of subjects (excluding disease progression) were pneumonia (7.9%), atrial fibrillation (3.2%), and febrile neutropenia (2.8%).

Combination Therapy Studies

The safety of ibrutinib administered as combination therapy to 130 subjects was evaluated in 3 clinical studies: PCYC-1108-CA, PCYC-1109-CA, and PCI-32765DBL1002. In Study PCYC-1108-CA, ibrutinib is administered in combination with either the FCR (fludarabine, cyclophosphamide, and rituximab) or the BR (bendamustine and rituximab) regimen chemotherapy. In Study PCYC-1109-CA, ibrutinib is administered in combination with the monoclonal antibody ofatumumab in patients with relapsed and refractory CLL. In Study PCI-32765DBL1002, ibrutinib is administered in combination with standard R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone).

Across these combination studies, the most common adverse event has been diarrhea (47.7%), nausea (33.1%), infusion related reaction (29.2%), and fatigue (26.2%). Neutropenia (24.6%) has been the most common hematologic toxicity, followed by anemia (20.0%) and thrombocytopenia (19.2%).

Adverse events that were Grades 3 or 4 or higher in severity were reported in 57.7% of subjects. The most common have been hematologic: neutropenia (21.5%), anemia and thrombocytopenia (7.7% each), and febrile neutropenia (6.2%). Pneumonia (7.7%) was the most frequently reported nonhematologic Grade 3 or higher adverse event.

Overall, 36.2% of treated subjects have experienced at least 1 serious adverse event. The only event reported as related occurring in more than 2 subjects has been pneumonia. The most commonly reported serious adverse events were febrile neutropenia and pneumonia (6.2% each), cellulitis (3.8%), atrial fibrillation (3.1%), and dehydration and dyspnea (2.3% each).

Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each).

Treatment-related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Stevenson 2011).

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/μL), often associated with reduction of lymphadenopathy has been observed in most subjects (75%) with relapsed/refractory CLL/SLL and some subjects (33%) with relapsed/refractory MCL treated with ibrutinib monotherapy. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis in subjects with CLL/SLL on ibrutinib monotherapy typically occurs during the first few weeks (median time 1.1 weeks) of ibrutinib therapy and typically resolves within a median of 18.7 weeks while on treatment.

Available data in subjects with MM that have been treated with ibrutinib monotherapy in a Phase 1 study, there has been no evidence of treatment-related lymphocytosis.

Hemorrhagic Events

There are reports of hemorrhagic events in subjects treated with ibrutinib in both monotherapy and combination clinical studies. The majority of these hemorrhagic adverse events were of Grade 1 or 2 in severity, including minor hemorrhagic events like contusion, epistaxis and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Hemorrhagic events of Grade 3 or higher, including central nervous system hemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies. Subjects were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists (Section 6.3.3).

Subjects in the current study will be monitored closely for hemorrhagic adverse events. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (Section 6.4).

1.3. Carfilzomib

The proteasome is a multi-catalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are then cleaved within the proteasome by 1 or more of 3 separate N-terminal threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

Carfilzomib for injection is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib (BTZ), showed less off-target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to BTZ; the latter showed off-target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur 2011).

Carfilzomib (KYPROLIS™) is approved in the US for the treatment of patients with MM who have received at least two prior therapies including BTZ and an IMiD and have demonstrated progressive disease (PD) on or within 60 days of completion of the last therapy. In addition, carfilzomib has been studied in other cancers including Waldenstrom's Macroglobulinemia, non-Hodgkin's lymphoma, mantle cell lymphoma, and a variety of solid tumors.

1.3.1. Summary of Nonclinical Data: Carfilzomib

Based upon in vitro and in vivo studies, it is anticipated that more intense and sustained proteasome inhibition can be achieved with carfilzomib relative to BTZ, resulting in enhanced antitumor activity. Continuous 72 hour exposure to carfilzomib was associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture (Demo 2007). Incubation of hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated

proteins and induction of apoptotic cell death. Carfilzomib was also cytotoxic in bortezomib-resistant tumor cell lines (Suzuki 2011, Kuhn 2007).

Preclinical studies in rats and monkeys have been performed in which carfilzomib was administered intravenously (IV) for 5 consecutive days followed by 9 days of rest for 2 cycles. Proteasome inhibition of more than 80% was achieved, suggesting that high-level inhibition of the proteasome with the epoxyketone class is possible, affording new opportunities to escalate dose to optimize antitumor effects (Yang 2011).

1.3.2. Summary of Clinical Data in Multiple Myeloma: Carfilzomib

Carfilzomib clinical development in MM initially involved single agent testing at various doses, which served as the foundation for understanding the safety, tolerability and efficacy of carfilzomib (Alsina 2012, Hájek 2012, Jagannath 2012, O'Connor 2009, Siegel 2012). Each treatment cycle was 4 weeks, and carfilzomib was administered as a 2 to 10 minute IV infusion on Days 1, 2, 8, 9, 15 and 16. The carfilzomib dose was 20 mg/m^2 in Cycle 1, followed by 27 mg/m^2 in Cycle 2 and for all subsequent administrations and resulted in ORR of 23.7% in a relapsed/refractory patient population (Siegel 2012, Vij 2012a, Vij 2012b).

An ongoing trial, Study PX-171-007, has explored the single-agent safety and efficacy characteristics of carfilzomib at doses ranging from 20 mg/m^2 to 36 mg/m^2 by IV bolus (2-10 minute injections). Additional cohorts of MM subjects were subsequently investigated whereby carfilzomib doses from 36 mg/m^2 to 70 mg/m^2 were administered over a longer infusion time (30-minute infusions), and the maximum tolerated dose (MTD) in myeloma subjects was 20/56 mg/m^2. The 30-minute infusion of carfilzomib was better tolerated than the 2-10 minute bolus and enabled a higher MTD. The overall safety profile for a 30-minute infusion of carfilzomib at 20/56 mg/m^2 is similar to that seen in previous Phase 2 studies of 27 mg/m^2 carfilzomib given over 2–10 minutes and no new or unexpected adverse events have been observed. The most common constitutional adverse events included fatigue, nausea, pyrexia, and headaches and were generally low grade. The most common hematologic adverse events were thrombocytopenia and anemia (Badros, 2012).

The same study (Study PX-171-007) explored a combination of dexamethasone (20 mg on Days 1, 2, 8, 9, 15, and 16, and 40 mg on Day 22) with carfilzomib in MM subjects administered by 30-minute infusion at 20/45 mg/m^2 and 20/56 mg/m^2 and found it to be tolerable and safe (Badros 2012). The safety and efficacy of the 20/56 mg/m^2 carfilzomib regimen in combination with dexamethasone is being examined in the ongoing Phase 3 ENDEAVOR study (Study 2011-003).

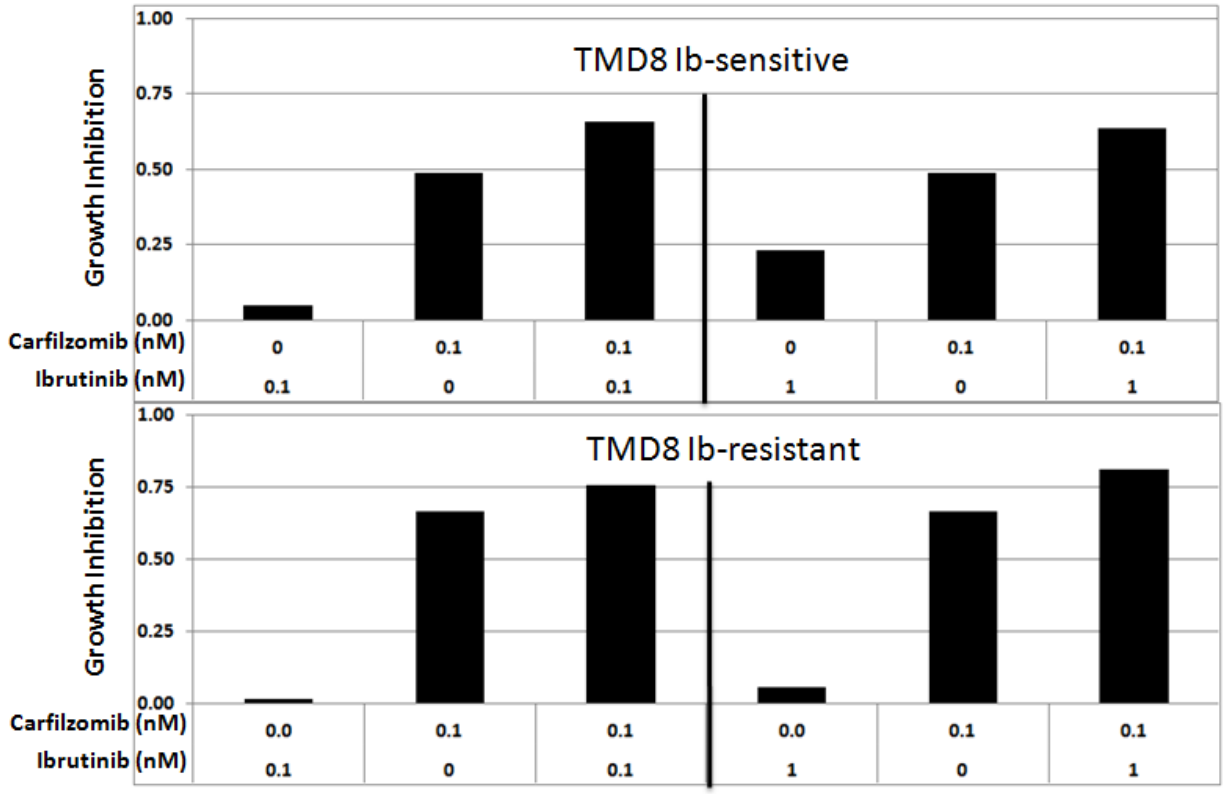
An additional study demonstrated increased activity of carfilzomib as measured by ORR, in 34 MM subjects treated with single-agent carfilzomib at the MTD of 20/56 mg/m^2. These relapsed MM subjects had an average of 5 prior lines of therapy with 78% of subjects refractory to BTZ at the time of study entry. The ORR was 50% for all subjects and 57% in BTZ refractory subjects. The median PFS is 4.6 months and the median OS has not been reached with a median follow-up of 9.6 months (Lendvai 2012).

The results of the PX-171-007 safety analysis revealed no new or unexpected adverse events observed with escalated doses up to 56 mg/m^2, with the safety and efficacy of doses above 27mg/m^2 alone and in combination being examined in multiple ongoing studies, including the Phase 3 CLARION study. There is also evidence of an improvement in efficacy based upon the ORR of 50% demonstrated in heavily pretreated patients treated at doses above the labeled indication. (Lendvai 2012, Siegel 2012) Based upon these findings we will examine ibrutinib in combination with standard doses as well as escalated doses of carfilzomib to evaluate both safety and efficacy based on the trial design.

1.4. Rationale for the Combination

Clinically, ibrutinib is an attractive agent to combine with carfilzomib because of the excellent tolerance of ibrutinib, which is administered orally. More specifically, evidence has been presented of ibrutinib-BTZ supra-additivity or synergy in vitro with MM cells (Rushworth 2013) and also with MCL and DLBCL cell lines (Dasmahapatra 2013). Concentrations of ibrutinib that were applied were relatively high (≥1 μM) as compared to concentrations generally achieved clinically (100-400 nM). More recently Ou et al (Proc. AACR, 2013) has noted similar ibrutinib-carfilzomib synergy in MCL lines in vitro at high ibrutinib concentrations, as have researchers at Pharmacyclics testing activated B-cell like DLBCL cell lines at ibrutinib concentrations as low as 0.1 nM (unpublished data, see Figure 1). It is intriguing that supra-additivity was often noted in ibrutinib or BTZ resistant cell lines, suggesting the combination may overcome some resistance mechanisms. Although this data was with non-MM cell lines, the results are important in establishing a proof-of-principal for an underlying mechanism that may be generalizable. Recent results more directly applicable to MM were obtained in an in vitro screening study of combinations of other drugs with ibrutinib, conducted by Zalicus, Inc. (Commissioned by Janssen Pharmaceutical, unpublished data on file). In this study, evidence of supra-additive effects of ibrutinib and carfilzomib were noted with three MM cell lines: AMO-1, INA-6 and HuNS1, with Synergy Scores of 3.5, 2.9 and 3.7 respectively (with >1 indicating additivity). These MM cell lines are known to express BTK which supports the interpretation that this was an on-target effect. Evidence for supra-additivity with bortezomib was not as robust. As is the case for several B-lymphroliferative diseases, interactions of the malignant cells with the microenvironment may exert protective effects; such interactions may be disrupted by ibrutinib in vivo. There is also some potential for synergistic effects on bone metabolism in vivo, as ibrutinib has been noted to have osteoclast inhibitory effects (Tai 2012), while proteosome inhibitors stimulate osteoblastic activity (Zangari 2011, Zangari 2012).

Figure 1: Synergy between Carfilzomib and Ibrutinib in ABC-DLBCL Lines



Carfilzomib potentiates ibrutinib activity in ibrutinib sensitive lines (top) and resistant lines (bottom) .
The panels also show the synergistic inhibitory effect of carfilzomib with ibrutinib at 0.1 nM (left) and ibrutinib at 1 nM (right) (Pharmacyclics unpublished data).

1.5. Study Rationale

This multicenter study will be conducted in two separate Phases.

The Phase 1 Dose Escalation portion of the study is designed to establish the MTD of ibrutinib in combination with carfilzomib following the classical 3+3 dose escalation schema. In the Phase 1 Dose Expansion portion of the study, up to two cohorts will be extended to a maximum of 18 subjects to ensure a more accurate assessment of the initial toxicity and efficacy profile of this novel combination regimen.

After a favorable evaluation of the obtained safety and efficacy profile at the recommended phase 2 dose (RP2D), Phase 2b portion will be initiated and conducted as a randomized, placebo controlled, double-blinded, multicenter study. The study is designed to evaluate whether treatment with ibrutinib in combination with carfilzomib will result in a clinically meaningful improvement in PFS compared to carfilzomib and placebo in subjects who have received at least two prior lines of therapy including BTZ and an IMiD.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

2.1.1. Primary Objective

Phase 1:

- To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of ibrutinib in combination with carfilzomib.
- To describe the toxicities associated with the combination of ibrutinib and carfilzomib in subjects with relapsed or relapsed and refractory multiple myeloma (MM).

