Investigator-Sponsored Trial

STUDY PROTOCOL

CRAB CTC Study Number: 11-001
Version 9.0
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Amendment #1: April 30, 2013
Amendment #2: August 21, 2013
Amendment #3: November 20, 2013
Amendment #4: November 14, 2014
Amendment #5: November 18, 2014
Amendment #6: February 7, 2015
Amendment #7: February 14, 2018

Study Title: Phase 1b/II Trial of Carfilzomib with Irinotecan in Irinotecan-Sensitive Malignancies (Phase Ib) and Small Cell Lung Cancer Subjects (Phase II) Who Have Progressed on Prior Platinum-based Chemotherapy
(Onyx #IST Reference Number: CAR-IST-553/Amgen Protocol Number 20159842)

IND Number: 117350
Institution Name: CRAB Clinical Trials Consortium (multi-site study)

Principal Investigator Information:
Name: Susanne M. Arnold, MD
Address: 800 Rose Street, cc445; Lexington, KY 40536
Phone No: 859-323-8043
Fax No: 859-257-7715
Email Address: smarno0@uky.edu

Co-Investigators: Listed below

Statistician: John J. Crowley, PhD

Data Manager: Vicki Green

Key Investigators and Study Personnel Contact Sheet

<table>
<tr><td colspan="2">Sponsor/ Contract Research Organization - CRAB Clinical Trials Consortium
Cancer Research And Biostatistics Clinical Trials Consortium (CRAB CTC)
1730 Minor Avenue, Suite 1900, Seattle, WA 98101-1468

KEY INVESTIGATOR AND STUDY PERSONNEL CONTACT SHEET (UPDATED 1 OCTOBER 2014)

Phase 1b/II Trial of Carfilzomib with Irinotecan in Small Cell Lung Cancer Subjects Who Have Progressed on Prior Platinum-based Chemotherapy

SPONSOR-INVESTIGATOR:
Susanne M. Arnold, MD</td></tr>
<tr><td>BIOSTATISTICIANS

John Crowley, PhD
Ph: (206) 839-1719
Fax: (206) 652-4612
Email: johnc@crab.org</td><td>

Kari Chansky
Ph: (206) 839-1783
Fax: (206) 652-4612
Email: karic@crab.org</td></tr>
<tr><td></td><td></td></tr>
<tr><td>CRAB CTC OPERATIONS OFFICE:

Amy Stoll-D'Astice
Program Manager, CRAB CTC 11-0001 Operations
1730 Minor Ave., Suite 1900
Seattle, WA 98101-1468
Ph: (602) 570-2383
Email: amys@crab.org

CRAB CTC CONTRACTING:

Doug Mounce
Grants and Contract Manager
Ph: (206) 839-1787
Email: dougm@crab.org

CRAB CTC REGULATORY AFFAIRS

Grace Powell
Regulatory/Quality Assurance Manager
Ph: (206) 839-1790
Fax: (206) 342-1688
Email: gracep@crab.org</td><td>CRAB DATA MANAGEMENT :

Vicki Green, Data Coordinator
(Subject Registration and Data Submission)
Ph: (206) 342-1692
Fax: (206) 342-1688
Email: webhelpCRS@crab.org

CRAB SITE MONITORING

Dona Marrah
Clinical Monitor Manager
Ph: (206) 652-1341
Email: donam@crab.org

REPORTING SERIOUS ADVERSE EVENTS

See protocol Section 9.5
Report to CRAB Operations Office
Ph: (206) 342-1692 within 24 hours of the SAE</td></tr>
</table>

ADDITIONAL KEY INVESTGATOR AND STUDY CONTACTS

OTHER CONTACT INFORMATION:	
SPONSOR – INVESTIGATOR AND MEDICAL MONITOR *(also responsible for treatment and dose modification questions)* Susanne M. Arnold, MD University of Kentucky Markey Cancer Center 800 Rose Street, cc445; Lexington, KY 40536 Ph : (859) 323-8043 Fax: 859-257-7715 Email: smarno0@uky.edu	DRUG DISTRIBUTION *Carfilzomib:* Provided by Amgen. Email: DrugSupport@Amgen.com CORRELATIVE SAMPLE COLLECTION KITS Dr. Mark Leggas Department of Pharmaceutical Sciences College of Pharmacy University of Kentucky 789 South Limestone, Room 323 Lexington, KY 40536-0596 E-mail: mark.leggas @uky.edu (859) 257-2633 Office (859) 257-7564 Fax Email: mark.leggas@uky.edu
CRAB CTC Co-Investigators and Participating Sites: Susanne M. Arnold, MD University of Kentucky Markey Cancer Center 800 Rose Street Lexington, KY 40536	Glen J. Weiss, MD – Phase I only Western Regional Medical Center, Inc 14200 W. Celebrate Life Way Goodyear, AZ 85338
Michael A. Thompson, MD, PhD Aurora Health Care, Aurora Cancer Care 2801 W. Kinnickinnie River Parkway, Suite 930 Milwaukee, WI 53215	John T. Hamm, MD Norton Cancer Institute, Norton Healthcare Pavilion 315 E. Broadway Louisville, Ky 40202
Rachel Sanborn, MD Providence Portland Medical Center 4805 NE Glisan Street Portland, OR 97213	Joseph Rosales, MD Virginia Mason Cancer Institute 1100 9th Ave, Seattle, WA 98101
Maria Baggstrom, MD Washington University School of Medicine 4990 Childrens Place St, Louis, MO 63110	Maurice Willis, MD University of Texas Medical Branch 301 University Boulevard Galveston, TX 77555

Investigator Signature Sheet

I have read the attached protocol, CRAB CTC Study 11-001 and agree that it contains all the necessary details for performing the study.

I will provide copies of the amended protocol and of the preclinical and clinical information on the test article, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test article and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. In the event that the CRAB CTC issues any protocol modifications and/or any informed consent form (ICF) modifications, I will not implement any such modifications until approval has been granted by the IRB/IEC.

The investigational drug will not be transferred to any third party, and upon completion of the study at my site, any unused supplies of investigational agent will be returned in accordance with the protocol.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) [current International Conference of Harmonization (ICH) guidelines], and the Declaration of Helsinki including all amendments, and the US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

_____ _____

Investigator's Signature Date

_____

Investigator’s Printed Name

_____

Investigational Site Name

PROTOCOL SYNOPSIS

TITLE: **CTC 11-001: Phase 1b/II Trial of Carfilzomib with Irinotecan in Irinotecan-Sensitive Malignancies (Phase Ib) and Small Cell Lung Cancer Subjects (Phase II) Who Have Progressed on Prior Platinum-based Chemotherapy**
(Amgen IST Reference Number: CAR-IST-553)

OBJECTIVES:

Primary Objectives:

Phase 1b*: Determine maximum tolerated dose (MTD) of Carfilzomib (Day 1, 2, 8, 9, 15, and 16) in combination with Irinotecan (Days 1, 8 and 15) in subjects with relapsed small and non-small cell lung cancer or other irinotecan-sensitive cancers.*

Phase II: Assess 6 month survival of relapsed small cell lung cancer in subjects treated with this combination therapy.

Secondary Objectives:

Phase 1b: *Response rate, safety/tolerability, biomarker endpoints (see below). Biomarker testing to occur for all subjects in Phase 1b.*

Phase II: response rate, safety/tolerability, progression-free survival and biomarker endpoints:

- Chymotrypsin-like activity in PBMC (LMP7 and b5 activity) as a measure of carfilzomib's effect on proteasome activity in 15 subject in each stratum.
- Topoisomerase-I protein expression as a measure of carfilzomib's capacity to prevent irinotecan induced topoisomerase-I degradation in 15 subjects in each stratum.
- Gamma-H2AX protein expression in PBMC, as a measure of irinotecan-mediated DNA damage and as a measure of carfilzomib's capacity to prevent irinotecan induced topoisomerase-I degradation in 15 subjects in each stratum.