Phase 2b:

- To evaluate the efficacy of carfilzomib in combination with ibrutinib compared to carfilzomib in combination with placebo as assessed by the PFS in subjects with relapsed or relapsed and refractory MM.

2.1.2. Secondary Objectives

Phase 1:

- Overall response rate (ORR) (≥ PR; according to the International Myeloma Working Group (IMWG) criteria [Rajkumar 2011]).
- DOR.

Phase 2b:

To compare the treatment groups in terms of the following:

- ORR (≥ PR; according to the IMWG [Rajkumar 2011]).
- DOR.
- Overall survival (OS).
- Time to progression (TTP).
- To evaluate the safety and tolerability of ibrutinib in combination with carfilzomib.

2.1.3. Exploratory Objectives

- To evaluate duration of the clinical benefit rate including subjects with minimal response (MR) or better according to the IMWG.
- To evaluate prognostic and predictive biomarkers and genetics relative to treatment outcomes.

Phase 1:

- To determine the PK and pharmacodynamics of ibrutinib (eg, BTK occupancy of drug, levels of secreted protein or bone biomarkers) in subjects with MM.

Phase 2b:

- To evaluate time-to-next treatment (TTNT).
- To evaluate patient-reported outcomes (PROs) and disease-related symptoms according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma (EORTC QLQ-MY20) and EuroQol dimension questionnaire (EQ-5D).

2.2. Hypothesis

The hypothesis of this study is that treatment of ibrutinib in combination with carfilzomib will lead to prolonged PFS compared to carfilzomib monotherapy in subjects who have received at least two prior lines of therapy including BTZ and an IMiD.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

The study will be conducted in two Phases.

Phase 1 will be an open-label study. The Dose Escalation portion of the study is designed to establish the MTD of ibrutinib in combination with carfilzomib. Up to three cohorts (Table 2) may be explored and dose escalation will follow the 3+3 dose escalation schema. In Dose Expansion, a maximum of two cohorts will be expanded up to a total of 18 subjects per cohort in the absence of dose-limiting toxicity (DLT) to ensure a more accurate assessment of the initial toxicity and efficacy profile.

Phase 2b will be randomized, placebo-controlled, double-blind study designed to evaluate whether treatment with ibrutinib in combination with carfilzomib will result in an improvement in PFS compared to carfilzomib and placebo in subjects who have received at least two prior lines of therapy including BTZ and an IMiD.

Approximately 176 subjects, inclusive of Phase 1 and Phase 2b, will be enrolled. Both Phases include a Screening Phase, Treatment Phase and a Follow-Up Phase (Figure 2). The Screening Phase assessments will be performed within 28 days prior to study treatment. Eligible subjects must have diagnosis of MM that meets published diagnostic criteria, have received at least two prior lines of therapy including BTZ and an IMiD, and have documented relapse/refractory disease according to IMWG consensus criteria. The Treatment Phase will extend from first dose until criteria for permanent discontinuation of ibrutinib are met (Section 5.7). During the Treatment Phase, efficacy evaluations will be performed at the beginning of each cycle and will include an overall disease assessment, complete blood count (CBC), physical examination, and assessment of PROs (Phase 2b only).

The Post-treatment Follow-up Phase will begin once a subject discontinues ibrutinib treatment and will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

- Subjects who discontinue for reasons other than disease progression (ie, for adverse event or Investigator decision), will complete an End of Treatment Visit (30 ± 3 days from the last dose of ibrutinib or carfilzomib, whichever is later), and should continue to have disease evaluations (12 weeks ± 14 days).

- Subjects who discontinue due to disease progression will complete an End of Treatment Visit and be followed for survival and subsequent anti-cancer therapy (12 weeks ± 14 days) until study ends.

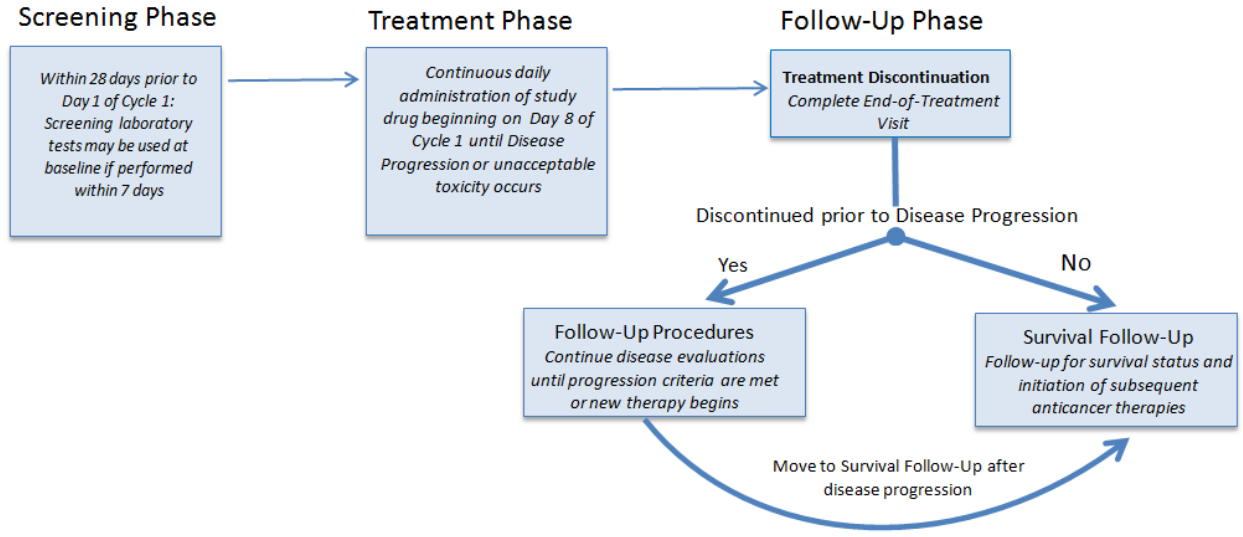
It is imperative that survival status be assessed and that the date of death is documented for each subject that has died.

A Data Monitoring Committee (DMC) will be commissioned for this study. In Phase 1, the DMC will review safety and advise on the RP2D. In Phase 2b, the DMC will review the unblinded safety data on an ongoing basis.

Table 1: Dosing Schedule

Cycle	Cycle 1			Cycle ≥2		
Days	D1/2	D8/9	D15/16	D1/2	D8/9	D15/16
Ibrutinib or Placebo (Phase 2b only)	0 mg	560-840 mg (4-6 capsules) continuously Days 8 - 28		560-840 mg (4-6 capsules) continuously Days 1 – 28		
Carfilzomib	20 mg/m^2	27-36 mg/m^2	27-36 mg/m^2	27-36 mg/m^2	27-36 mg/m^2	27-36 mg/m^2

Figure 2: Study Design Schematic



3.2. Phase 1 Dose Escalation and Expansion Overview

Phase 1 will be conducted at approximately 20 clinical centers in the US, with up to 42 total subjects enrolled. In the Dose Escalation portion, up to three dose levels will be explored and dose escalation will follow the 3+3 principles. In the Dose Expansion portion, a maximum of 2 cohorts will be expanded up to a total of 18 subjects per cohort (inclusive of subjects enrolled in the Dose Escalation portion) in the absence of DLT. The decision to expand a cohort will be made after review of the dose escalation data, and enrollment to a particular cohort(s) may be stopped at any time.

Ibrutinib will be administered orally daily at 560 or 840 mg and will be initiated on Day 8 of Cycle 1. Treatment should be continuous (without interruption) and will be self-administered (unless otherwise specified in this protocol). Carfilzomib will be administered IV over 30 (+10) minutes, on two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). The Cycle 1 carfilzomib starting dose is 20 mg/m^2 on Days 1 and 2, and if tolerated the dose will be increased to 27 or 36 mg/m^2/day on Day 8 of Cycle 1 and stay at that level for subsequent cycles). See Section 5.4 for study treatment details.

After enrollment completion of Phase 1, further enrollment into Phase 2b will commence after the RP2D is identified and the initial safety and efficacy data are evaluated as favorable by the Sponsor. The RP2D will be determined on the basis of PK, safety, and efficacy data obtained during Phase 1.

3.3. Phase 2b Double-blind, Placebo Controlled Efficacy Evaluation Overview

Phase 2b (efficacy evaluation) will be a randomized, placebo-controlled, international, multicenter study. This portion of the study will be conducted at approximately 60 international clinical centers, with approximately 134 subjects enrolled. Subjects will be treated according to the identified RP2D. The final Phase 2b dose level will be selected by the Sponsor. Eligible subjects will be randomized in a 1:1 ratio to Treatment Arm A or B:

- Treatment Arm A: carfilzomib in combination with ibrutinib.
- Treatment Arm B: carfilzomib in combination with matching placebo.

Subjects randomized to the 'placebo' arm will receive matching number of placebo capsules. Subjects will be stratified at randomization by the refractory status to the most recent line of therapy and the number of prior line of therapy (2-4 versus ≥5). Randomization will also be stratified by geographic region: US versus non-US. Geographic region will not be used as a factor in the statistical analysis except for the summary. Refractory to the most recent treatment is defined as a) nonresponsive or b) relapse while on therapy or relapse within 60 days of the last treatment. Nonresponsive is defined as either failure to achieve minimal response or development of PD while on therapy.

Ibrutinib will be administered orally daily at the RP2D starting on Day 8 of Cycle 1. Treatment should be continuous (without interruption) and will be self-administered. Carfilzomib will be administered IV over 30 (+10) minutes, on two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). The Cycle 1 carfilzomib starting dose is 20 mg/m^2 and if tolerated the dose will be increased to the RP2D on Day 8 of Cycle 1 and stay at that level for subsequent cycles.

4. SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the Investigator should consult with the Medical Monitor before enrolling a subject in the study. Eligibility will be confirmed by the Sponsor's Medical Monitor prior to enrollment.

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Subjects with MM who have received at least two prior lines of therapy (Appendix 5) including BTZ and an IMiD and had either no response or documented disease progression to the most recent treatment regimen.
2. Measurable disease of MM as defined by at least ONE of the following:
    - Serum monoclonal protein (SPEP) ≥1 g/dL
    - >200 mg of monoclonal protein in the urine on 24 hour electrophoresis (UPEP)
    - Serum free light chain (SFLC): involved FLC ≥10 mg/dL (≥100 mg/L) AND abnormal kappa to lambda serum free light chain ratio

Laboratory

3. Adequate hematologic function within 7 days prior to enrollment (Phase 1) or randomization (Phase 2b), defined as:
    - Absolute neutrophil count (ANC) ≥750/mm^3
    - Platelet counts ≥75,000/mm^3 (or ≥50,000/mm^3 if bone marrow involvement is ≥50%)
    - Hemoglobin level ≥8 g/dL

    Results must be independent of transfusion and growth factor support for at least 7 days, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which requires at least 14 days.

4. Adequate hepatic and renal function within 7 days prior to enrollment (Phase 1) or randomization (Phase 2b):
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
    - Estimated Creatinine Clearance (Cockcroft-Gault) ≥30 mL/min

Demographic

5. Men and women ≥ 18 years of age on the day of signing the informed consent.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Ethical/Other

7. Female subject of childbearing potential must have a negative serum (human chorionic gonadotropin) or urine pregnancy test within 3 days prior to enrollment (Phase 1) or randomization (Phase 2b) and agree to use dual methods of contraception during the study and for 1 month following the last dose with ibrutinib. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion.
8. Male subject must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.
9. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
10. Willing to provide blood and tissue samples for correlative research purposes (Phase 1 and selected Phase 2 sites).

4.2. Exclusion Criteria

Subjects must not meet any of the following exclusion criteria to be eligible to enroll in this study:

Disease-Related

1. Primary refractory disease defined as nonresponsive in patients who have never achieved a minimal response or better with any therapy.
2. History of plasma cell leukemia, primary amyloidosis, POEMS syndrome.
3. Radiotherapy within 21 days prior to first administration of study treatment. However, if the radiation portal was localized to single lesion or fracture site and covered by ≤5% of the bone marrow reserve (by investigator estimate), the subject may be enrolled irrespective of the end date of radiotherapy.

4. Recent prior chemotherapy
    - Alkylators (eg, melphalan, cyclophosphamide) ≤21 days prior to first administration of study treatment
    - Anthracyclines ≤21 days prior to first administration of study treatment
    - High dose corticosteroids, IMiDs (thalidomide or lenalidomide), or proteasome inhibitors (eg, BTZ) ≤21 days prior to first administration of study treatment
    - Monoclonal antibody ≤6 weeks prior to first administration of study treatment.
5. Peripheral neuropathy Grade ≥2 at screening.
6. Prior treatment with ibrutinib (PCI-32765) or any other protein kinase inhibitory drug or drug targeting the BCR signal transduction pathway.
7. Prior treatment with carfilzomib if subjects were considered non-responsive to carfilzomib.

Concurrent Conditions

8. Major surgery or a wound that has not fully healed within 4 weeks prior to first administration of study treatment.
9. Infection requiring systemic treatment within 2 weeks prior to first administration of study treatment, or unexplained fever within 2 weeks prior to first administration of study treatment.
10. Concomitant therapy with denosumab (bisphosphonate is allowed).
11. Unable to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction.
12. Diagnosed or treated for malignancy other than MM, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study treatment and felt to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease.
13. Uncontrolled diabetes mellitus.
14. History of stroke or intracranial hemorrhage within 6 months prior to first administration of study treatment.
15. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
16. Requires treatment with strong CYP3A4/5 inhibitors (Appendix 7).
17. Left ventricular ejection fraction (LVEF) ≥40%; 2-d transthoracic echocardiogram (ECHO) is the preferred method of evaluation; multiple gated acquisition scan (MUGA) is acceptable if ECHO is not available.

18. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months prior to first administration of study treatment, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
19. Known history of human immunodeficiency virus (HIV) or active infection with Hepatitis C Virus (HCV) or Hepatitis B Virus (HBV) or any uncontrolled active systemic infection.
20. Any life-threatening illness, medical condition, or organ system dysfunction, which in the investigator's opinion, could compromise the subject's safety, or interfere with the absorption or metabolism of ibrutinib capsules.
21. Women who are pregnant or breast-feeding.
22. Any medical or psychiatric condition that, in opinion of investigator, could interfere with the subject's ability to give informed consent, compliance, or treatment.