- Topoisomerase-I expression by immunohistochemistry will be determined in banked tissue, if available, in all subjects, as a biomarker of response.

STUDY DESIGN:

Study Design:

1. Phase 1b: standard 3+3 design using five dose levels of Carfilzomib.

2. Phase II: A single arm trial of this therapy (using the MTD as determined in Phase Ib) in 88 small cell lung cancer subjects who have progressed on prior platinum based therapy. Stratified by platinum sensitive vs. platinum refractory disease (see Section 3.1).

STUDY POPULATION:

Phase Ib: *Advanced small or non-small cell lung cancer, or other cancer in which irinotecan therapy has been shown to be effective and for whom no curative therapy exists.*

Phase II: Extensive stage small cell lung cancer with progression or recurrence after exactly one platinum-containing regimen

SECONDARY ENDPOINTS:

Secondary Objectives:

Phase 1b: *Response rate, safety/tolerability, biomarker endpoints (see below). Biomarker testing to occur for all subjects in Phase 1b.*

Phase II: response rate, safety/tolerability, progression-free survival and biomarker endpoints:

- Chymotrypsin-like activity in PBMC (LMP7 and b5 activity) as a measure of carfilzomib's effect on proteasome activity in 15 subjects in each stratum.
- Topoisomerase-I protein expression in PBMC as a measure of carfilzomib's capacity to prevent irinotecan induced topoisomerase-I degradation in 15 subjects in each stratum.
- Gamma-H2AX protein expression in PBMC, as a measure of irinotecan-mediated DNA damage and as a measure of carfilzomib's capacity to prevent irinotecan induced topoisomerase-I degradation in 15 subjects in each stratum.

- Topoisomerase-I expression by immunohistochemistry will be determined in banked tissue, if available, in all subjects, as a biomarker of response.

SCHEMA

Phase I portion

Subject Registration

↓

Up to 6 cycles of Irinotecan + Carfilzomib at assigned dose level (see Section 6.2.1)*

**at investigator discretion and in absence of criteria for removal from treatment (see section 8.0)*

↓

Post treatment follow-up: 30 days or until drug-related toxicities resolve to grade 1 or less, whichever occurs last

Temporary closure after all subjects accrued to finalize determination of Phase II dose

↓

Phase II portion

Subject Registration and stratification

↓

Up to 6 cycles* of Irinotecan + Carfilzomib at assigned dose level (see Section 6.2.4)

*at investigator discretion and in absence of criteria for removal from treatment (see section 8.0)

↓

Post treatment follow-up: 2 years after initial registration, or until death, or until study closure whichever occurs first

A subject may be enrolled to either the Phase I portion or the Phase II portion, but not both.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degrees Centigrade
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (also PTT)
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
bid	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
Cmax	maximum or peak concentration of a drug after its administration
CR	complete response
CrCl	creatinine clearance
CRF	case report form(s)
CRO	clinical research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	Deciliter
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep venous thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator Brochure

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	kilogram(s)
LDH	lactate dehydrogenase
mg	milligram(s)
min	minute(s)
mIU	Milli International Units
mL	milliliter(s)
MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
MR	minimal response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetics
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QDx5	daily dosing for five days
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
RP2D	recommended phase II dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose in 10% of animals
TLS	tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis

VGPR	very good partial response
WBC	white blood count

1 INTRODUCTION

1.1 DISEASE SPECIFIC BACKGROUND

Small cell lung cancer accounts for approximately 15% of all lung cancer diagnoses in the United States (US)[1], with 60-80% response rates to platinum-based chemotherapy in extensive disease. Despite its sensitivity to chemotherapy, small cell lung cancer is characterized by extensive disease dissemination at presentation and the overall prognosis remains poor, with a 2-year overall survival of less than 5% and a median survival of approximately 9-11 months[2]. This poor prognosis is attributable, in part, to the lack of effective salvage regimens for this disease. Currently, the only FDA-approved second-line therapies are oral and parenteral topotecan, although irinotecan is also commonly used in primary and relapsed disease. Novel combination therapies are desperately needed in this disease in order to improve survival.

1.2 PROTEASOME BACKGROUND

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

1.3 CARFILZOMIB BACKGROUND

Carfilzomib (PX-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib[3, 4]

1.3.1 CARFILZOMIB TOXICOLOGY STUDIES

In the initial Good Laboratory Practice (GLP)-compliant toxicity studies done by the drug maker, Onyx, carfilzomib was administered to rats and monkeys as two complete two-week cycles of QDx5 with nine days rest[5]. Administration to rats at 12 mg/m^2, the severely toxic dose in 10% of animals (STD_{10}), caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with

carfilzomib compared with bortezomib. Daily administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The dose-limiting toxicities (DLTs) of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In 6-month rat and 9-month chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the active anti-tumor regimen being used in ongoing Phase II studies in myeloma and solid tumors[3]. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity, including neuropathology, observed, even at high doses. This is in stark contrast to that observed with bortezomib[6, 7]. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to relate to Cmax effects. Of note, neutropenia was not observed; rather, transient neutrophilia was seen following acute dosing. Renal, cardiovascular and gastrointestinal toxicities were similar to those observed with bortezomib. Finally, cyclical thrombocytopenia, likely due to inhibition of platelet budding from megakaryocytes, was similar to that seen with bortezomib. Proteasome inhibition in the blood in excess of 90% was achievable at well-tolerated doses, which contrasts with the ~70% proteasome inhibition achievable with bortezomib at its maximum tolerated dose (MTD). In summary, these animal toxicity studies support the tolerability of carfilzomib in clinical studies, even on intensive dosing schedules and at doses achieving proteasome inhibition in excess of what can be achieve with bortezomib at its MTD on a less intensive schedule.

1.3.2 CARFILZOMIB PRECLINICAL ANTITUMOR ACTIVITY

Based upon the results of *in vitro* and *in vivo* studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti-tumor activity relative to bortezomib. Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture[3, 8]. Incubation of hematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines[3, 8].

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level. Bortezomib at its MTD has no activity in this xenograft model using the standard Day 1, Day 4 schedule[3].

1.3.3 PHASE 1 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

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

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

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

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

1.3.4 PHASE 2 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY

Two Phase 2 clinical studies are ongoing with carfilzomib in MM subjects, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM. In both studies, subjects were dosed with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional subjects with relapsed or refractory MM treated in ongoing Phase II studies. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increases in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of treatment-emergent peripheral neuropathy, 2.2% Grade 3/4, was observed in PX-171-003-A0 despite the fact that 78% of subjects had Grade 1/2 neuropathy upon study entry[10].

The response rate in PX-171-003-A0 was 18% PR, 7% MR and 41% SD in these subjects that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time

to progression on the PX-171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months) [10].

A "stepped up" dosing schedule, referred to as 20/27 mg/m^2, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of carfilzomib. Subjects receive 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. The study completed enrollment of 266 subjects by the end of 2009 and may form the basis for an accelerated approval NDA filing by the end of 2010. To date, this dosing schedule has been well tolerated[9]. An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 subjects to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 2.2% in A1 (from 15% in A0), most likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 15% Grade 1/2 and one (0.7%) Grade 3/4 event reported to date on PX-171-003-A1[10]. In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date.[10]

In PX-171-004, a first cohort of subjects received 20 mg/m2. The subset of subjects (N=54) that had not seen bortezomib had an ORR of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated subjects (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR) [11, 12]. The median TTP was 7.6 and 5.3 months in these two groups, respectively. Thus, carfilzomib can induce very high levels of response in subjects who have not previously been treated with bortezomib and, even in bortezomib-treated subjects, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of subjects with progressive MM entering the study. Subjects on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

The protocol was amended to allow subjects to increase to 27 mg/m2 in Cycle 2 or later based on tolerability, similar to that used in PX-171-003 – A1.