5. TREATMENT OF SUBJECTS

5.1. Phase 1 Dose Escalation

Dose Escalation: A minimum of three subjects will be entered within each cohort with expansion as needed to determine the DLT. If one of three subjects experience study treatment (ibrutinib and/or carfilzomib) related DLT during the first treatment cycle, the same cohort will be expanded to six subjects. If one of six subjects experiences a study treatment related DLT during the first treatment cycle, the next cohort may be enrolled. If at any time during a cohort, ≥2 subjects experience a study treatment related DLT, the MTD will have been exceeded, additional enrollment within the cohort will cease, and dose escalation will stop (Table 2) ie, if there are 2 DLTs in Dose Level 1, Dose Level -1 will be enrolled. The MTD will be defined as the dose level *below* which study treatment related DLT is observed in ≥33% (ie, ≥2 of 3 or ≥2 of 6) subjects in a cohort.

Table 2: Phase 1 Dosing Levels

28-day Dosing Cycle	Ibrutinib[a]	Carfilzomib[b]
Dose Level -1	420 mg once daily	20 / 27 mg/m^2
Dose Level 1 (starting dose)	560 mg once daily	20 / 27 mg/m^2
Dose Level 2	560 mg once daily	20 / 36 mg/m^2
Dose Level 3	840 mg once daily	20 / 36 mg/m^2

a. Ibrutinib will be administered orally daily on Days 8-28 in Cycle 1 and thereafter on Days 1-28

b. Carfilzomib will be administered IV on Days 1, 2, 8, 9, 15, and 16 per cycle. Prior to carfilzomib administration subjects will be given 4 mg dexamethasone (oral or IV) during cycle 1 only with re-initiation as clinically appropriate

Dose escalation guidelines for sequential cohorts are summarized in Table 3 below:

Table 3: Dose Escalation Guidelines for Sequential Cohorts

No. of Subjects with Drug-Related DLT at a Given Dose Level	Dose Escalation*
0 of 3	Proceed to next dose cohort level
1 of 3	3 more subjects are treated at the same dose level
≥2 of 3	Dose escalation stops. MTD is next lower dose level.
1 of 6	Proceed to next dose cohort level
≥2 of 6	Dose escalation stops. MTD is next lower dose level.
≤1 of 6 at the highest tested dose level	MTD not identified use this dose in Phase 2b

* The number of subjects within a cohort and dose groups may be expanded, to further establish safety, if needed.

Before applying the dose escalation rules, 3 subjects in a given dose level must have completed 28 days (1 cycle) of therapy and have been evaluated for toxicity (Cycle 2, Day 1). If the first 3 subjects within a cohort tolerate the first 28-day cycle of treatment without experiencing a DLT, as defined below, the next cohort may enroll.

Once the RP2D is identified, subjects enrolled in lower dose levels, with no dose reductions or DLTs, will be allowed to escalate to the RP2D .

Missed doses of carfilzomib, and ibrutinib will not be made up. Doses of carfilzomib may be rescheduled by up to 1 day. Anticipated delays of a scheduled carfilzomib dose by >1 day may be approved at the discretion of the medical monitor after discussion with the investigator.

Note: In the Dose Escalation phase, if a subject ends treatment within the first cycle for reasons other than study treatment related toxicity, ie, withdraws consent, they will be replaced.

5.2. Definition of Dose Limiting Toxicity

DLT assessments will only be conducted during the Dose Escalation in Phase 1 for the first cycle. DLTs are defined as follows:

Hematologic:

- Grade 4 neutropenia (ANC <500/mm^3) lasting for >10 days and/or the necessity for use of G-CSF, GM-CSF or pegylated G-CSF
- Febrile neutropenia (ANC <1,000/mm^3 with a fever ≥38.3ºC)
- Grade 4 thrombocytopenia (<25,000/ mm^3) that persists for ≥7 days, despite holding treatment
- Grade 3-4 thrombocytopenia associated with bleeding requiring blood products

Non-Hematologic:

- Grade ≥2 neuropathy with pain
- Grade ≥3 unmanageable non-hematologic toxicity
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic / antidiarrheal therapy
- Grade ≥4 fatigue persisting for >7 days

Other:

- Inability to administer most of the planned doses for both drugs during Cycle 1
    - More than one missed carfilzomib dose due to toxicity associated with the study treatment will be considered as a DLT
    - Three (3) or more days of missed ibrutinib treatment due to toxicity associated with the study treatment will be considered as a DLT.

5.3. Randomization and Blinding

Subjects who meet all the inclusion/exclusion criteria are eligible to enter the study.

Phase 1:

- Is an open-label study, there will be no randomization or stratification of subjects.

Phase 2b:

- Eligible subjects will be randomized 1:1 to either ibrutinib or matching placebo capsules in combination with carfilzomib.
- Subjects will be stratified at randomization by:
    1) Refractory status to the most recent line of therapy.
    2) Number of prior lines of therapy (2-4 versus ≥5).

The purpose of stratification is to maintain balance across treatment arms in regards to the allocation of subjects with different prognoses for progression and survival.

5.4. Treatment Regimens

All eligible subjects will be treated with carfilzomib.

Phase 1:

Ibrutinib will be administered at 560 mg (4 capsules) or 840 mg (6 capsules) according to the designed treatment level (Table 2).

Phase 2b:

During the conduct of the double-blinded portion of the study, subjects will be randomly assigned to treatment with either ibrutinib (Arm A) or matching ibrutinib/placebo (Arm B). Final dose level for conducting the Phase 2b portion will be selected by the Sponsor.

Missed doses of ibrutinib or matching ibrutinib/placebo and carfilzomib will not be made up. During the conduct of the Phase 2b, dose escalation for carfilzomib and/or ibrutinib at any time will not be allowed.

Arm A (28-day treatment cycles)

Carfilzomib:

- 20 mg/m^2 administered IV over 30 (+10) minutes on Day 1 and Day 2 of Cycle 1
- 27 or 36 mg/m^2 administered IV over 30 (+10) minutes on Day 8, 9, 15, and 16 in Cycle 1 and from Cycle 2 onwards on Day 1, 2, 8, 9, 15, and 16.
- 4 mg dexamethasone premedication will be administered orally or IV prior to each carfilzomib infusion during Cycle 1 only with reinitiation as clinically appropriate.

Ibrutinib:

- 560 or 840 mg (4 or 6 capsules) orally administered daily beginning from Day 8 in Cycle 1

Arm B (28-day treatment cycles)

Carfilzomib:

- 20 mg/m^2 administered IV over 30 (+10) minutes on Day 1 and Day 2 of the first cycle
- 27 or 36 mg/m^2 administered IV over 30 (+10) minutes on Day 8, 9, 15, and 16 in Cycle 1 and from Cycle 2 onwards on Day 1, 2, 8, 9, 15, and 16.
- 4 mg dexamethasone premedication will be administered orally or IV prior to each carfilzomib infusion during Cycle 1 only with reinitiation as clinically appropriate.

Matching Ibrutinib/Placebo:

- 4 or 6 capsules of matching ibrutinib/placebo orally administered daily beginning from Day 8 in Cycle 1

5.5. Ibrutinib or Ibrutinib/Placebo

For the purposes of this study ibrutinib refers to open label study product used in Phase 1, ibrutinib/placebo refers to blinded study product used in Phase 2b of the study. All subjects in both phases of the study will follow guidelines for ibrutinib dosing and toxicity management. Study drug refers to both ibrutinib and ibrutinib/placebo.

5.5.1. Formulation, Packaging, and Storage of Ibrutinib or Ibrutinib/Placebo

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

Matching placebo capsules are provided as a hard gelatin capsule and look identical to ibrutinib capsules.

The study drug capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements:

- Phase 1 (open-label), each bottle will have a study specific label which will include ibrutinib 140 mg.
- Phase 2b (double-blind), each bottle will have a study specific label with a unique identification number.

5.5.2. Dosage and Administration of Ibrutinib

The first dose of study drug will be administered orally on Day 8 of Cycle 1, of the Treatment Phase, after which study drug will be self-administered daily by the subjects on an outpatient basis.

Study drug will be dosed 0-60 minutes after the end of carfilzomib infusion by clinic staff on PK days.

Study drug should be administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Each dose of study drug should be taken at least 2 hours after a meal or at least 30 minutes before the next meal, at approximately the same time each day. Ingestion of grapefruit and Seville oranges (see Appendix 7) should be avoided for the duration of study drug treatment due to CYP3A4/5 inhibition.

If the subject misses a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. Study drug dosing is continuous (without interruption) throughout the Treatment Phase. If Day 1 carfilzomib dosing is delayed for toxicity that does not require study drug to be held for toxicity, dosing should continue at investigator discretion. If a Day 1 (of any Cycle) carfilzomib infusion is delayed due to scheduling delays, study drug dosing should continue.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 5.7.

Dose modifications for toxicity are outlined in Section 5.5.4.

Unused study drug capsules dispensed during previous visits must be returned and drug accountability records updated at the beginning of the next cycle. Returned capsules must not be re-dispensed to the same subject or to another subject.

5.5.3. Dose Delay of Ibrutinib

Treatment with study drug should be withheld for any unmanageable, potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity. Please see Section 6.3.3 for guidelines for management of study drug in subjects who require anticoagulant treatment. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the Medical Monitor.

Study drug may be withheld for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

5.5.4. Dose Modification of Ibrutinib

The dose of study drug should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities occur:

- Grade 4 ANC (<500/μL) for more than 7 days. See Section 6 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (<50,000/μL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (<25,000/μL)
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity.

Table 4: Ibrutinib Dose Modifications

Action to be taken - Hematologic Adverse Events	
• May resume therapy once ANC ≥750, follow dose modification guidelines below after first occurrence • May resume therapy once platelets >25,000 and no evidence of clinically significant bleeding, follow dose modification guidelines below after first occurrence	
Occurrence	**Action to be Taken - Non-hematologic Adverse Events**
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, Phase 1: 420 mg/day for 560 mg /day cohort; or 700 mg/day for 840 mg/day cohort or Phase 2b: reduce daily dose by 1 capsule/day)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, Phase 1: 280 mg/day for 560 mg/day cohort; or 560 mg/day for 840 mg/day cohort or Phase 2b: reduce daily dose by 2 capsules/day)
Fourth	Discontinue study drug*

*If study drug is discontinued for toxicity, subject will end the Treatment Phase of the study.

Dose changes must be recorded in the Dose Administration CRF.

At the Investigator's discretion, the dose of study drug may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

5.5.5. Overdose Instructions

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose. Treatment of adverse events associated with overdose should be supportive for the underlying symptoms.

5.6. Carfilzomib

5.6.1. Formulation, Packaging, and Storage of Carfilzomib

Carfilzomib for injection is supplied as an individually cartoned single-use vial containing a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder. Refer to the pharmacy manual/site investigational product manual for detailed guidance on carfilzomib storage guidance.

5.6.2. Dosage, Preparation and Administration of Carfilzomib

Carfilzomib vials contain no antimicrobial preservatives and are intended only for single use.

The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution. Refer to the pharmacy manual/site investigational product manual for detailed instructions for reconstitution.

Carfilzomib is administered IV over 30 (+10) minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. In Cycle 1, carfilzomib is administered at a dose of 20 mg/m^2. If tolerated in Cycle 1, the dose should be increased to 27 or 36 mg/m^2/day on Day 8 Cycle 1 and stay at that level for subsequent cycles. See Section 5.6 for study treatment details. Treatment may be continued until disease progression or until unacceptable toxicity occurs

The dose is calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA >2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of ≤20%.

5.6.2.1. Administration Precautions of Carfilzomib

The quantity of carfilzomib contained in one single-use vial (60 mg carfilzomib) may exceed the required dose. Caution should be used in calculating the quantity delivered to prevent overdosing.

Do not mix carfilzomib with or administer as an infusion with other medicinal products.

The IV administration line should be flushed with 0.9% Normal Saline (0.9% NS) or 5% Dextrose Injection, USP immediately before and after carfilzomib administration. Carfilzomib should not be administered as a bolus.

5.6.2.2. Hydration and Fluid Monitoring

Hydration to reduce the risk of renal toxicity and of tumor lysis syndrome with carfilzomib treatment should be administered during Cycle 1 only. Maintain adequate fluid volume status throughout treatment and monitor blood chemistries closely. Prior to each dose in Cycle 1, give 250 mL to 500 mL of IV 0.9% NS or other appropriate IV fluid. Give an additional 250 mL to 500 mL of IV fluids if clinically appropriate following carfilzomib administration. Monitor subjects during this period for fluid overload. Hydration following the completion of Cycle 1 should only occur as clinically appropriate on a per subject basis.

5.6.2.3. Dexamethasone Premedication

Pre-medicate with dexamethasone 4 mg orally or IV prior to all doses of carfilzomib during Cycle 1 only to reduce the incidence and severity of infusion reactions. Dexamethasone premedication may be reinstated (4 mg orally or IV) if these symptoms develop or reappear during subsequent cycles.

5.6.3. Dose Modification of Carfilzomib

Table 5: Dose Modification for Carfilzomib Toxicity

Hematologic Toxicity[a]	**Recommended Action**
• Grade 3 or 4 Neutropenia • Grade 4 Thrombocytopenia	• Withhold dose. • If fully recovered before next scheduled dose, continue at same dose level. • If recovered to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce dose by one dose level (Table 6). • 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 until resolved or returned to baseline. • After resolution, consider if restarting carfilzomib at a reduced dose is appropriate (Table 6). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Pulmonary Hypertension	• Withhold until resolved or returned to baseline. • Restart at the dose used prior to the event or reduced dose, (Table 6), 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	• Withhold until resolved or returned to baseline. • Consider restarting at the next scheduled treatment with one dose level reduction (Table 6). • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Hepatic Toxicity • Grade 3 or 4 elevation of transaminases, bilirubin or other liver abnormalities	• Withhold until resolved or returned to baseline. • After resolution, consider if restarting carfilzomib is appropriate; may be reinitiated at a reduced dose (Table 6) with frequent monitoring of liver function. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Renal Toxicity • Serum creatinine equal to or greater than 2 × baseline	• Withhold until renal function has recovered to Grade 1 or to baseline and monitor renal function. • If attributable to carfilzomib, restart at the next scheduled treatment at a reduced dose (Table 6). • If not attributable to carfilzomib, 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.
Peripheral Neuropathy • Grade 3 or 4	• Withhold until resolved or returned to baseline. • Restart at the dose used prior to the event or reduced dose (Table 6), at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Other • Grade 3 or 4 non-hematological toxicities	• Withhold until resolved or returned to baseline. • Consider restarting at the next scheduled treatment with one dose level reduction (Table 6). • 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 3.0

Table 6: Dose Reduction of Carfilzomib

Current Dose Level	20 mg/m^2	27 mg/m^2	36 mg/m^2
Dose Reduction 1	15 mg/m^2	20 mg/m^2	27 mg/m^2
Dose Reduction 2	Discontinue	15 mg/m^2	20 mg/m^2
Dose Reduction 3		Discontinue	15 mg/m^2
Dose Reduction 4			Discontinue

5.7. Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If the subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Confirmed PD.
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further study drug capsule administration.
- Withdrawal of consent for treatment by subject.
- Investigator decision (such as chronic noncompliance, significant protocol deviation or best interest of subject).
- Study termination by Sponsor.
- Subject becomes pregnant.