Further information about the Phase 2 studies is presented in the Investigator's Brochure.

1.3.5 UPDATED EXPERIENCE WITH CARFILZOMIB

As of 12 January 2015, approximately 2949 individual subjects have been treated with carfilzomib as participants of Phase 1, 2, and 3 Onyx-sponsored clinical studies. Of these subjects, 137 subjects with solid tumors have been treated with carfilzomib in completed Onyx-sponsored clinical studies. As of 12 Janaury 2015, Onyx Pharmaceutical Co, Ltd has enrolled 65 subjects in 3 studies being conducted in Japan. The clinical development of carfilzomib initially focused on patients with relapsed and refractory multiple myeloma, assessing carfilzomib as monotherapy in these patients with few therapeutic options. Subsequently, carfilzomib is being evaluated as a component of combination therapy for treatment in earlier lines of therapy for patients with multiple myeloma, including newly diagnosed multiple myeloma patients.

Carfilzomib for Injection was approved in 2012 in the United States (US) (brand name Kyprolis) under the US Food and Drug Administration's (FDA) accelerated approval program for the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Carfilzomib received approval in Israel (under the State of Israel Ministry of Health), Argentina (under the National Administration of Medicaments, Food and Medical Technology [ANMAT]), and Mexico (under the Federal Commission for the Protection against Sanitary Risks [COFEPRIS]) in 2014. These approvals, including accelerated approval in the US, were based on the results of the were based on the results of the Phase 2 PX-171-003 – Part 2 (A1) study, where an overall response rate (ORR) of 22.9%, duration of response (DOR) of 7.8 months, progression-free survival (PFS) of 3.7 months, and overall survival (OS) of 15.4 months were observed. The approved carfilzomib dose is 20 mg/m2 during Cycle 1, and if tolerated, the dose is increased to 27 mg/m2 during Cycle 2, given twice weekly for 3 of every 4 weeks, with infusion durations of 2 to 10 minutes.

The clinical development of carfilzomib initially focused on patients with relapsed and refractory multiple myeloma, assessing carfilzomib as monotherapy in these patients with little or no therapeutic options. Subsequently, carfilzomib is being evaluated as a component of combination therapy for treatment in earlier lines of therapy for patients with multiple myeloma, including newly diagnosed multiple myeloma patients. The clinical program has also expaneded to include solid tumors (e.g. small cell lung cancer [SCLC] and pediatric lymphoblastic leukemia (ALL).

Results from Phase 3 Trials

Five phase 3 studies have been completed or are still ongoing. A thorough and comprehensive assessment of carfilzomib safety was conducted by Onyx with safety information available from a large clinical development program. Important adverse drug reactions (ADRs) identified from the pivotal phase 3 studies PX-171-009 (ASPIRE) and PX-171-011 (FOCUS) as well as across the integrated safety database have been well-characterized as documented in the Investigator's Drug Brochure for carfilzomib. There was no evidence of cumulative or new-onset toxicity with prolonged exposure to carfilzomib. Overall, the safety and efficacy data from the clinical program support continued development of carfilzomib in subjects with multiple myeloma and solid tumors and expansion to the pediatric acute lymphoblastic leukemia (ALL) population. As of January 2015, study 2011-003 (ENDEAVOR), Study 2012-005 (CLARION), and study CFZ014 (A.R.R.O.W.) remain ongoing.

The clinical development program for carfilzomib has provided the ability to assess safety across patient populations with a broad spectrum of baseline characteristics relevant to the indicated patients with multiple myeloma, including patients with the following characteristics in Phase 2 and 3 multiple myeloma studies: (1) advanced disease; Onyx Pharmaceuticals, Inc. Investigator's Brochure Carfilzomib for Injection (2) refractory and heavily pretreated; (3) newly diagnosed disease; (4) multiple comorbidities (e.g., renal insufficiency and renal failure, anemia, thrombocytopenia, or cardiovascular disease); (5) pre-existing peripheral neuropathy; (6) prior bortezomib therapy (including a substantial number of patients with multiple myeloma refractory to bortezomib or who cannot tolerate bortezomib); (7) various ages (age range of 21 to 91 years); (8) similar proportion by sex to the general population; and (9) a substantial proportion of patients of African American ethnicity.

The safety profile remains consistent with the mechanism of action of proteasome inhibitors, but with predictably lower rates of peripheral neuropathy, based on the epoxyketone structure that improves proteasome inhibition selectivity. Extensive analysis in renally impaired patients has indicated that no dose adjustment for baseline renal insufficiency is required. The independent efficacy of carfilzomib monotherapy also obviates the need for high doses of steroids, making the carfilzomib regimen steroid-sparing and an important treatment option for patients who need to avoid the toxicity associated with therapeutic doses of corticosteroids. Analysis of the substantial proportion of patients who continued on carfilzomib therapy for extended durations indicated that the drug was well tolerated, without cumulative or late-effect toxicity.

1.4 DOSE RATIONALE

Data supports that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m^2. Maximum proteasome inhibition was seen at doses 11 mg/m^2 and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data i shows rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half-life of < 60 minutes at the 20 mg/m^2 dose. Large, single arm studies of the 27 mg/m^2 dose are ongoing and suggest that this dose is very well tolerated with subjects being treated for >10 cycles without cumulative toxicities.

By the end of 2009, 269 subjects with relapsed and refractory multiple myeloma have been enrolled in the PX-171-003-A1 study. The goal of dose escalating to 27 mg/m^2 beginning with Cycle 2 is to improve ORR, DOR, and TTP.

Safety and efficacy results are available for 2 completed phase 3 studies, PX-171-009 (ASPIRE) and Study PX-171-011 (FOCUS). FOCUS was an open-label phase 3 study of carfilzomib versus a combination of corticosteroids and cyclophosphamide as supportive care. Carfilzomib as a single agent was well tolerated at a dose 20 mg/m^2 and 27 mg/m^2 in cycles 10 and higher. The study did not show superiority of carfilzomib over supportive care in overall survival; however, carfilzomib as monotherapy did show a higher overall response rate as compared to that of supportive care. Results from phase 3 study ASPIRE comparing carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma showed that patients in the CRd arm showed significantly longer rates of progression free survival. Stepped up dosing of 20/27 mg/m^2 during cycles 1-12 and 27 mg/m^2 was well tolerated with improvement in overall quality of life reported. Three other phase 3 studies 2011-003 (ENDEAVOR), 2015-005 (CLARION), and CFZ014 (A.R.R.0.W.) remain ongoing with very good responses reported.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 minute infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of carfilzomib *above the MTD* at a dose of 48 mg/m^2 include evidence of prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m^2 when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m^2) as a 30 minute continuous infusion was well tolerated, with no changes in BUN and

creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of carfilzomib for 30 minute was gastrointestinal bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced C_{max} of carfilzomib vs that with bolus dosing. Inhibition of the pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD in the multiple myeloma (MM) setting when administered as a 30 minute infusion has been determined to be 20/56 mg/m2. Twenty-seven mg/m2 of carfilzomib (bolus administration over 2-10 minutes) is well tolerated in MM subjects overall and can be tolerated for >12 cycles in late stage MM subjects with substantial comorbidities.

A phase 1b/2 dose escalation study (PX-171-007) of single agent carfilzomib administered was completed and as of 19 July 2011, 65 subjects with solid tumors received treatment in the l Phase 2 portion of the study at the 20/36 mg/m^2 MTD established in the phase 1b portion (bolus administration over 2-10'). A review of the tolerability of 36 mg/m^2 carfilzomib in these subjects indicates that this regimen was very well tolerated with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m^2 carfilzomib experience with bolus dosing (see IB for details). Three subjects completed > 12 cycles of therapy at 36 mg/m^2 with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability of carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

In the PX-171-007 trial, more recently subjects have been treated with carfilzomib given as a 30-minute infusion in order to potentially minimize Cmax-related infusion events. The protocol was amended and doses of 20/36 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m^2 for all subsequent doses), 20/45, 20/56 mg/m2 and so forth are being investigated. Doses of 20/56 mg/m2 are currently being given in two separate cohorts of subjects with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose level (20/56 mg/m^2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m^2, dexamethasone was increased from 4mg/dose to 8mg with the 56mg/m^2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven subjects have received 20/56mg/m^2 and are tolerating it. Subjects with advanced, refractory MM being treated at 36mg/m^2 and 45mg/m^2 have shown very good tolerability (>6 months in some cases) with

documented minimal and partial responses in these heavily pretreated subjects. These data indicate that carfilzomib 30-minute infusion can be given at very high levels, with >95% inhibition of blood proteasome levels achievable and with (at least) acute tolerability. All protocols using ≥ 36mg/m^2 carfilzomib are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of carfilzomib in subjects with relapsed and refractory multiple myeloma was reported in abstract form at the 2009 American Society of Hematology meeting which demonstrated that carfilzomib can be safely administered to subjects with substantial renal impairment (CrCl < 30, including subjects on dialysis) without dose adjustment.[14] These data indicate that carfilzomib does not exacerbate underlying renal dysfunction, and confirm the "pre-renal" etiology of the BUN/creatinine elevations observed with IV bolus carfilzomib.

In the advanced and refractory multiple myeloma population, the Phase 3 Study PX-171-011 (FOCUS) did not meet the primary objective of demonstrating superiority of carfilzomib monotherapy over the active doublet therapy in the control arm (corticosteroids and optional cyclophosphamide). The median OS with carfilzomib monotherapy was 10.2 months versus 10.0 months for active control. The PFS was similar in both study arms of PX-171-011 (carfilzomib monotherapy 3.7 months versus active control arm 3.3 months, HR = 1.091 [95% CI: 0.843–1.410]).

The efficacy observed in the monotherapy program supported the development of carfilzomib in combination with lenalidomide and low-dose dexamethasone, based on the hypothesis that this combination may result in the ability to deliver optimized proteasome inhibition leading to improved efficacy. Results from the randomized, pivotal, Phase 3 Study PX-171-009 (ASPIRE) demonstrated that carfilzomib in combination with lenalidomide (Revlimid) and low-dose dexamethasone (CRd) in subjects with relapsed multiple myeloma has unprecedented efficacy with an 8.7-month improvement in median PFS when compared with (Revlimid) lenalidomide with low-dose dexamethasone (Rd) (HR = 0.69), and a median PFS of 26.3 months with CRd treatment. Data from Study PX-171-009 (ASPIRE) was submitted to regulatory authorities in the first quarter of 2015 for marketing authorization (currently in review as of January 2015) for the use of carfilzomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy.

1.5 STUDY RATIONALE

Proteasome inhibition affects the levels of numerous cell cycle control proteins, apoptosis, cell adhesion, angiogenesis, and chemoresistance proteins.[13,14] Carfilzomib and other proteasome inhibitors interrupt cellular pathways integral to the survival of small cell lung cancer,[15-17] namely the dysregulated apoptotic pathway involving activated nuclear factor-kB (NF-kB).[18] NF-kB activates the transcription of anti-apoptotic and proliferation genes, mediating tumor cell survival in response to cytotoxic stress and resulting in chemoresistance, a common problem in small cell lung cancer. Carfilzomib prevents proteasomal degradation of IkB, the inhibitor of NF-kB, and also modulates levels of the anti-apoptotic gene Bcl-2 and the tumor suppressor p53. Overexpression of Bcl-2, a key mediator of resistance to apoptosis following chemotherapy, is an important problem in SCLC;[17] the vast majority of SCLC cases have bcl-2 overexpression, and low levels of bcl-2 and b1-integrin are associated with improved survival in SCLC[19]. Topoisomerase-1 is thought to cause apoptosis via mechanisms other than NF-kB, adding to the potential synergy of these compounds. In addition, topoisomerase-1 is overexpressed in the majority of subjects with SCLC [18] and decreased degradation of this enzyme is expected to lead to further enhancement of this mechanism of apoptosis.

The hypothesis that proteasome inhibition will augment the effect of systemic chemotherapy in solid tumors is not new. In fact, earlier studies using the compound Bortezomib (VELCADE®, Millennium) which only reversibly inhibits the 26S proteasome, with Carboplatin and Gemcitabine showed promising response rates and median survival of 11 months in non-small cell lung cancer (NSCLC)[20]. Other studies have not shown improvement in response rate or survival with the combination of proteasome inhibitor and Docetaxel or Pemetrexed,[21] despite substantial preclinical information which would have predicted benefit[18, 22-24]. The use of Carfilzomib in combination with a topoisomerase inhibitor is expected to differ from previous efforts with other proteasome inhibitors because of its sustained proteasome inhibition and its potential synergy with this class of drugs.

<u>Camptothecins</u>

Camptothecins inhibit topoisomerase I. As a class, camptothecins have shown efficacy in small cell lung cancer in a variety of settings. Several phase II studies demonstrated clinical benefit including the trials of Perez-Soler et al., who showed clinical benefit in 10 out of 32 subjects with extensive stage SCLC in the second line with parenteral topotecan, 1.25 mg/m^2 daily on Days 1-5 every 21 days[2] and Ardizzoni et al. who used a higher dose (1.5 mg/m^2) but the same schedule, in

101 subjects with relapsed extensive stage disease with median overall survival (6.9 months for sensitive subjects and 4.7 months for refractory subjects (P=0.002).[25] The pivotal phase III study which led to FDA approval of topotecan in relapsed small cell lung cancer was by Von Pawel et al,[26] and included *2*11 subjects with sensitive (> 60 days since prior therapy) relapse and randomized them to either topotecan (107 subjects) daily for 5 days or to cyclophosphamide, doxorubicin, and vincristine (CAV), each given every 21 days. Topotecan showed no significant improvement in the median time to progression (13.3 weeks vs.12.3 weeks, p=0.552) or median survival (25 weeks vs. 24.7 weeks, p=0.795), however, subjects treated with topotecan had improvement in cancer-related symptoms (dyspnea, hoarseness, anorexia, and fatigue) as well as hematologic toxicity.

Another camptothecin, irinotecan, has established activity in small cell lung cancer, as well as non-small cell lung cancer, colorectal cancer and ovarian cancer. As a single agent, Negoro and colleagues treated 35 subjects with 100 mg/m^2 with a response rate of 50% in untreated subjects and 33% in previously treated subjects.[27] Additional phase II studies of weekly irinotecan by Masuda, et al[28], demonstrated an objective response rate of 47% and a median survival of 26 weeks (similar to other camptothecins). Le Chevalier and colleagues[29] used an every 3-week schedule of irinotecan, 350 mg/m^2, given to 32 chemotherapy-naive SCLC subjects and showed an objective response rate of 16% and a median survival of 4.5 months. Thus, the median survival of camptothecins in the second –line setting in SCLC ranges from 24 to 35 weeks, with those subjects in sensitive relapse having a median survival of 4 to 8 weeks longer than those with refractory relapse. In addition, irinotecan has also been demonstrated to be effective when combined with cisplatin in the front line setting, in extensive stage small cell lung cancer. A Japanese study by Noda, and colleagues demonstrated superiority of this combination when compared to cisplatin and etoposide.[30] While, these results were not replicated in a Southwest Oncology Group (SWOG) study, the combination is considered an alternative to cisplatin and etoposide in this disease.[31] The similar efficacy and favorable toxicity of weekly irinotecan delivery justifies its use in the current proposal.