Subjects who withdraw for any reason after the Phase 1 Dose Expansion will not be replaced. An End of Treatment visit (Section 8.3.5) is required for all subjects except for those subjects who have withdrawn full consent (see Section 9).

6. Concomitant Therapy

Concomitant therapy must be recorded throughout the study beginning 14 days prior to Cycle 1, Day 1 until 30 days after the last dose of study treatment.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

Erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors filgrastim and pegfilgrastim are allowed. Transfusional support (packed red blood cells and platelets) may be given in accordance with institutional policy.

In Phase 1, Dose Escalation: Erythropoietic and hematopoietic growth factors (filgrastim and pegfilgrastim) as well as transfusional support (packed red blood cells and platelets) should not be given in Cycle 1 determination of DLT. If they are administered this will be an indication of DLT.

6.2. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study treatment.

Short courses (<14 days) of corticosteroids (at dosages equivalent to prednisone ≤20 mg per day) for treatment of non-cancer-related medical reasons are permitted as is carfilzomib premedication as required.

The use of sargramostim and *platelet growth factors (eg, thrombopoietin)* are prohibited. Erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors (filgrastim and pegfilgrastim) are prohibited during Phase I Dose Escalation, Cycle 1, but are allowed as indicated in Section 6.1.

The Sponsor should be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.3. Medications to be Used With Caution

6.3.1. CYP Inhibiting/Inducing Drugs

Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A4/5 can increase ibrutinib exposure.

Co-administration of ketoconazole, a strong CYP3A4/5 inhibitor, in 18 healthy subjects, increased dose normalized exposure C_{max} and $AUC_{0\text{-last}}$ of ibrutinib by 29- and 24-fold, respectively. However, in 38 patients treated with mild and/or moderate CYP3A4/5 inhibitors, the ibrutinib exposure (AUC) was ≤2-fold the upper limit of the range of 76 patients not treated concomitantly with CYP3A4/5 inhibitors. Clinical safety data in patients treated with weak, moderate, or strong CYP3A4/5 inhibitors did not reveal meaningful increases in toxicities. Since no exposure data are available in subjects treated concomitantly with strong inhibitors of CYP3A4/5 (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone), these inhibitors should be avoided. If a strong CYP3A4/5 inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A4/5 (see Section 5.5.2).

Co-administration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) may decrease ibrutinib plasma concentrations and should be avoided.

For subjects who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK blood samples during concomitant use of ibrutinib with strong or moderate CYP3A4/5 inhibitors will be requested for ibrutinib exposure confirmation (see Section 7.5.2).

A list of common CYP3A4/5 inhibitors or inducers is provided in Appendix 7; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

6.3.2. Concomitant Use of QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered and if needed, the Medical Monitor may be contacted.

6.3.3. Concomitant Use of Antiplatelet Agents and Anticoagulants

There have been reports of hemorrhagic events in subjects treated with ibrutinib. These include minor hemorrhagic events like contusion, epistaxis and petechiae; and major hemorrhagic events including gastrointestinal, intracranial hemorrhage and hematuria. It is not clear whether or not these events are attributable to ibrutinib, however, it is possible that treatment with the ibrutinib could increase the risk of bruising or bleeding.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided. Please refer to the current IB for additional information.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. STUDY EVALUATIONS

7.1. Screening / Administrative

All routine laboratory and clinical screening assessments must be performed within 28 days before the first administration of study drug (Cycle 1, Day 1), unless otherwise indicated in Section 8.2 (longer windows allowed for baseline radiologic assessments). Screening tests may be used at baseline if done within 7 days of Cycle 1, Day 1.

Some laboratory assessments may be performed at a Central Laboratory. Please review the Central Laboratory Manual for details.

7.1.1. 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 approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.2. Confirmation of Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4). Measurable disease documented by SPEP, UPEP and/or SFLC is required prior to enrollment. Multiple myeloma diagnosis will be confirmed as well as the stage at original diagnosis and current disease status (relapsed or relapsed and refractory) will be documented if all requisite clinical results are available.

7.1.3. Medical History and Demographics

The subject's complete history including concurrent medical signs and symptoms will be collected and recorded.

Disease history, including the date of initial diagnosis, documentation of relapsed/refractory disease, prior anticancer treatments with best responses and date of progression to these treatments will be collected and recorded.

7.1.4. Prior and Concomitant Medications

All medications from 14 days before Cycle 1, Day 1 through 30 days after the last dose of study treatment will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until death, subject withdrawal of full consent, loss to follow-up, or study termination by Sponsor, whichever comes first.

7.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition must be recorded from the time the ICF is signed until 30 days after the last dose of study treatment. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.2.

7.2. Study Assessments

7.2.1. Physical Examination, Height, and Weight

The Screening and End of Treatment physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

A limited symptom-directed physical examination is required at Day 1 of each cycle, Suspected Disease Progression visits and Follow-up visits.

7.2.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance index is provided in Appendix 2.

7.2.3. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

7.2.4. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening and Day 1 of Cycle 2 for all subjects. Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. Abnormalities noted at Screening should be included in the medical history.

Additional 12-lead ECGs may be performed at any time during the study, as determined necessary by the investigator.

7.2.5. Echocardiogram (ECHO)

An ECHO will be performed at Screening on all subjects to assess cardiac function and confirm eligibility. ECHO is the preferred method of evaluation; multiple gated acquisition scan (MUGA) is acceptable if ECHO is not available. Abnormalities noted at Screening should be included in the medical history.

Additional evaluations may be performed at any time during the study, as determined necessary by the investigator.

7.3. Efficacy Assessments

Efficacy evaluations will be conducted at the beginning of each cycle. Response assessments will be made using the IMWG response criteria (Appendix 3). In Phase 1 assessments will be performed at a Local Laboratory, in Phase 2b assessments will be sent to a Central Laboratory.

All screening, Cycle 1 Day 1 and complete response (CR) efficacy assessments will be evaluated and will include quantitative immunoglobulins, serum and urine electrophoresis, serum and urine immunofixation, and serum free light chain assay.

After the determination of measurable disease at Cycle 1 Day 1 assessment, only the parameters that qualify for response assessment will be measured;

- If SPEP and UPEP both meet criteria both will be performed at each cycle
- If only SPEP meets criteria only SPEP will be required at each cycle
- If only UPEP meets criteria only UPEP will be required at each cycle
- If neither SPEP or UPEP meet criteria, only SFLC assay will be required at each cycle
- At the investigators discretion additional evaluations may be performed but they are not to be used for response assessment.

If at any time CR is suspected, all assessments including serum and urine must be performed as per the IMWG response assessment guidelines.

7.3.1. Serum and Urine Protein Electrophoresis

Samples will be collected at Screening, and prior to study drug administration on Day 1 of Cycle 1. Additional sample collection per Section 7.3.

7.3.2. Serum Free Light Chain Assay

Samples will be collected at Screening, and prior to study drug administration on Day 1 of Cycle 1. Additional sample collection per Section 7.3.

7.3.3. Serum and Urine Immunofixation

Samples will be collected at Screening. Repetitive serum and urine immunofixation on study is only required to confirm CR (conducted on the first observation that the subject has no detectable M-protein) and then repeated on Day 1 of each cycle until disease progression.

7.3.4. Quantitative Serum Immunoglobulins (IgA, IgG and IgM)

Samples will be collected at Screening, prior to study drug administration on Day 1 of each cycle, End of Treatment, Suspected Disease Progression and Follow-up visits.

7.3.5. C-Reactive Protein and Serum β2-microglobulin

Samples will be collected at Cycle 1, Day 1 only.

7.3.6. Bone Radiological Assessment

A radiologic skeletal survey for evaluation of bone lesions is required. Bone radiological assessment includes a lateral radiograph of the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora, and humeri. Bone radiological assessments are to be done within 50 days prior to the first administration of study drug. Magnetic resonance imaging and computed tomography scans are to be performed as clinically indicated. If evidence of plasmacytoma noted on radiographic imaging at screening, subsequent response assessments must include follow-up studies as appropriate.

Additional radiologic skeletal surveys may be performed at any time during the study, as determined necessary by the investigator.

7.3.7. Bone Marrow Aspirate/Biopsy

A unilateral bone marrow aspirate/biopsy will be obtained at Screening and submitted to a Local Laboratory to document bone marrow involvement and evaluate for morphology.

Phase 1: Bone marrow aspirate is to be evaluated at a Local Laboratory by fluorescent in situ hybridization (FISH) to allow for identification of t(4;14), t(11;14) and del 17p. If the test has been performed within 90 days, it does not need to be repeated.

Phase 2b: Bone marrow aspirate to be submitted to a Central Laboratory for FISH.

Phase 1 and selected Phase 2b sites: An additional 6 mL of bone marrow aspirate will be collected for biomarker assessments (Section 7.6).

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, an additional bone marrow aspirate/biopsy should be obtained to confirm the CR. Bone marrow for confirmation of CR should include staining for CD138 and κ/λ mono-clonality by immunohistochemistry or immunofluorescence.

7.3.8. Survival and Subsequent Anticancer Therapies

Survival

After disease progression, subjects will be contacted to assess survival status every 12 weeks (± 14 days) from End of Treatment Visit until death, subject withdrawal of full consent, or loss to follow-up until 2 years after the last subject is randomized or study termination by Sponsor, whichever comes first. At the time of the analysis and at study closure, a survival sweep will be conducted. All subjects who are not known to have died or withdrawn consent prior to survival sweep will be contacted at that time.

Subsequent Anticancer Therapies

After study treatment is complete, the following information on subsequent anticancer therapies will be collected every 12 weeks (± 14 days) from End of Treatment Visit until death, subject withdrawal of full consent, loss to follow-up until 2 years after the last subject is randomized or study termination by Sponsor, whichever comes first:

- Receipt of subsequent anticancer therapies
- Indication for initiation of subsequent anticancer therapy
- Response to subsequent anticancer therapies

7.3.9. Patient-Reported Outcome (PRO) Assessment (Phase 2b only)

The PRO instruments, EQ-5D and EORTC QLQ-MY20, will be administered in this study on Day 1 of Cycle 1 and every other cycle thereafter (eg, Cycle 3, Cycle 5, etc.), as well as at Suspected Disease Progression and Follow-up visits. It is preferable that questionnaires be administered at the beginning of each visit prior to any procedures or physician assessments according to the Schedule of Assessments (Appendix 1).

The EQ-5D is a standardized instrument for use as a measure of health outcome consisting of a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questionnaires are categorical and should not be analyzed as cardinal numbers. The scores for the 5 dimensions are normalized to a single utility score ranging from 0 to 1, representing the general health status of the individual. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D in this study (Appendix 8).

The EORTC QLQ-MY20 (Appendix 9) is a 20-item questionnaire to assess the quality of life in multiple myeloma patients.

7.4. Clinical Laboratory Assessments

7.4.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

7.4.2. Serum Chemistry

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, and uric acid.

7.4.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a local laboratory.

7.4.4. Pregnancy Test

Pregnancy tests (urine or serum) are required at Screening only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.4.5. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody and will be evaluated by local laboratory at Screening. Hepatitis B surface antigen must be confirmed negative prior to enrollment (Phase 1) or randomization (Phase 2b). If Hepatitis B core antibody is positive, then Hepatitis B polymerase chain reaction (PCR) to quantitate Hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to enrollment (Phase 1) or randomization (Phase 2b) in subjects who are Hepatitis B core antibody positive. Subjects who are hepatitis C PCR positive will be excluded.

7.4.6. Thyroid-stimulating Hormone (TSH)

Sample for TSH will be drawn prior to study drug administration on Day 1 of Cycle 1. If the TSH result is abnormal, samples for free T4, T3, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies testing will be drawn and an endocrinology consult should be considered when appropriate.

7.5. Pharmacokinetics and Pharmacodynamics (Phase 1 and Selected Phase 2b Sites)

PK and pharmacodynamic sample collection will be conducted on all subjects in Phase 1 and may be continued at selected Phase 2b sites. If PK collection continues in Phase 2b, Pharmacyclics will inform selected sites when additional samples are no longer required.

7.5.1. Pharmacokinetics and Pharmacodynamics Sample Collection

During treatment with ibrutinib and carfilzomib, venous blood samples will be collected from all subjects for the determination of plasma concentrations of ibrutinib and its metabolite, PCI-45227, at time points specified in Table 7 below:

Table 7: Pharmacokinetics and Pharmacodynamics Sample Collection Schedule

			Time after ibrutinib dosing			
Cycle	Day	Predose[b]	1 hour (1h ± 15 min)	2 hour (2 h ± 30 min)	4 hour (4 h ± 30 min)	6 hour (5 h to 8h)
1	1	Y				
1	8	X,Y	X	X	X,Y	X
1	9[a]	X,Y				
2	1	X,Y	X	X	X,Y	X
2	2[a]	X,Y				

X = Pharmacokinetics timepoint
Y = Pharmacodynamics timepoint
[a] Samples should be collected approximately 24 (± 2 h) hour after previous study dose of ibrutinib
[b] Samples should be collected approximately 30-60 minutes before study dose of ibrutinib

On the day of the sampling visit, the subject will not take a dose of ibrutinib before arrival at the clinic. Study drug intake will be observed by clinic staff. Ibrutinib will be administered 0-60 minutes after the end of the carfilzomib infusion. The time of the PK sample and the time of the ibrutinib dose will be recorded in the medical record and CRF for Days 8 and 9 of Cycle 1, and for Days 1 and 2 of Cycle 2, plus time for dose of ibrutinib on Day 28 of Cycle 1. Additionally record the time meals are taken before and after the dose of ibrutinib on Day 8 of Cycle 1 and Day 1 of Cycle 2.

Pharmacodynamics will continue to be collected on Day 1 of Cycles 4, 6, 8, 10 and 12, Suspected Disease Progression and End of Treatment visits.

7.5.2. Pharmacokinetics Sample Collection for Subject Treated with Concomitant CYP3A4/5 Inhibitors on Ibrutinib Treatment

For subjects who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A4/5 inhibitor/inducer has started and is still in use. PK samples will be collected at:

- Pre-dose (Sample should be obtained approximately 24 (± 2 h) hours post the previous study dose and approximately 30-60 minutes before study dose of ibrutinib
- 1 hour ± 15 min
- 2 hours ± 30 min
- 4 hours ± 30 min

7.5.3. Pharmacokinetics Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ibrutinib and the PCI-45227 metabolite using validated, specific, and sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods. Other potential ibrutinib metabolites may be explored. Carfilzomib concentrations will not be determined in this study.

7.5.4. Pharmacokinetics Parameters

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models to provide estimates of PK parameters (eg, oral clearance) or metrics of systemic exposure (eg, AUC). Model-derived plasma concentrations or metrics of exposure parameters (eg, minimum concentration [C_{min}] or AUC) may be further analyzed to explore PK correlation between ibrutinib exposure and relevant clinical or biomarker information.

For subjects who received CYP3A4/5 inhibitors, as data permits, a comparison of ibrutinib and PCI-45227 plasma concentrations after ibrutinib administration alone and in combination with CYP3A4/5 inhibitors will be explored.

7.5.5. Pharmacodynamics Analytical Procedures

Peripheral blood mononuclear cell (PBMC) cells will be isolated from whole blood samples before and after ibrutinib treatments. After the complete collection of PBMCs from the various time points, equal protein from each sample will be labeled with a biotinylated derivative of ibrutinib (probe), and subjected to probe enzyme-linked immuno-sorbent (ELISA) assays that determine the occupancy of probe in each sample. BTK occupancy is defined as (100% - probe occupancy %).

7.5.6. Pharmacodynamics Parameters

Baseline BTK by the ELISA assay described above will be determined prior to the first dose of carfilzomib (D1) and prior to the first dose of ibrutinib (D8) in order to detect any possible effect of carfilzomib on BTK baseline levels. BTK occupancy by ibrutinib after the first ibrutinib dose and at steady-state will be calculated as compared to both the D1 (pre-carfilzomib) and D8 (pre-dose of ibrutinib) BTK occupancy will be compared to that achieved in other studies of ibrutinib and is expected to be ≥90%.

7.6. Biomarkers (Phase 1 and Selected Phase 2b Sites)

7.6.1. Genetic and Molecular Prognostic Markers

Cytokines, chemokines, bone metabolism biomarkers, and exploratory investigations of predictive biomarkers and mechanisms of resistance will be tested in both blood and urine. Samples will be collected at the same time as pharmacodynamic samples (see Section 7.5.1) on Days 1, 8 and 9 of Cycle 1, Days 1 and 2 of Cycle 2 and on Day 1 of Cycles 4, 6, 8, 10 and 12, Suspected Disease Progression and End of Treatment visits. Testing will include IL-6, SDF-1, RANKL, MIP-1α and other secreted proteins. Testing will be performed at a central laboratory. Samples will be collected from all Phase 1 subjects. Sample collection(s) may continue at selected sites in Phase 2b.

Bone marrow aspirate/biopsy will be collected at Screening, Cycle 2, Day 15 (± 2 weeks) and at disease progression. Additional bone marrow aspirate/biopsy are required at any time to confirm a CR if the subject has no detectable monoclonal protein and if clinical indicated (eg, prolonged cytopenia or progression). These samples will be utilized or maintained to evaluate potential biomarkers related to disease response and to investigate potential mechanisms of treatment resistance. These samples may later be characterized by technologies such as gene expression profiling, mutational analysis by sequencing, and intracellular signaling pathway analysis. Inhibition of BTK and other related kinases may also be explored. These efforts may identify genes and pathways associated with primary or later development of resistance to ibrutinib and potentially identify biomarkers that could assist with future development of this compound.

7.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the CRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

8. Study Procedures

8.1. Overview

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments Table (Appendix 1) summarizes the frequency and timing of efficacy, PRO, PK, biomarker, and safety measurements applicable to this study. The PK assessments are detailed in the PK Sample Collection Schedule (Table 7).

It is preferable that all visit-specific PRO assessments (Phase 2b only) during a visit should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Adverse event information will be collected using the NCI CTCAE Version 4.03.

8.2. Screening Phase

Screening procedures will be performed up to 28 days before Cycle 1, Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. All study tests and procedures should be performed at the study center at which the subject was enrolled and will be receiving treatment. After signing the ICF, screening, and being deemed eligible for entry, subjects will be enrolled in the study.

Screening Visit

The following procedures will be performed at the Screening Visit within 28 days prior to treatment unless otherwise noted:

- Informed consent
- Review of eligibility criteria
- Medical history and demographics
- Prior medications (including over-the-counter drugs, vitamins and herbs)
- Physical examination, including weight and height
- Evaluation of ECOG performance status
- Vital signs
- 12-lead ECG
- Echocardiogram

- Laboratory Tests (Section 7.4):
  - Hematology within 7 days prior to enrollment (Phase 1) or randomization (Phase 2b)
  - Serum chemistry within 7 days prior to enrollment (Phase 1) or randomization (Phase 2b)
  - Coagulation studies
  - Hepatitis serologies
  - Pregnancy test for women of childbearing potential (urine or serum), within 3 days prior to enrollment (Phase 1) or randomization (Phase 2b)
  - Serum and urine protein electrophoresis (SPEP and UPEP)
  - Serum free light chain assay (SFLC)
  - Serum immunofixation
  - Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- X-ray skeletal survey (may be performed within 50 days prior to C1D1)
- Bone marrow aspirate/biopsy (Section 7.3.7)
- Magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET)/CT in those with known or suspected plasmacytoma

8.3. Treatment Phase

The Treatment Phase must begin within 7 days of enrollment (Phase 1) or randomization (Phase 2b). If laboratory tests are required to be collected on Day 1 of Cycle 1, subject must continue to meet all eligibility criteria to begin treatment.

After Cycle 1, pre-dose assessments may be performed up to 2 days prior to Day 1 of a cycle. Pre-dose assessments for Days 8 and 15 may be performed 1 day prior to day of treatment.

If Carfilzomib dosing requires a schedule adjustment for administrative reasons of more than ±1 day contact the Medical Monitor to discuss.

Day 1 administration of carfilzomib must be at least 11 days from the last cycle carfilzomib administration.

8.3.1. Cycle 1

8.3.1.1. Cycle 1, Day 1

Pre-Dose

The following procedures will be performed prior to dosing Cycle 1 Day 1 visit unless otherwise noted. **Screening tests may be used at baseline** if done within 7 days of Cycle 1, Day 1 where indicated.

- PRO assessments (Phase 2b only) – preferable to be performed prior to any assessments
- Laboratory Tests:
  - Hematology and chemistry to be redrawn if not collected within 7 days of C1D1
  - TSH, C-Reactive protein, and β2-microglobulin

- SPEP, UPEP, SFLC, quantitative serum immunoglobulins

- Phase 1, and selected Phase 2b sites - Central Laboratory Manual for Details:
  - Blood sample collection for pharmacodynamics
  - Serum and Urine Biomarkers (requires 12 hours fasting)
- Adverse events and concomitant medications (if applicable)
- Symptom-directed physical examination, including weight
- ECOG
- Vital signs

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated

8.3.1.2. Cycle 1, Day 2

Pre-Dose

- Laboratory Test: chemistry
- Adverse events and concomitant medications

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated

8.3.1.3. Cycle 1, Day 8

Pre-Dose

- Laboratory Tests: hematology and chemistry
- Adverse events and concomitant medications
- Symptom-directed physical examination, including weight
- Vital signs
- Phase 1, selected Phase 2b sites:
  - Record time of last meal prior to administration of study drug
  - Central Laboratory Tests: Blood sample collection for PK and pharmacodynamics 30-60 minutes before study drug dose

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated
- Phase 1, selected Phase 2b sites:
  - Administration of study drug 0-60 minutes post the end of carfilzomib infusion
  - Record time of meal following administration of study drug
  - Central Laboratory Tests: Blood sample collection for PK / pharmacodynamics (times from study drug dose):

    1 hour (window 45 to 75 minutes) after dosing (for PK only)
    2 hours (window 1.5 to 2.5 hours) after dosing (for PK only)
    4 hours (window 3.5 to 4.5 hours) after dosing (for PK and pharmacodynamics)
    6 hours (window 5 to 8 hours) after dosing (for PK only)
- Phase 2b non-PK only: Administration of study drug.

  Subject will self-administer once daily beginning Cycle 1 Day 8. A dose diary will be provided and subject is to return any unused study drug and diary at day 1 of the next cycle.

8.3.1.4. Cycle 1, Day 9

Pre-Dose

- Laboratory Test: chemistry
- Adverse events and concomitant medications

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated
- Phase 1 PK, selected Phase 2b sites:
  - Blood sample collection for PK and pharmacodynamics 24 hours (±2 hours) after the first dose of study drug and 30-60 minutes prior to second dose
  - Administration of study drug 0-60 minutes post the end of carfilzomib infusion
  - A dose diary will be provided and subject is to return any unused study drug and diary at day 1 of the next cycle

8.3.1.5. Cycle 1, Day 15

Pre-Dose

- Laboratory Tests: hematology and chemistry
- Adverse events and concomitant medications
- Symptom-directed physical examination, including weight
- Vital signs

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated

8.3.1.6. Cycle 1, Day 16

Pre-Dose

- Adverse events and concomitant medications

Dosing and Post-Dose

- Hydration with 250 mL to 500 mL 0.9% NS or other appropriate fluid
- Administration of dexamethasone pre-medication and carfilzomib
- Additional 250 mL to 500 mL of IV fluids if clinically indicated

8.3.2. Cycles 2-3

8.3.2.1. Cycles 2-3, Day 1

Pre-Dose

- PRO assessments (Phase 2b only) – Cycle 3 preferable to be performed prior to any assessments
- Laboratory Tests: hematology and chemistry
- Efficacy Assessments:
  - SPEP, UPEP, SFLC, and quantitative serum immunoglobulins (Section 7.3)
  - Only to confirm CR: serum and urine immunofixation, then repeated every cycle until disease progression
- Adverse events and concomitant medications
- Collect subject diary and any remaining study drug from last cycle
- Symptom-directed physical examination, including weight
- ECOG

- Vital signs
- ECG (Cycle 2 only)
- Phase 1, selected Phase 2b sites: (Cycle 2)
  - Record time of last study drug dose (Cycle 1 Day 28)
  - Record time of last meal prior to administration of study drug
  - Central Laboratory Tests:
    - Blood sample collection for PK / pharmacodynamics 30-60 minutes before study drug dose and 24 hours (±2 hours) after the previous dose (Cycle 1 Day 28)
    - Serum and Urine Biomarkers (requires 12 hours fasting)

Dosing and Post-Dose

- Administration carfilzomib
- Phase 1, selected Phase 2b sites: (Cycle 2)
  - Administration of study drug 0-60 minutes post the end of carfilzomib infusion
  - Record time of meal following administration of study drug
  - Central Laboratory Tests: Blood sample collection for PK / pharmacodynamics (times from study drug dose):
    - 1 hours (window 45 to 75 minutes) after dosing (for PK only)
    - 2 hours (window 1.5 to 2.5 hours) after dosing (for PK only)
    - 4 hours (window 3.5 to 4.5 hours) after dosing (for PK and pharmacodynamics)
    - 6 hours (window 5 to 8 hours) after dosing (for PK only)

8.3.2.2. Cycles 2-3, Day 2

Pre-Dose

- Adverse events and concomitant medications

Dosing and Post-Dose

- Administration of carfilzomib
- Phase 1, selected Phase 2b sites: (Cycle 2)
  - Blood sample collection for PK and pharmacodynamics 24 hours (±2 hours) after the first dose of study drug and 30-60 minutes prior to second dose.