Rationale for Carfilzomib sequencing and combination with topoisomerase inhibitors

Sequencing information for Carfilzomib and other chemotherapeutic drugs is limited. Extrapolating from data using bortezomib, it was shown by several groups that bortezomib sensitized NSCLC and pancreatic cancer cells to gemcitabine, as well as inducing apoptosis in vitro and in vivo.[18],[32]

Sequence dependent enhanced activity was observed by Mortenson and colleagues when bortezomib was given after gemcitabine/carboplatin in NSCLC cell line studies.[23]

Inactivation of proteasome function allows for increased apoptosis and potentially enhanced antitumor effects in response to treatment with many chemotherapeutic agents. Combination treatment of Carfilzomib with a Topoisomerase-I (Topo-I) inhibitor (e.g., a camptothecin analogue) is anticipated to be at least additive and potentially synergistic as the apoptosis induced by camptothecins in cancer cells may not involve NF-κB. In addition, proteasome inhibition may interfere with Topo-I degradation, a necessary step in DNA damage repair after exposure to Topo-I poisons. Thus, we hypothesize that Carfilzomib will enhance the anti-tumor efficacy of Irinotecan in relapsed small cell lung cancer.

Rationale for MTD

The phase Ib component of the current trial has completed enrollment. A total of 22 patients were screened with 16 being enrolled. No DLTs were observed at the 20/27 mg/m2 dose level. Two patients experienced DLTs at the 20/45 mg/m2 dose. One event was grade 4 thrombocytopenia lasting ≥ 7days and the other was ≥ grade 3 diarrhea. Cohort 2 (20/36 mg/m2) included 6 patients, with one patient experiencing a DLT. The MTD was established at the dose level investigated in Cohort 2. The recommended phase II dose has been determined to be: Carfilzomib 20/36 mg/m2 (stepped up dosing) with Irinotecan 125 mg/m2. The phase II component will investigate this combination in patients with relapsed small cell lung cancer.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

Phase 1b: Determine maximum tolerated dose (MTD) of Carfilzomib (Day 1, 2, 8, 9, 15, and 16) in combination with Irinotecan (Days 1, 8 and 15) in subjects with relapsed small and non-small cell lung cancer or other irinotecan-sensitive cancers.

Phase II: Assess 6 month survival of relapsed small cell lung cancer in subjects treated with this combination therapy.

2.2 SECONDARY OBJECTIVES:

Phase 1b study: Response rate, safety/tolerability, and biomarker endpoints:

- Carfilzomib proteasome chymotrypsin-like activity in PBMC (LMP7 and b5 activity): relative to the start of irinotecan infusion: pre-dose, 90 min, 2 hr, 5.5 hr on Day 1 of Cycle 1, and pre-carfilzomib infusion on Day 2 of Cycle 1, in all subjects.
- Irinotecan-mediated DNA damage by gamma-H2AX protein expression in PBMC obtained from all subjects relative to the start of irinotecan infusion: pre-dose, 90 min, 2 hr, 5.5 hr on Day 1 of Cycle 1, and pre-carfilzomib infusion on Day 2 of Cycle 1.
- Topoisomerase-I protein expression in PBMC.
- When available, banked tumor tissue for immunohistochemical expression of Topoisomerase-I in all subjects.

Phase II study: response rate, safety/tolerability, progression-free survival and biomarker endpoints:

- Carfilzomib proteasome chymotrypsin-like activity in PBMC (LMP7 and b5 activity): relative to the start of irinotecan infusion: pre-dose, 90 min, 2 hr, 5.5 hr on Day 1 of Cycle 1, and pre-carfilzomib infusion on Day 2 of Cycle 1, in **15 subjects in each stratum** of Phase II.
- Irinotecan-mediated DNA damage by gamma-H2AX protein expression in PBMC obtained from all subjects relative to the start of irinotecan infusion: pre-dose, 90 min, 2 hr, 5.5 hr on Day 1 of Cycle 1, and pre-carfilzomib infusion on Day 2 of Cycle 1 in **15 subjects in each stratum**.

- Topoisomerase-I protein expression in PBMC in **15 subjects in each stratum**
- When available, banked tumor tissue for immunohistochemical expression of Topoisomerase-I in all subjects.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

1. Phase 1b: standard 3+3 design using five dose levels of Carfilzomib. Two dose de-escalations are built into the protocol for safety.

Table 2. Dose escalation schema

3+3 design	***Doses***	
	Carfilzomib*	***Irinotecan***
Cohort -2	*20 mg/m^2*	*75 mg/m^2*
Cohort -1	*20 mg/m^2*	*100 mg/m^2*
Cohort 1	***20/27 mg/m^2***	***125 mg/m^2***
Cohort 2	***20/36 mg/m^2***	***125 mg/m^2***
Cohort 3	***20/45 mg/m^2***	***125 mg/m^2***
Cohort 4	***20/56 mg/m^2***	***125 mg/m^2***
Cohort 5	***20/70 mg/m^2***	***125 mg/m^2***

Cycle 1 Day 1 & Day 2 doses are 20 mg/m2. All subsequent days as specified, i.e. 20/27 mg/m2 means Cycle 1 Day 1 & Day 2 doses are 20 mg/m2 and all other days are 27mg/m2.

Phase II: Stratified, single arm trial using MTD of Carfilzomib 20/36 mg/m2 with Irinotecan 125 mg/m2 as established from Phase Ib, in up to 88 small cell lung cancer subjects who have relapsed on a prior platinum regimen.

Stratification for phase II component:. Patients will be accrued in two separate strata; each stratum has its own accrual target and may be closed or open to accrual independently:

a. Platinum sensitive disease: initial response to platinum-based chemotherapy with progression > 90 days after last treatment.
b. Platinum refractory disease: No response to platinum-based chemotherapy or progression within 90 days of completing platinum-based therapy. Subjects that progressed during or within one month of completion of platinum-based chemotherapy will be excluded.

3.2 NUMBER OF CENTERS

A minimum of 8 investigative study sites will participate on this trial.

3.3 ESTIMATED STUDY DURATION AND RECRUITMENT

Study duration/timelines: September 2013 – December 2018.

Recruitment: phase 1b: 6 to 9 month recruitment; phase II: 18 to 24 month recruitment.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study. **Criteria to the Phase II study are below, criteria specific only to the Phase Ib portion are grayed, .**

1. Subjects must have histologically or cytologically-confirmed diagnosis of progressive or recurrent malignancy as follows:
    a. *Phase Ib: advanced small or non-small cell lung cancer, or other cancer in which irinotecan therapy has been shown to be effective and for whom no curative therapy exists. Subjects who progressed during or within one month of completing platinum-based chemotherapy will be excluded. Subjects who received primary curative chemoradiation therapy, but who recur within the primary tumor site, previously radiated field or with distant metastases are also allowed to participate. Subjects who have clinical evidence of recurrent cancer do not require a confirmatory biopsy to be eligible for this trial. No limit will be placed on prior regimens received, but prior irinotecan is not allowed.*
    b. Phase II: extensive stage small cell lung cancer with tumor progression or recurrence after treatment with 1 platinum-containing regimen for recurrent or metastatic disease. Subjects who progress during or within one month of completing platinum-based chemotherapy will be excluded. Subjects who received primary curative chemoradiation therapy for limited disease, but who recur within the primary tumor site, previously radiated field or with distant metastases are allowed to participate. Subjects who have clinical evidence of recurrent small cell lung cancer do not require a confirmatory biopsy to be eligible for this trial. Prior irinotecan is *not* allowed.
2. Subjects must have measurable disease per RECIST criteria 1.1 (see Appendix B-section 1) performed within 28 days prior to enrollment to treatment. Eligible subjects must be registered within 3 working days prior to initiation of protocol chemotherapy. All other required tests to assess non-measurable disease must be performed within 42 days prior to enrollment to treatment.
3. Subjects with known brain metastases are eligible only if he/she has been treated for brain metastasis, are asymptomatic after treatment, have a stable CT or MRI of the brain within 28 days of enrollment to treatment and are not receiving corticosteroid therapy to control symptoms from brain metastasis. Only a non-enzyme inducing anticonvulsant (e.g., Keppra)

will be permitted for those subjects requiring anticonvulsants. (Topical and/or inhaled steroids are allowed.)