8.3.2.3. Cycles 2-3, Day 8

Pre-Dose

- Laboratory Test: hematology
- Adverse events and concomitant medications

Dosing and Post-Dose

- Administration of carfilzomib

8.3.2.4. Cycles 2-3, Day 15

Pre-Dose

- Laboratory Test: hematology
- Adverse events and concomitant medications
- Symptom-directed physical examination, including weight
- Vital signs
- Phase 1, selected Phase 2b sites: Cycle 2 Day 15 (±2 weeks) Bone Marrow Aspirate Biomarker see Central Laboratory Manual for details

Dosing and Post-Dose

- Administration of carfilzomib

8.3.2.5. Cycles 2-3, Days 9 and 16

Pre-Dose

- Adverse events and concomitant medications

Dosing and Post-Dose

- Administration of carfilzomib

8.3.3. Cycle 4 (and subsequent cycles)

8.3.3.1. Cycle 4 (and subsequent cycles), Day 1

Pre-Dose

- PRO assessments (Phase 2b only) – Cycles 5, 7, and every other Cycle preferable to be performed prior to any assessments
- Laboratory Tests: hematology and chemistry
- Efficacy Assessments:
  - SPEP, UPEP, SFLC, and quantitative serum immunoglobulins (Section 7.3)
  - Only to confirm CR: serum and urine immunofixation, then repeated every cycle until disease progression
- Central Laboratory Tests (Phase 1, selected Phase 2b sites) – Cycles 4, 6, 9 and 12:
  - Blood sample collection for pharmacodynamics
  - Serum and Urine Biomarkers (requires 12 hours fasting)
- Adverse events and concomitant medications

- Collect subject diary and any remaining study drug from last cycle
- Symptom-directed physical examination, including weight
- ECOG
- Vital signs

Dosing and Post-Dose

- Administration of carfilzomib

8.3.3.2. Cycle 4 (and subsequent cycles), Days 2, 8, 9 and 16

Pre-Dose

- Laboratory Test: hematology (Day 8 only)
- Adverse events and concomitant medications

Dosing and Post-Dose

- Administration of carfilzomib

8.3.3.3. Cycle 4 (and subsequent cycles), Day 15

Pre-Dose

- Laboratory Test: hematology
- Adverse events and concomitant medications

Dosing and Post-Dose

- Administration of carfilzomib

8.3.4. Suspected Disease Progression Visit

If, at any time, there is suspected disease progression, the following assessments should be performed to confirm progression if not already performed within 7 days:

- PRO assessments (Phase 2b only) – preferable to be performed prior to any assessments
- Laboratory Tests: hematology, chemistry
- Efficacy Assessments:
  - SPEP, UPEP, SFLC, and quantitative serum immunoglobulins (Section 7.3)
  - Only to confirm CR: serum and urine immunofixation, then repeated every cycle until disease progression
- Central Laboratory Tests (Phase 1, selected Phase 2b sites):
  - Blood sample collection pharmacodynamics
  - Serum and Urine Biomarkers (requires 12 hours fasting)
  - Bone Marrow Aspirate

- Adverse events and concomitant medications
- Symptom-directed physical examination, including weight
- ECOG
- Vital signs

8.3.5. End of Treatment Visit

The End of Treatment Visit will be performed 30 days (±3 days) after the last administration of study drug. The following procedures will be performed:

- PRO assessments (Phase 2b only) – preferable to be performed prior to any assessments
- Laboratory Tests: hematology, chemistry
- Efficacy Assessments:
  - SPEP, UPEP, SFLC, and quantitative serum immunoglobulins (Section 7.3)
  - Only to confirm CR: serum and urine immunofixation
- Central Laboratory Tests (Phase 1, selected Phase 2b sites):
  - Blood sample collection pharmacodynamics
  - Serum and Urine Biomarkers (requires 12 hours fasting)
- Adverse events and concomitant medications
- Collect subject diary and any remaining study drug from last cycle
- Symptom-directed physical examination, including weight
- ECOG performance status
- Vital signs

8.4. Follow-Up Phase

8.4.1. Follow-up Procedures (Until Disease Progression)

For subjects who discontinue treatment for reasons other than disease progression, the following assessments will be performed every 12 weeks (±14 days) until disease progression or study closure, whichever is earlier:

- PRO assessments (Phase 2b only) preferable to be performed prior to any assessments
- Laboratory Tests: hematology, chemistry
- Efficacy Assessments:
  - SPEP, UPEP, SFLC, and quantitative serum immunoglobulins (see Section 7.3).
  - Only to confirm CR: serum and urine immunofixation, then repeated every cycle until disease progression
- Symptom-directed physical examination, including weight

- ECOG performance status
- Vital signs and weight
- Survival status and new anticancer therapy

8.4.2. Survival Follow-up

Once a subject progresses, receipt of subsequent anticancer therapy and survival status will be assessed every 12 weeks (±14 days) until death, withdrawal of full consent by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first.

- Survival status and new anticancer therapy
- PRO assessments (Phase 2b only) for the first 2 Survival Follow-Up assessments

9. SUBJECT COMPLETION/WITHDRAWAL

9.1. Discontinuation of Treatment

Study drug and carfilzomib treatment will be discontinued in the event of any of the following events:

- Confirmed progressive disease
- Unacceptable toxicity
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

A subject who discontinues study treatment for reasons other than disease progression (eg, adverse event, Investigator decision) will undergo an End of Treatment Visit and be followed for progression and survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues study treatment due to disease progression and should provide documentation of disease progression for review by the Sponsor's Medical Monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

9.2. Withdrawal From the Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up

- Study termination by Sponsor
- Death

If a subject withdraws consent, it should be defined in the medical record whether the subject withdraws full consent to treatment and all further contact or if the subject withdraws partial consent, ie, they no longer wish to receive treatment, but will participate in the End of Treatment Visit and/or Long-term Follow-up.

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

10. STATISTICAL METHODS

Statistical analysis will be performed by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods for the analysis of the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

10.1. Analysis Populations

10.1.1. Intent-to-Treat Population

Phase 2b: The Intent-to-Treat (ITT) population is defined as all eligible subjects who are randomized into the Phase 2b study. Eligible subjects are defined as all subjects who signed the ICF, with a confirmed diagnosis of MM who had received at least two prior lines of therapy and had documented relapse/refractory disease according to IMWG consensus criteria (Appendix 3), and a baseline assessment. All efficacy analyses will be based on the ITT population.

10.1.2. Response-evaluable Population

Phase 1: The Response-evaluable population is defined as all eligible subjects who received at least 1 dose of study treatment, regardless of whether there is a post-baseline disease assessment.

10.1.3. Safety Population

The safety population will consist of all enrolled subjects who received at least one dose of study treatment. The safety population will be used for the analysis of safety data and for the summary of subject disposition.

10.1.4. Additional Analysis Populations

Additional analysis population, which may be used in sensitivity analyses for primary and secondary efficacy objectives or analyses for exploratory objectives, will be defined in the statistical analysis plan.

10.2. Sample Size Determination

Phase 1: This is a standard 3+3 design to determine the maximally tolerated dose and toxicity profile of ibrutinib. Dose escalation will follow the 3+3 principles and up to 2 cohorts in the absence of dose-limiting toxicity will be expand up to 18 subjects per cohort. Expansion beyond

the 3+3 principles will allow a more accurate evaluation of the RP2D and preliminary efficacy results. This study is not powered for comparison of treatment arms.

Phase 2b: A sample size of approximately 134 eligible subjects will be enrolled to observe 101 PFS events in this study. For the calculation, the median PFS of 4 months for carfilzomib and placebo arm and the enrollment rate of 10 subjects per month were assumed. Assuming exponential survival distribution and 75% improvement in median PFS of the carfilzomib in combination with ibrutinib arm over carfilzomib and placebo arm (hazard ratio of 0.57), the study has at least 80% power to achieve a statistical significance level of 2.5% (1-sided).

10.3. Subject Information

The distribution of subjects for each of the analysis populations will be provided. The number of subjects enrolled by each investigative site and country, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation. Demographic and baseline vital sign variables will be summarized. Baseline disease characteristics (documented in the source documents and CRF) will also be summarized.

10.4. Efficacy Analyses

10.4.1. Primary Endpoint

The primary efficacy endpoint of Phase 2b part of this study is PFS. A set of written rules and formulae will be developed based on the IMWG Response Criteria (Appendix 3) to evaluate laboratory and other data for response and progression. Progression-free survival will be assessed on all subjects in the ITT population. Subjects who had the event (ie, PD or death) after the start of subsequent anti-cancer therapy, or are progression-free and alive at the time of clinical cutoff, or have unknown status will be censored on the date of the last adequate disease assessment that is on or before the start of subsequent anti-cancer therapy. Sensitivity analysis will be performed for PFS without censoring at subsequent therapy if initiated prior to documented PD.

10.4.2. Secondary Endpoints

- The ORR will be assessed according to the IMWG criteria and is defined as the proportion of subjects who achieve a PR or better over the course of the study.

- The DOR is defined as the interval between the date of initial documentation of a response and the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders only. Subjects who start new anticancer treatment before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of new anticancer therapy. Responders are subjects in the ITT population who achieve PR or better according to the IMWG response criteria. Non responders (≤MR) will be excluded from the analysis for DOR.

- OS is defined as the time from date of randomization until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who are completely lost to follow-up for survival will be censored at randomization date.

- TTP is defined as the time from the start of treatment until date of disease progression, with deaths from other causes than progression censored.

10.4.3. Exploratory Endpoints

Exploratory endpoints may include the following:

- Duration of the clinical benefit rate including subjects with minimal response (MR) or better according to the IMWG.
- Prognostic and predictive biomarkers and genetics relative to treatment outcomes.

Phase 1:

- PK and pharmacodynamics of ibrutinib (eg, BTK occupancy of drug, levels of secreted protein or bone biomarkers) in subjects with MM.

Phase 2b:

- TTNT
- PROs and disease-related symptoms according to EORTC QLQ-MY20 and EQ-5D

10.5. Analysis Methods

10.5.1. Analysis for Phase 1

The Phase 1 part of this study is an algorithm-based dose-escalation trial to find the MTD of ibrutinib in combination with carfilzomib and to characterize the most frequent adverse events and the DLTs. Dose-limiting toxicities will be evaluated and will include all adverse events experienced through Phase 1.

The Phase 1 secondary efficacy endpoints are the ORR and DOR according to the IMWG response criteria. The point estimate of the rate and the corresponding exact binomial 95% confidence interval (CI) will be calculated. For DOR, the distribution of DOR as assessed will be provided using Kaplan-Meier estimates for responders.

10.5.2. Primary Efficacy Analyses

Progression free survival is defined as the time from the date of randomization to confirmed disease progression or death from any cause, whichever occurs first. Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who had the event (ie, PD or death) after the start of a subsequent anti-cancer therapy, or are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored on the date of the last adequate disease assessment that is on or before the start date of the

subsequent anti-cancer therapy. For subjects without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization. Subjects who have 2 or more consecutive missing disease assessments immediately before PD or death will be censored for analysis of PFS at the time of last adequate disease assessment. Adequate disease assessment is defined according to the IMWG criteria.

The analysis of PFS will be performed on Phase 2b subjects in the ITT population to compare PFS for the 2 treatment arms using a stratified log-rank test stratified by BTZ refractory and double refractory. Distribution of PFS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% CI. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. A sensitivity analysis of PFS will be conducted without censoring at subsequent therapy if initiated prior to documented PD.

10.5.3. Secondary Efficacy Analysis

The secondary efficacy analyses for Phase 2b will based on the ITT population. Overall response rate PR or better), and its 95% CI will be calculated using normal approximation to the binomial distribution.

DOR will be analyzed for subjects who achieve response (PR or better) during the study, defined as the interval between the date of initial documentation of a response and the date of first documented evidence of progressive disease, death, or date of censoring if applicable. Subjects who had the event (ie, PD or death) after the start of subsequent therapy, are progression-free and alive at the time of clinical cutoff, or have unknown status will be censored at the last adequate disease assessment before the start of subsequent therapy. The distribution (median and Kaplan-Meier curves) of duration of response will be estimated using the Kaplan Meier method.

The clinical response rate including MR or better will be analyzed similar to the analysis of ORR.

OS will be analyzed in the ITT population to compare OS for the 2 treatment arms using a stratified log-rank test, stratified by the refractory status to the last treatment regimen and the number of prior regimens. Distribution of OS will be summarized for each treatment arm using the Kaplan-Meier estimate of median and its corresponding 95% CI.

10.5.4. Exploratory Efficacy Analysis

The distribution of TTNT will be estimated using the Kaplan-Meier method. Analysis method will be detailed in the statistical analysis plan.

Descriptive statistics for change in scores from baseline to each assessment time point will be summarized for the PROs and disease-related symptoms according to EORTC QLQ-MY20 and EQ-5D (Phase 2b only)

10.5.5. Pharmacokinetic Analyses

The plasma concentration data for ibrutinib and PCI-45227 at each timepoint will be summarized using descriptive statistics.

Non-compartmental analysis of ibrutinib and PCI-45227 plasma concentration-time data will be performed using WinNonlin.

Ibrutinib and PCI-45227 data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study agent; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Derived PK parameters may be subjected to further explore PK/pharmacodynamic correlation between exposure with relevant clinical or biomarker information.

Bioanalytical data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models using NONMEM. Available subject characteristics (demographics, laboratory variables, genotypes, etc) will be tested as potential covariates affecting PK parameters. The results of the population PK analyses will be presented in a separate report.

10.5.6. Pharmacodynamics Analysis Plan

The pharmacodynamics of ibrutinib binding to patient's cells is determined by a competitive probe assay which measures the amount of BTK that is not bound by ibrutinib. PCI-41025 is the “probe” that consists of ibrutinib linked to biotin via a long chain linker. Labeled probe will produce a signal which allows for the detection of BTK not occupied by drug. PBMC of patients is isolated pre- and post-treatment. Protein lysate is extracted from the PBMC and is subsequently analyzed on an ELISA platform by using MSD Electrochemiluminescent Detection Technology. Lysate is analyzed to achieve a signal for probe and total BTK. Total BTK is determined with an anti Human BTK antibody to capture all BTK, bound and unbound, in the lysate. The percentage of BTK occupied by ibrutinib can be determined by comparing signal of probe before and after treatments normalized to total BTK. BTK occupancy is further derived by subtracting normalized probe occupancy from 100 (BTK occupancy= 100- probe occupancy).

BTK occupancy will be listed for all subjects with samples that can be evaluated. Subjects will be excluded from the PD analysis if samples were not received within 36 hrs of shipment, or if samples are hemolysed, degraded, clotted or compromised during the shipments. In general, BTK occupancy will be summarized for each cohort using descriptive statistics (mean, median, standard error and range).

10.5.7. Safety Analyses

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of study drugs. The baseline value for safety assessments will be defined as the last value on or before the day of the first dose of study drugs if we do not specify. The safety analyses will be based on the monitoring of adverse events, survival status, ECOG performance status, vital signs measurements, and clinical laboratory results.

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital signs measurements. Exposure to ibrutinib first dose and reasons for discontinuation from study treatment will be tabulated. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of adverse events; the relationship of adverse events to ibrutinib; and the action taken with respect to ibrutinib treatment due to adverse events.

The verbatim terms used in the CRF by Investigators to identify non-hematological adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are those adverse events occurring after the first dose of study drugs and within 30 days following the last dose of study drug; any adverse event that is considered study drug-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens after the first administration of study drug in severity or is subsequently considered drug-related by the Investigator. All treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, Version 4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be converted based on the normal ranges and standardized using the SI unit. Selected hematologic and chemistry laboratory parameters are detailed in Section 7.4. Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value. Percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

All laboratory values will be converted to standard international units. and will be graded using the NCI CTCAE Version 4.03. Standard methods for summarizing laboratory variables will be used, including the use of summary statistics and shift tables.

10.5.8. Data Monitoring Committee

The safety of this study will be monitored by an independent DMC. In Phase 1 the DMC will review safety and efficacy data and advise on the RP2D. In Phase 2b the DMC will review the safety data on an ongoing basis.

The independent DMC will be chaired by a physician with expertise in MM. The DMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Adverse Event Definitions and Classifications

11.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug. [ICH-E2A]

For the purposes of this clinical study, adverse events include events which are either new or represent detectable exacerbations of pre-existing conditions.