4. Subjects may have received previous radiation therapy, but it must have been completed at least 21 days prior to enrollment to treatment and the subject should have recovered from all associated toxicities. Measurable disease must be present outside the previous radiation field or a new lesion inside the radiation port must be present. There must be no anticipated need for concurrent radiation therapy during protocol treatment.
5. Subjects may have received prior surgery provided that at least 28 days have elapsed since major surgery (thoracic or other major surgeries) and the subject has recovered from all associated toxicities. Subjects must have disease outside of the previous surgical resection area or a new lesion must be present.
6. Subjects may have received prior chemotherapy provided that at least 14 days have elapsed from last dose of chemotherapy and the subject has recovered from all associated toxicities.
7. Subjects must have a serum creatinine ≤ the institutional upper limit of normal OR a creatinine clearance ≥ 60 cc/min, measured or calculated (Cockcroft-Gault formula), obtained within 14 days prior to enrollment to treatment. Eligible subjects must be registered within 3 working days prior to initiation of protocol chemotherapy.
8. Subjects must have adequate hepatic function as documented by a bilirubin ≤ 2 x the institutional upper limit of normal, an alkaline phosphatase ≤ 2 x the institutional upper limit of normal, and an SGOT ≤ 2 x the institutional upper limit of normal all obtained within 14 days prior to enrollment to treatment.
9. Subjects must have an ANC ≥ 1,500/µl and a platelet count ≥ 100,000/µl obtained within 14 days prior to enrollment to treatment.
10. Subjects must be 18 years of age or older.
11. Subjects must have a Zubrod Performance Status as follows (see Appendix B – section 4):
    a. *Phase Ib:* *0 or 1*
    b. Phase II: 0, 1 or 2
12. Subjects must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
13. Male subjects must agree to practice contraception.

14. All subjects must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

4.2 EXCLUSION CRITERIA

1. No prior irinotecan or carfilzomib
2. Must not have evidence of leptomeningeal metastases.
3. Must be no anticipated need for concurrent radiation therapy during protocol treatment.
4. Subjects that progressed during or within one month of completion of first-line platinum-based chemotherapy will be excluded.
5. Subjects must not be pregnant or lactating females.
6. Must have had no major surgery within 28 days prior to enrollment to treatment.
7. Must not have acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to enrollment to treatment.
8. Must not have known human immunodeficiency virus infection.
9. Must not have known active or clinically significant hepatitis A, B or C infection.
10. Must not have had any unstable angina or myocardial infarction within 4 months prior to enrollment to treatment, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
11. Must not have any uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment to treatment.
12. Must not have any evidence of moderate or severe pulmonary hypertension.
13. Must not have any evidence of other clinically active cancer and have no history of prior malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival

during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal glands or pancreas.

14. Must not have any significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to enrollment to treatment.
15. Must not have any known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
16. Must have no contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment.
17. Must not have any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

4.3 STRATIFICATION FACTORS FOR PHASE II COMPONENT:

In the phase II component of the study, subjects will be stratified according to the following:

Platinum sensitive disease: an initial response to platinum-based chemotherapy with subsequent progression observed greater than 90 days after last platinum treatment OR

Platinum refractory disease: No response to platinum-based chemotherapy or progression within 90 days of completing platinum-based therapy. Subjects that progressed during or within one month of completion of platinum-based chemotherapy will be excluded.

5 SUBJECT REGISTRATION/ENROLLMENT

Eligible subjects must be registered within 3 working days prior to initiation of protocol chemotherapy.

This study uses a web based subject registration/enrollment system for data submission, through the data management services of Cancer Research And Biostatistics (CRAB). The subject registration ("registration") form is accessed online through the study website https://ctc-11-001.crab.org/Login.aspx. Access is protected and available to authorized users only. For questions or assistance using this site, please contact: webhelpCRS@crab.org.

6 TREATMENT PROCEDURES

6.1 DRUG PREPARATION AND ADMINISTRATION.

- **Carfilzomib** for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Sterile Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. Refer to Study Manual for full instructions. The dose will be calculated using the subject's actual BSA at baseline, or Day 1. Subjects with a BSA > 2.2 m^2 will receive a dose of carfilzomib based upon a 2.2 m^2 BSA.
- For subjects considered at risk for TLS, **oral hydration** may be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment.
- **IV hydration** will be given prior to carfilzomib during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid given over 30 to 60 minutes. If lactate dehydrogenase (LDH) or uric acid is elevated > 1.5 times IULN (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload. Note: On Days 1, 8 and 15 of cycle 1, irinotecan is given prior to carfilzomib and this satisfies the prehydration requirement, provided the irinotecan is mixed in at least 250 mL of fluid.
- If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.
- Dexamethasone 8 mg PO/IV will be administered prior to all carfilzomib doses during Cycle 1 and after that as described in section 6.5.1.
- Carfilzomib will be given as an IV infusion over approximately 30 minutes. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1. During these observation times, **post dose IV hydration** (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) may be given over 30 to 60 minutes. Subjects should be monitored periodically during this period for evidence of fluid overload.

- **Irinotecan** is commercially available and supplied in amber vials and appears as a pale yellow transparent solution. Two vial sizes are available: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. Prior to administration, irinotecan will be diluted with 5% dextrose in water (preferred diluent) or 0.9% sodium chloride solution to a total volume of 250-500 ml (final concentration of 0.12 to 2.8 mg/ml). Irinotecan will be administered intravenously over 90 minutes prior to Carfilzomib infusion.
- **Dose adjustments for Carfilzomib or Irinotecan do not need to be made for weight gain/loss of ≤ 10%**

6.2 TREATMENT PLAN

6.2.1 PHASE I PORTION OF THE STUDY

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Irinotecan	125 mg/m^2	IV infusion (over 90 min)	1, 8, 15	q 28 days
Carfilzomib	20/ * mg/m^2	IV infusion (over 30 min)	1, 2, 8, 9 15 and 16	q 28 days

* Cycle 1 Day 1 & Day 2 doses are 20 mg/m2. All subsequent days as specified, i.e. 20/27 mg/m2 means Cycle 1 Day 1 & Day 2 doses are 20 mg/m2 and all other days are 27mg/m2.

Dosage schedule, phase 1b:

	Doses	
3+3 design	**Carfilzomib***	**Irinotecan**
Cohort -2	20 mg/m^2	75 mg/m^2
Cohort -1	20 mg/m^2	100 mg/m^2
Cohort 1	**20/27 mg/m^2**	**125 mg/m^2**
Cohort 2	**20/36 mg/m^2**	**125 mg/m^2**
Cohort 3	**20/45 mg/m^2**	**125 mg/m^2**
Cohort 4	**20/56 mg/m^2**	**125 mg/m^2**
Cohort 5	**20/70 mg/m^2**	**125 mg/m^2**

* Cycle 1 Day 1 & Day 2 doses are 20 mg/m2. All subsequent days as specified, i.e. 20/27 mg/m2 means Cycle 1 Day 1 & Day 2 doses are 20 mg/m2 and all other days are 27mg/m2.