Disease progression is not an adverse event; rather it may be the cause of an adverse event. The clinical diagnosis that is associated with disease progression must be reported as all other adverse events. Disease progression should never be used as an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any adverse events experienced by the subject through the completion of final study procedures.
- Adverse events not previously observed in the subject that emerge during the protocol-specified adverse event reporting period, including signs or symptoms associated with MM that were not present before the adverse event reporting period.
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered adverse events:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an adverse event unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered a serious adverse event, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other serious adverse event criteria, the event will be considered a serious adverse event. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not serious adverse events.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as adverse events or serious adverse events, but rather the cause for the test or procedure should be reported.
- **Asymptomatic treatment-related lymphocytosis:** This event should also not be considered an adverse event. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures. Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline and ≥5,000/μL that occurs in the setting of improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (hemoglobin or platelet count), or disease-related symptoms.

11.1.2. Serious Adverse Event

Note: The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an adverse event (see below). Serious is a regulatory definition.

A serious adverse event (experience) or reaction is any untoward medical occurrence that:

- Results in death (ie, the actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an adverse event meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization for more than 24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the adverse event results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

11.1.3. Unexpected Adverse Events

An "unexpected" adverse event is an adverse event that is not listed in the Ibrutinib Investigator's Brochure and carfilzomib package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. Unexpected also refers to adverse events mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.1.4. Causality

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related: Another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the adverse event indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible adverse event causes.

Related: The adverse event is clearly related to use of the investigational product.

11.1.5. Severity Criteria

Definitions found in the NCI CTCAE version 4.03 will be used for grading the severity (intensity) of non-hematologic adverse events. The NCI CTCAE Version 4.03 categorizes Grades 1 through Grade 5 with unique clinical descriptions of severity for each referenced adverse event. Should a subject experience any adverse event not listed in the NCI CTCAE Version 4.03, the following grading system should be used to assess severity:

- Grade 1 (mild adverse event) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (moderate adverse event) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (severe adverse event) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (life-threatening or disabling adverse event) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (death related to an adverse event) – experiences which result in death

11.2. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

The Investigator is responsible for ensuring that all adverse events and serious adverse events observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All serious adverse events must also be reported on the Serious Adverse Event Worksheet and to the Sponsor (see Section 11.2.3).

11.2.1. Adverse Event Reporting Period

All adverse events whether serious or non-serious, will be documented in the source documents from the time signed and dated informed consent is obtained until 30 days following the last dose of study drug. Only serious adverse events will be reported to the Sponsor during this time. From the first dose of study drug adverse events and serious adverse events will be recorded in the CRFs and will continue until 30 days after the last dose of study drug. At the End of Treatment visit, the Investigator should instruct each subject to report to the Investigator any subsequent adverse events that the subject's personal physician believes could be related to prior study drug treatment or study procedures.

If a serious adverse event is present at the End of Treatment Visit, the serious adverse event should be followed to resolution, until the Investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to his or her baseline state of health or the Investigator does not expect any further improvement or worsening of the event. Any SAE occurring more than 30 days after the last dose of study treatment and is deemed related to study treatment, must be reported to the Sponsor.

If a death occurs within 30 days after the last dose of study treatment, the death must be reported to the Sponsor as a serious adverse event. Furthermore, the Investigator should notify the Sponsor of any death, serious adverse event, or other adverse event of concern occurring at any time after a subject has discontinued study treatment or study participation, if the event is believe to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital abnormality/birth defect in a subsequently conceived offspring of a subject that participated in this study.

11.2.2. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Worksheet.

Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to study drug or carfilzomib and any actions taken.

11.2.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Worksheet and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, fax and email) for Drug Safety can be found on the Serious Adverse Event Worksheet form and instructions.

All deaths should be reported with the primary cause of death as the adverse event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report or the adverse event/serious adverse event most proximal to death should be the term reported. Autopsy and postmortem reports must be forwarded to Pharmacyclics Drug Safety, or designee, as outlined above.

If study treatment is discontinued because of an serious adverse event, this information must be included in the serious adverse event report.

11.2.4. Other Malignancies

In addition to all routine adverse event reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.2.5. Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor within 24 hours of awareness (irrespective of seriousness, even if non-serious) following the procedure described above for serious adverse events and will require enhanced data collection.

11.2.5.1. Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, any hemorrhagic event which results in the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.2.5 above.

11.2.5.2. Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage, and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest according to Section 11.2.5 above.

11.2.6. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving ibrutinib capsules who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug will be reported. Any occurrence of pregnancy will be recorded on the Pregnancy Report Form Part I and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. With consent, the pregnant woman will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

12. ETHICAL ASPECTS

This clinical study was designed and will be implemented in accordance with the protocol, the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.1. Study-Specific Design Considerations

In addition to receiving study treatment, all participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted response criteria from the IMWG. Safety assessments will occur through regular clinic visits including laboratory analyses.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may

be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

12.2. Regulatory Ethics Compliance

12.2.1. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form Food and Drug Administration (FDA) 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the Investigator's Brochure; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report serious adverse events to the Sponsor or designee and IRB/REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.2.2. Institutional Review Board, Research Ethics Board, and Independent Ethics Committee Approval

The Investigator will submit this protocol, the ICF, Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the IRB/REB/IEC before the implementation of changes in this study. The Investigator is also responsible for providing the IRB/REB/IEC with any required information before or during the study, such as serious adverse event expedited reports or study progress reports.

The IRB/REB/IEC must comply with current US regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: 1) a copy of the IRB/REB/IEC letter that grants formal approval; and 2) a copy of the IRB/REB/IEC-approved ICF.

12.2.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible adverse events, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.2.4. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.2.5. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA 1572) will provide a signed Financial Disclosure Form in accordance with §21 CFR Part 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

12.2.6. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance will be undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the study.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

13.2. Regulatory Documentation

13.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

13.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal Investigator
- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to Good Clinical Practices (GCP) and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, then a general statement may be substituted for this list. If an Investigator or a member of the investigational staff is a member of the IEC/IRB, then documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of Investigator (eg, Form FDA 1572)
- Documentation of Investigator qualifications (eg, curriculum vitae)
- Completed Investigator financial disclosure form from the principal Investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first subject:

- Completed Investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

13.3. Subject Identification, Enrollment, and Screening Logs

The Investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification number and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The Investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

13.4. Treatment Compliance

The Investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. On PK sampling days for ibrutinib only, the timing of meals in relation to the ibrutinib intake will also be recorded.

The study drug is to be prescribed only by the principal Investigator or a qualified physician listed as a sub-investigator on required forms. Records should be kept on the study drug accountability form provided by the Sponsor or its designee (any alternative forms must be preapproved by the Sponsor). Further instructions regarding accountability for study drug are provided in the Pharmacy Manual. Administration of the study drug must be recorded in the subject's source documentation. The study drug may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

13.5. Drug Accountability

The Investigator is responsible for ensuring that all study drug and carfilzomib received at the site is inventoried and accounted for throughout the study. Accountability records must be maintained and readily available for inspection by Sponsor's site monitor during on-site monitoring visits. All study drug and carfilzomib will be stored in a limited access area according to the Sponsor's instructions.

Study drug or carfilzomib should be dispensed under the supervision of the Investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist, and will be supplied only to subjects participating in the study. The Investigator agrees neither to dispense the study drug or carfilzomib from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

At study initiation, the Sponsor or delegate will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

13.6. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

13.7. Case Report Form Completion

Case report forms (CRF) will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed as soon as reasonable possible. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of the CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

13.8. Data Quality Assurance/Quality Control

The Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (§21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

13.9. Record Retention

The Investigator must keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the Investigator's Brochure, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed, dated and completed CRFs, and documentation of CRF corrections, serious adverse event forms transmitted to Pharmacyclics and notification of serious adverse events and related reports, source documentation, normal laboratory values, decoding procedures for blinded

studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the Investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

13.10. Study Monitoring and Audits

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, Standard Operating Procedures, and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

13.11. Study Completion/Termination

13.11.1. Study Completion

The end of the study will occur 2 years after the last subject is randomized, or the Sponsor terminates the study, whichever comes first. The study is considered complete when the last subject completes the last study assessment.

13.11.2. Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further drug development

13.12. Use of Information and Publication

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics.

14. REFERENCES

Aggarwal R, Ghobrial IM, Roodman GD. Chemokines in multiple myeloma. Exp Hematol 2006;34:1289-1295.

Alsina M, Trudel S, Furman RR, et al. A phase 1 single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. Clinical Cancer Research 2012;18:4830-4840.

Arastu-Kapur S, Anderl JL, Kraus M, et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events. Clin Cancer Res 2011;17:2734-43.

Badros A, Papadopoulos K, Zojwalla N, et al. A Phase Ib Study of 30-minute Infusion Carfilzomib 20/45 and 20/56 mg/m^2 plus 40mg weekly Dexamethasone in Patients with Relapsed and/or Refractory (R/R) Multiple Myeloma. Blood 2012;120:Abstract 4036.

Bishop GA, Haxhinasto SA, Stunz LL, et al. Antigen-specific B-lymphocyte activation. Crit Rev Immunol 2003;23:165–197.

Dasmahapatra, G, Patel H, Dent P, et al. The Bruton tyrosine kinase (BTK) inhibitor PCI-32765 synergistically increases proteasome inhibitor activity in diffuse large-B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) cells sensitive or resistant to bortezomib. British Journal of Haematology 2013;161:43-56.

Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007;67:6383-91.

Hájek R, Bryce R, Ro S, et al. Design and rationale of FOCUS (PX-171-011): A randomized, open-label, phase 3 study of carfilzomib versus best supportive care regimen in patients with relapsed and refractory multiple myeloma (R/R MM) BMC Cancer. 2012;12:415.

Jagannath S, Vij R, Stewart AK, et al. An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2012;12:310-8.

Kawano M, Hirano T, Matsuda T, et al. Autocrine generation and requirement of BSF-2/IL-6 for human multiple myelomas. Nature 1988;332:83-85.

Kuhn DJ, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood 2007;110:3281–3290.

KYPROLIS™ [carfilzomib package insert]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; 2012.

Lendvai N, Landau H, Lesokhin A, et al. Phase II Study of Infusional Carfilzomib in Patients with Relapsed or Refractory Multiple Myeloma. ASH Annual Meeting Abstracts 2012; 120: 947.

NCI. SEER Cancer Statistics Review 1978-2008. 2009 [cited 21 August 2011]; Available from: http://seer.cancer.gov/csr/1975_2008/results_merged/sect_19_nhl.pdf.

O'Connor OA, Stewart AK, Vallone M, 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;15:7085–7091.

Ou Z, Zhang L, Newberry K, et al. The bruton's tyrosine kinase inhibitor ibrutinib synergized with the proteasome inhibitor carfilzomib and overcame immunoproteasome-mediated carfilzomib resistance in mantle cell lymphoma. AACR 2013 Abstract 2432.

Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-1060.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.

Roodman GD, Choi SJ. MIP-1 alpha and myeloma bone disease. Cancer Treat Res 2004;118:83-100.

Roodman GD. Osteoblast function in myeloma. Bone 2011;48:135-140.

Roodman GD. Pathogenesis of myeloma bone disease. J Cell Biochem 2010a;109:283-291.

Roodman GD. Targeting the bone microenvironment in multiple myeloma. J Bone Miner Metab 2010b;28:244-250.

Rushworth SA, Bowles KM, Barrera LN, et al. BTK inhibitor ibrutinib is cytotoxic to myeloma and potently enhances bortezomib and lenalidomide activities through NF-κB. Cell Signal 2013:106-12.

Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B cell development and function: a genetic perspective. Immunol Rev 2000;175:120-127.

Shaffer AL, Rosenwald A, Staudt LM. Lymphoid malignancies: The dark side of B-cell differentiation. Nat Rev Immunol 2002;2:920–932.

Siegel D, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PC-171-0031-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012;120:2817-2825

Stevenson FK, Krysov S, Davies AJ, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood 2011;118: 4313–4320.

Suzuki E, Demo S, Deu E, et al. Molecular mechanisms of bortezomib-resistant adenocarcinoma cells. PLoS One. 2011;6:e27996.

Tai Y, Chang B, Kong S, et al. Bruton tyrosine kinase inhibition is a novel therapeutic strategy targeting tumor in the bone marrow microenvironment in multiple myeloma. Blood 2012;120:1877-1887.

Vij R, Siegel DS, Jagannath S, 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. British Journal of Haematology 2012a;158:739-748.

Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma. Blood 2012b;119:5661-5670.

Yang J, Wang Z, Fang Y, et al. Jiang J, et al. Pharmacokinetics, pharmacodynamics, metabolism, distribution, and excretion of carfilzomib in rats. Drug Metabolism and Disposition 2011;39:1873-1882.

Zangari M, Terpos E, Zhan F, et al. Impact of bortezomib on bone health in myeloma: a review of current evidence. Cancer Treat Rev. 2012;38:968-80.

Zangari M, Yaccoby S, Pappas L, et al. A prospective evaluation of the biochemical, metabolic, hormonal and structural bone changes associated with bortezomib response in multiple myeloma patients. Haematologica. 2011;96:333-6.

15. Appendices

Appendix 1: Schedule of Assessments

Phase	Screening Phase	Treatment Phase (28 days/cycle)																			Follow-Up Phase	
Study Cycle		Cycle 1						Cycle 2-3						Cycle 4 and Subsequent Cycles						Suspected PD Visit	EOT 30-day	Follow-up Procedures (Until PD)	Survival Follow-up
Study Day		1	2	8	9	15	16	1[t]	2	8[u]	9	15[u]	16	1[t]	2	8[u]	9	15[u]	16	anytime		q12 weeks	q12 weeks
Visit Window	*-28 days*																				*± 3 days*	*± 14 days*	*± 14 days*
Study Procedures																							
Screening/Administrative																							
Informed consent	X																						
Confirm eligibility	X	X																					
Medical history and demographics	X																						
Study Assessments																							
Physical exam (Height at screening only)[a]	X	X		X		X		X				X		X						X	X	X	
ECOG status	X	X						X						X						X	X	X	
Vital signs[b]	X	X		X		X		X				X		X						X	X	X	
12-lead ECG[c]	X							X	Additional tests may be performed, as determined necessary, at any time during participation in the study														
Echocardiogram	X	Additional tests may be performed, as determined necessary, at any time during participation in the study																					
PRO assessments (Ph 2b only)[d]		X						X						X						X	X	X	X[d]
Concomitant medications	Continuous from 14 days prior to C1D1 to 30 days after last dose of study drug																						
Adverse events[e]	Continuous from informed consent to 30 days after last dose of study drug																						
Study Drug Administration																							
Ibrutinib or Ibrutinib/Placebo[f]				X	Continuous daily self administration																		
Ibrutinib in-clinic administration (Ph 1 only)[g]				X	X			X	X														
Carfilzomib infusion[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Dexamethasone (po or IV)[i]		X	X	X	X	X	X																
Hydration[j]		X	X	X	X	X	X																

Phase	**Screening Phase**	**Treatment Phase (28 days/cycle)**																			**Follow-Up Phase**	
Study Cycle		Cycle 1						Cycle 2-3						Cycle 4 and Subsequent Cycles						Suspected PD Visit	EOT 30-day	Follow-up Procedures (Until PD)	Survival Follow-up
Study Day		1	2	8	9	15	16	1[t]	2	8[u]	9	15[u]	16	1[t]	2	8[u]	9	15[u]	16	anytime		q12 weeks	q12 weeks
Visit Window	*-28 days*																				*± 3 days*	*± 14 days*	*± 14 days*
Efficacy Assessment																							
Serum/Urine protein electrophoresis (SPEP/UPEP) and Serum free light chain assay (SFLC)[k]	X	X						X						X						X	X	X	
Serum/Urine immunofixation[l]	X	Additional tests may be performed to confirm CR																					
Quantitative immunoglobulin	X	X						X						X						X	X	X	
C-reactive protein and β2-microglobulin		X																					
Bone radiological asssessment[m]	X	Additional tests may be performed, as determined necessary, at any time during participation in the study																					
Bone marrow aspirate/ biopsy[n]	X	Additional test may be performed to confirm CR																					
Survival status and new anticancer therapy[o]																						X	X
Clinical Laboratory Assessments																							
Hematology[p]	X	X		X		X		X		X		X		X		X		X		X	X	X	
Serum chemistry[q]	X	X	X	X	X	X		X				X		X						X	X	X	
Coagulation (PT, PTT, INR)	X																						
Pregnancy test[r]	X																						
Hepatitis serologies[s]	X																						
TSH[v]		X																					
Biomarkers and Pharmacokinetic Assessments - Phase 1 and Selected Phase 2b Sites																							
PK (See separate schedule)[w]		X		X	X			X	X														
Bone marrow aspirate Biomarker[x]	X											X								X			
Pharmacodynamics and Biomarkers & mechanisms of resistance blood, serum and urine sample collection[y]		X	X	X	X			X	X					Day 1 of Cycles 4, 6, 9, and 12						X	X		

EOT=End of Treatment Visit

[a.] At Screening PE should include: skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, nervous system and weight. During study conduct a symptom-directed PE, including weight, is required.

[b.] Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

[c.] Performed at Screening and C2D1 after subject has been supine for 5 minutes. Not required at subsequent cycles unless medically indicated.

[d.] Collected at C1D1, and Day 1 of every other cycle (eg, C3D1, C5D1, etc). It is preferable that the questionnaires be administered at the beginning of each visit prior to any procedures or physician interactions. Collected until PD and for the 1st two Survival Follow-up contacts.

[e.] Adverse events are reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. In addition to all routine adverse event reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

[f.] Starting C1D8 subjects will be provided a dosing diary and dispensed ibrutinib to self-administer daily. Subject is to return unused ibrutinib and completed diary at day 1 of each subsequent cycle.

[g.] Ibrutinib will be administered in the treatment center on C1D8, C1D9 and C2D1 and C2D2. Time of dose is to be recorded in the medical record for PK and pharmacodynamic evaluation as well as C1D28 dose self administered at home. For C1D8 and C2D1 record time of last meal prior to administration of ibrutinib and time of meal following ibrutinib administration.

[h.] Carfilzomib is to be administered intravenously over 30 (+10) minutes. If dosing requires a schedule adjustment for administrative reasons of >± 1 day contact the medical monitor to discuss. Day 1 administration of carfilzomib must be at least 11 days from the last cycle carfilzomib administration.

[i.] Pre-medicate with dexamethasone 4 mg orally or IV, prior to carfilzomib. Reinstate in subsequent cycles if symptoms of infusion reaction develop or reappear.

[j.] Administer 250 mL to 500 mL of IV hydration with 0.9%NS (or other appropriate fluid) prior to each dose of carfilzomib in Cycle 1. Give additional 250 to 500mL of IV hydration if clinically appropriate following carfilzomib. Monitor subjects during this period for fluid overload. Hydration following the completion of Cycle 1 should only occur as clinically appropriate on a per subject basis.

[k.] SPEP, UPEP and SFLC will be collected at Screening and C1D1. Phase 1 tests will be submitted to a Local Laboratory, Phase 2b test will be submitted to a Central Laboratory. Subsequent on treatment assessments as follows (Section 7.3):

- If SPEP and UPEP both meet criteria both will be performed at each cycle
- If only SPEP meets criteria only SPEP will be required at each cycle
- If only UPEP meets criteria only UPEP will be required at each cycle
- If neither SPEP nor UPEP meet criteria, only SFLC will be required at each cycle.

If at any time CR is suspected, all assessments must be performed per IMWG guidelines.

[l.] Additional test required to confirm CR, conducted at first observation of CR and then repeated at Day 1 of each cycle until progression.

[m.] Radiologic skeletal bone survey for evaluation of bone lesions, includes; skull, antero-posterier and lateral views of the spine, and antero-posterier views of the pelvis, ribs, femora and humeri. Assessments to be done within 50 days of C1D1. MRI or CT scans are to be performed if clinically indicated. If evidence of plasmacytoma on imaging at screening, subsequent response assessments must include follow-up assessments.

[n.] To be submitted at screening to a local laboratory to document bone marrow involvement and evaluate for morphology. Bone marrow aspirate will be evaluated for FISH, in Phase 1 locally, in Phase 2b at Central Laboratory. Additional bone marrow biopsy procedure should be obtained to confirm CR.

[o.] After disease progression, subjects will be contacted to assess survival status approximately every 12 weeks (±14 days) to assess survival status. .
After ibrutinib treatment is discontinued all information on subsequent anticancer therapies will be collected approximately every 12 weeks (±14 days) until death, subject withdrawal, loss to follow up, or study termination by Sponsor, whichever comes first, to include: Receipt of subsequent anticancer therapies, indication for initiation of subsequent anticancer therapy and response to subsequent anticancer therapies.

[p.] Hematology (WBC, RBC, hgb, hct, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands if reported), to be collected within 7 days of Screening. C1D1 testing not required IF Screening test is within 7 days. While in treatment phase may be drawn up to 1 day prior to treatment, results to be reviewed prior to carfilzomib administration.

[q.] Chemistry (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, and uric acid) to be collected within 7 days of Screening. C1D1 testing not required IF Screening test is within 7 days. While in treatment phase may be drawn up to 1 day prior to treatment.

[r.] Pregnancy tests (urine or serum) are required at Screening only for women of childbearing potential and required within 3 days of enrollment (Phase 1) or randomization (Phase 2b). If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

[s.] Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody and will be evaluated. Hepatitis B surface antigen must be confirmed negative prior to enrollment. If Hepatitis B core antibody is positive, then Hepatitis B PCR to quantitate Hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to randomization in subjects who are Hepatitis B core antibody positive. Subjects who are hepatitis C PCR positive will be excluded.

[t.] Cycle 2 and beyond, Day 1 pre-dose assessments may be performed up to 2 days prior to Day 1 of a cycle.

[u.] Cycle 2 and beyond, Day 8 and 15 pre-dose assessments may be performed 1 day prior to treatment.

[v.] Sample for TSH will be drawn prior to study drug administration on Day 1 of Cycle 1. If the TSH result is abnormal, samples for free T4, T3, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies testing will be drawn and an endocrinology consult should be considered when appropriate.

[w.] Assessments pre- and post-dose ibrutinib, see Table 7 in Section 7.5.2

[x.] Bone marrow aspirate (6 mL) to be submitted to Central Laboratory for biomarker testing. Additional bone marrow biopsy procedures at Cycle 2 Day 15 (± 2 weeks), and disease progression.

[y.] Biomarker serum and urine collections require 12 hour fasting prior to collection. Cytokines, chemokines, bone metabolism biomarkers, exploratory investigations of predictive biomarkers and mechanisms of resistance.

[z.] A 2-d thoracic ECHO is the preferred method of evaluation; MUGA is acceptable if ECHO is not available.

Appendix 2: Eastern Cooperative Oncology Group Performance Status Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix 3: Definitions of Response

IMWG Response Criteria	
CATEGORY	**RESPONSE CRITERIA [a]**
Stringent complete response (sCR)	CR as defined below plus all of the following: • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b]
Complete response (CR)	• Negative immunofixation of the serum and urine • <5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas • If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
Very good partial response (VGPR)[e]	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h • If at on study, the only measurable non-bone marrow parameter was FLC, ≥90% or greater reduction in the difference between involved and uninvolved free light chain levels
Partial Response (PR)	• One of the following: ▪ If at on study, serum and urine measurable, a ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h ▪ If at on study, only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein ▪ If at on study, urine measurable (but serum not), a reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h ▪ If at on study, the only measurable non-bone marrow parameter was FLC, a ≥50% decrease in the difference between involved and uninvolved FLC levels ▪ If at on study, the bone marrow was only measurable parameter, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if a plasmacytoma present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minimal Response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24h urine M-protein by 50-89%, • In addition to the above criteria, if a plasmacytoma present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease

Progressive disease (PD)	Any one or more of the following: • Increase of 25% from lowest value in [g]: ▪ Serum M-component (absolute increase must be ≥0.5 g/dL)[c] ▪ Serum M-component increase ≥1 g/dL, if starting M component was ≥5 g/dL ▪ Urine M-component (absolute increase must be ≥200 mg/24 h) [c] ▪ If at on study, the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) [c] ▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c] Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder ▪ Development of new soft tissue plasmacytomas or bone lesions ▪ Hypercalcemia (≥11.5 mg/dL)
Relapse from CR or sCR [d]	Subject who has achieved confirmed CR who has any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow [f] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

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

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1;2.

[c] Positive immunofixation alone in a subject previously classified as CR will not be considered progression.

[d] This category will ONLY be used to analyze disease free survival

[e] This response category is not available for those subjects being followed by bone marrow only.

[f] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

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

Confirmation of Response Categories

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

- Bone marrow aspirate/biopsy is **only** required to document CR or sCR, except for subjects with bone marrow plasmacytosis evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is not required to confirm response in any case
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Measurable disease

- Serum M-protein ≥1 g/dL
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥10 mg/dL provided serum FLC ratio is abnormal

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

Appendix 4: International Staging System (ISS) for Myeloma Criteria

Stage	Criteria
Stage 1	β2-microglobulin <3.5 mg/dL Albumin ≥3.5g/dL
Stage 2	Neither 1 or 3
Stage 3	β2-microglobulin ≥5.5 mg/dL

Appendix 5: Lines of Therapy

According to the IMWG Consensus panel on uniform reporting criteria in clinical trials (Rajkumar 2011), a line of therapy consists of at least 1 or more cycles of a planned treatment regimen. This may consist of single-agent or combination therapy or a sequence of treatments administered in a planned manner. For example, a planned induction, followed by autologous stem cell transplant (ASCT) followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course is modified as a result of progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease.

Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the "Response Criteria" section of this document.

Appendix 6: Disease Classification (Study Population)

The definitions to define the patient populations studied are based on the ASH-FDA panel on endpoints in myeloma (Rajkumar 2011).

Classification	Definition
Relapsed Myeloma	Relapsed myeloma is defined as previously treated myeloma patients who after a period of being off-therapy require salvage therapy but do not meet criteria for "primary refractory myeloma" or "relapsed-and-refractory" categories.
Refractory Myeloma	Refractory myeloma is defined as disease that is non-responsive while on primary or salvage therapy or progresses within 60 days of last therapy. Non-responsive disease is either failure to achieve minor response or development of progressive disease while on therapy. There are 2 categories of refractory myeloma
Primary Refractory Myeloma*	Primary Refractory myeloma is defined as disease that is non-responsive in patients that have never achieved a minor response or better with any therapy. It includes: 1) non-responding, non-progressing; patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; and 2) progressive; primary refractory, progressive disease where patients meet criteria for true progressive disease[1].
Relapsed AND Refractory Myeloma*	Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy, or within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously prior to then progressing in their disease course.

Appendix 7: Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5 are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.3.1 on instructions for concomitant use of CYP3A4/5 inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
TELITHROMYCIN	Pioglitazone
Moderate inhibitors:	Rifabutin
Aprepitant	Rifampin
Erythromycin	St. John's Wort
Diltiazem	Troglitazone
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix 8: EQ-5D

Health Questionnaire

English version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

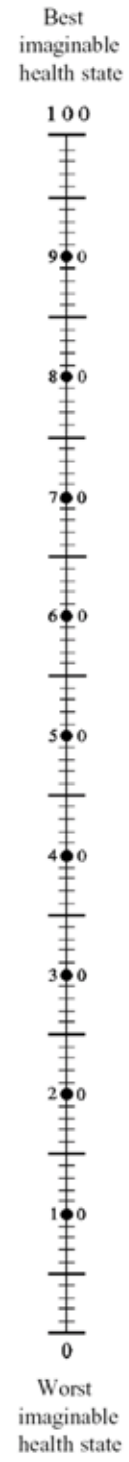
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

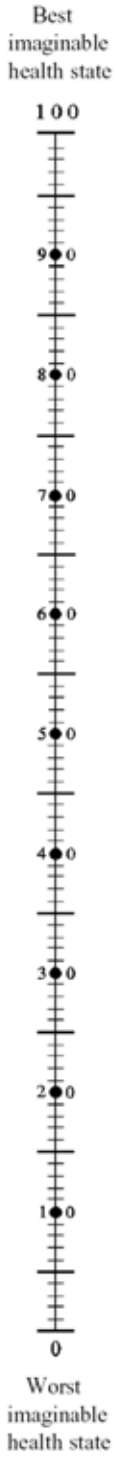
Your own health state today



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 9: EORTC QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4