Additional cycles of therapy may be administered provided the subject meets all of the following at the beginning of each cycle prior to treatment on Day 1 (at most 2 days prior to Day 1 of the next cycle):

- ANC ≥ 1,500/µL.
- Platelet count ≥ 100,000/µL.

- All other Grade 2, 3 or 4 non-hematological toxicities have resolved as required in section 6.3.3.
- Serum creatinine ≤ 1.5 x IULN OR measured or calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault.

6.2.2 EVALUATION FOR DOSE-LIMITING TOXICITY, PHASE I ONLY

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

A DLT is defined as any of the below treatment emergent toxicities **with attribution (possibly, probably or definitely related) to one or more of the study drugs** that occur during Cycle 1. Toxicities that occur in subsequent cycles will be handled through dose modifications (Section 6.3) but will not figure into the definition of MTD. Patients will be considered evaluable for DLT if they receive the assigned doses and schedule of chemotherapy throughout Cycle 1 or develop a DLT. If a patient does not develop a DLT, but does not complete Cycle 1 for any reason, then that patient will be considered not evaluable for DLT and be replaced.

Non-hematologic:

- *≥ Grade 2 neuropathy with pain*
- *≥ Any Grade 3 or 4 adverse event (excluding grade 3 nausea, vomiting, diarrhea lasting < 7 days or grade 3 fatigue).*
- *≥ Grade 3 nausea, vomiting, or diarrhea lasting ≥ 7 days despite maximal antiemetic/antidiarrheal therapy*
- *Grade 5 toxicity*

Note: Abnormal non-hematologic laboratory values ≥ grade 3 will be considered a DLT if they are determined to be clinically significant (i.e. result in dose interruption, delay or dose modification during cycle 1 or in a significant side effect as determined by the investigator) and possibly, probably or definitely related to study drug. If baseline value is elevated (or decreased) prior to enrollment, an increase (or decrease) will not be considered a DLT unless it worsens by 2 grades and is determined to be clinically significant by the treating investigator.

Hematologic:

- *Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting for ≥ 7 days*
- *Febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 38.3ºC)*
- *Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L) lasting ≥ 7 days despite dose delay*
- *Grade 3-4 thrombocytopenia associated with bleeding*
- *Grade 5 toxicity*

6.2.3 DOSE ESCALATION SCHEME - FOR PHASE I ONLY

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicities (DLT) are defined above.

Number of Subjects with DLT at a Given Dose Level	*Escalation Decision Rule*
0 out of 3	*Enter 3 subjects at the next dose level.*
≥2	*Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.*
1 out of 3	*Enter at least 3 more subjects at this dose level.* *a. If 0 of these 3 subjects experience DLT, proceed to the next dose level.* *b. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.*
≤1 out of 6 at highest dose level below the maximally administered dose	*This is generally the recommended phase II dose. At least 6 subjects must be entered at the recommended phase II dose.*

6.2.4 PHASE II PORTION OF THE STUDY

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Irinotecan	**125 mg/m^2**	**IV infusion (over 90 min)**	**1, 8, 15**	**q 28 days**
Carfilzomib	**20/36 mg/m^2**	**IV infusion (over 30 min)**	**1, 2, 8, 9 15 and 16**	**q 28 days**

* Cycle 1 Day 1 & Day 2 doses are 20 mg/m2. All subsequent days as specified, i.e. 20/27 mg/m2 means Cycle 1 Day 1 & Day 2 doses are 20 mg/m2 and all other days are 27mg/m2.

Additional cycles of therapy may be administered provided the subject meets all of the following at the **beginning of each cycle**:

- ANC ≥ 1,500/μL.
- Platelet count ≥ 100,000/μL.
- All other Grade 2, 3 or 4 non-hematological toxicities have resolved as required in section 6.3.3.
- Serum creatinine ≤ 1.5 x ULN OR measured or calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault.

6.3 DOSE REDUCTIONS/ADJUSTMENTS

6.3.1 DOSE LEVELS

Carfilzomib – Phase I portion of the study

Starting Dose	***Dose Level -1***	***Dose Level -2***
20/27 mg/m^2	*20/20 mg/m^2*	*Hold*
20/36 mg/m^2	*20/27 mg/m^2*	*20/20 mg/m^2*
20/45 mg/m^2	*20/36 mg/m^2*	*20/27 mg/m^2*
20/56 mg/m2	*20/45 mg/m^2*	*20/36 mg/m^2*
20/70 mg/m2	*20/56 mg/m^2*	*20/45 mg/m^2*

Carfilzomib – Phase II portion of the study

Starting Dose	Dose Level -1	Dose Level -2
20/36 mg/m^2	**20/27 mg/m^2**	**20/20 mg/m^2**

* Cycle 1 Day 1 & Day 2 doses are 20 mg/m2. All subsequent days as specified, i.e. 20/27 mg/m2 means Cycle 1 Day 1 & Day 2 doses are 20 mg/m2 and all other days are 27mg/m2.

In the event that carfilzomib is held on Day 2, 8, 9, 15 and/or 16 of therapy, missed doses are not to be made up. All dose reductions are permanent and no dose re-escalation will be allowed on this trial.

Irinotecan- Phase I and II portions of the study

Starting Dose	Dose Level -1	Dose Level -2
125 mg/m2	**100 mg/m^2**	**75 mg/m^2**

**If Dose level -1 is utilized*

In the event that irinotecan is held on Day 8 and/or Day 15, missed doses are not to be made up. All dose reductions are permanent and no dose re-escalation will be allowed on this trial.

6.3.2 DOSE REDUCTIONS FOR CARFILZOMIB AND IRINOTECAN HEMATOLOGIC TOXICITIES:

The following table outlines the dose reduction guidelines for carfilzomib and irinotecan for thrombocytopenia and neutropenia that occurs at any point during the prior cycle:

Event Name	**Neutropenia**	
Grade of Event	**Recommended Action for *Carfilzomib***	**Recommended Action for *Irinotecan***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	No change in dose	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
*Subjects requiring a delay of >3 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.		
No prophylactic growth factor support is allowed in cycle 1, but growth factor support in the event of neutropenia is encouraged and should be administered at the discretion of the treating physician and per National Comprehensive Cancer Network Guidelines (http://www.nccn.org).		

Event Name	**Thrombocytopenia**	
Grade of Event	**Recommended Action for**	**Recommended Action for**

	Carfilzomib	***Irinotecan***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose.
Grade 3	No change in dose	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
*Subjects requiring a delay of >3 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.		

6.3.3 DOSE REDUCTIONS OF CARFILZOMIB AND IRINOTECAN FOR NON-HEMATOLOGIC TOXICITIES

Dose adjustment guidelines for non-hematologic toxicities that occur at any point during the prior cycle are summarized as follows:

Event name	**Recommended Action**	**Recommended Action**
Grade of Event	**Carfilzomib**	**Irinotecan**
Allergic reaction/hypersensitivity		
Grade 2 – 3	Hold until ≤ Grade 1, reinstitute at full dose.	No change in dose
Grade 4	Discontinue	No change in dose
Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	Hold irinotecan until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection **Grade 3 or 4**	Hold carfilzomib until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.	Hold irinotecan until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.
Peripheral Neuropathy **Grade 2 treatment emergent with pain or Grade 3neuropathy**	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement if indicated.**	No change in dose
Peripheral Neuropathy **Grade 4 neuropathy**	Discontinue	Discontinue
Serum creatinine elevation **Grade 2, 3 or 4**	Hold until ≤ Grade 1. Resume at one dose level lower, if indicated.**	Hold until ≤ Grade 1. Resume at one dose level lower, if indicated.**

Hepatic Impairment **Grade 3 or 4 elevation of transaminases or bilirubin**	Hold Carfilzomib until < Grade 2. Resume at one dose level lower, if indicated.**	Hold Irinotecan until < Grade 2. Resume at one dose level lower, if indicated.**
Congestive heart failure **Grade 3 or 4**	Any subject with symptoms of grade 3 or 4 congestive heart failure, whether or not drug related, must have the dose held until resolution to grade 2 or less, or return to baseline, after which treatment may continue at 1 dose decrement, or the subject may be withdrawn from the study. If no resolution after 2 weeks, the subject will be withdrawn from the study.	No change in dose
Pulmonary Hypertension Grade 2, 3, or 4	Hold Carfilzomib until < Grade 2. Resume at one dose level lower, if indicated.**	No change in dose
Diarrhea		
Grade 2 or Grade 3 lasting < 3 days*	No change in dose	Hold Irinotecan until < Grade 2. Resume at same dose level.
Grade 3 (lasting > 3 days) or 4*	Hold Carfilzomib until < Grade 2. Resume at one dose level lower, if indicated.**	Hold Irinotecan until < Grade 2. Resume at one dose level lower, if indicated.**
*Recommended management: Loperamide antidiarrheal therapy dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		
Nausea/Vomiting		
Grade 2	No change in dose.	Hold Irinotecan until < Grade 2. Resume at same dose level.
Grade 3	No change in dose	Hold Irinotecan until < Grade 2. Resume at one dose level lower, if indicated.**

Grade 4	Hold Carfilzomib until < Grade 2. Resume at one dose level lower, if indicated. **	Hold Irinotecan until < Grade 2. Resume at one dose level lower, if indicated. **
Other Non-Hematologic Toxicity		
Other non-hematologic toxicity assessed as drug--related ≥ Grade 3	Hold dose until toxicity resolves to < Grade 2 or baseline. Resume at one dose level lower, if indicated. **.	Hold dose until toxicity resolves to < Grade 2 or baseline. Resume at one dose level lower, if indicated. **.
*Subjects requiring a delay of >3 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.		

6.3.4 *ADDITIONAL INFORMATION REGARDING MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA*

Based on an analysis of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) conducted in May 2014, 9 cases were identified (4 MDS and 5 AML), 4 of which (2 MDS and 2 AML) were reported by the investigator as related to carfilzomib. Of the 9 cases, 7 are from company-sponsored clinical studies, 2 are from ISTs and none were identified from the postmarketing experience.

A medical review of the 9 cases revealed that 8 of the events of MDS/AML were reported in the setting of underlying relapsed/refractory multiple myeloma in subjects previously treated with multiple chemotherapy regimens and radiation; 2 of these 8 subjects also had a prior history of MDS prior to study entry. The ninth case was reported from an IST for subjects with underlying relapsed AML and acute lymphoblastic leukemia, and thus, this report of AML did not represent a new disorder for that subject.

There is an inherent increased risk of developing secondary malignancies in multiple myeloma patients, including MDS and AML independent of therapy. Approximately 10,000 cases of MDS are diagnosed annually in the US, corresponding to an annual age- adjusted incidence rate of approximately 3.3 to 3.4 per 100,000. Using population-based data from Sweden, there is an 11.51-fold (95% CI: 8.19–15.74) increased risk of AML/MDS for patients diagnosed with MM, including both treated and untreated patients, compared with Swedish general population, corresponding to an incidence rate of 139 per 100,000 person-years (Mailankody 2011). Prior treatment exposure to other chemotherapy agents including

melphalan, lenalidomide, and thalidomide contribute to the risk; MDS and/or AML are documented in the labeling for these agents.

All 9 subjects had other risk factors (e.g., prior treatment exposure to other chemotherapy agents including melphalan, lenalidomide, and thalidomide; all of which include MDS and/or AML documented in their labeling). Three of the 9 subjects actually had a previous diagnosis of MDS or AML at study entry. Therefore, a meaningful causal association with the administration of carfilzomib could not be established. Events of MDS or AML will continue to be monitored in the clinical study and postmarketing setting.

Finally, in addition to these 9 cases, 5 cases (2 MDS and 3 AML) were reported in the 1110 control arm subjects enrolled into 1 of 4 ongoing, company-sponsored, Phase 3 clinical studies. None of these 5 subjects were exposed to carfilzomib. These 5 cases serve to emphasize the elevated inherent risk for MDS/AML experienced by myeloma patients independent of treatment exposure.

6.3.5 ADDITIONAL INFORMATION REGARDING TOXICITY

6.3.5.1 Increased Creatinine or Decreased CrCl

No dose adjustment is required in patients with mild, moderate, or severe renal impairment or patients on chronic dialysis. Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after the dialysis procedure. The renal safety profile of carfilzomib provides evidence of its tolerability in heavily pretreated patients with multiple myeloma and concomitant renal insufficiency (Harvey 2012). A PK study (Study PX-171-005) was conducted in 50 multiple myeloma subjects who had various degrees of renal impairment. Carfilzomib was administered IV over 2 to 10 minutes, on 2 consecutive days, weekly for 3 weeks (Days 1, 2, 8, 9, 15, and 16) every 28 days. Subjects received an initial dose of 15 mg/m2, which could be escalated to 20 mg/m2 starting in Cycle 2, if 15 mg/m2 was well tolerated in Cycle 1. Escalation of the carfilzomib dose to 27 mg/m2 at Cycle 3 and beyond was allowed for subjects who tolerated the 20 mg/m2 dose in Cycle 2. Results from this study suggest that subjects with mild to severe renal dysfunction, including dialysis patients, can receive CFZ at doses shown to be efficacious and well-tolerated in multiple myeloma patients with normal renal function.

6.3.5.2 Infections

Subjects with grade 3 or 4 active or suspected infections should have treatment withheld until infection has resolved and anti-infective treatment has been completed. After the infection has resolved and anti-infective treatment has been completed, treatment may continue at the original dose. If there is no resolution of toxicity after 3 weeks, the subject will be withdrawn from the study.

6.3.5.3 Congestive Heart Failure (CHF)

Any subject with symptoms of grade 3 or 4 CHF or any other suspected acute cardiac event, whether or not drug related, must have the dose held until resolution. After the event has resolved or returned to baseline, treatment may continue at 1 dose decrement, with the approval of the Medical Monitor, or the subject may be withdrawn from the study. If there is no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.

6.3.5.4 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in 2% of patients treated with carfilzomib and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Unless otherwise specified in the individual protocol, withhold carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment.

6.3.5.5 Myocardial Infarction

Death due to cardiac arrest has occurred within a day of carfilzomib administration. New onset or worsening congestive heart failure or myocardial ischemia have occurred following administration of carfilzomib. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, and ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications and manage promptly. Unless otherwise specified in the individual protocol, withhold carfilzomib for Grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib based on a benefit/risk assessment. Patients with NYHA Class III and IV heart failure, myocardial infarction in the preceding 6 months, or conduction abnormalities uncontrolled by medications were not eligible for the clinical studies. These patients may be at greater risk for cardiac complications. Dyspnea, predominately Grade 1 and 2, was reported in 35% of subjects enrolled in clinical studies (see Section 6.7, Undesirable Effects). Evaluate patients with dyspnea based on the clinical presentation and manage accordingly. Unless otherwise specified in the individual protocol, reduce or interrupt dose as appropriate.

6.3.5.6 Hepatic Toxicity

Cases of hepatic failure, including fatal cases, have been reported (< 1%). Carfilzomib can cause elevations of serum transaminases and bilirubin. Monitor liver enzymes frequently. Please use section 6.3.3 as a guide to reduce or interrupt carfilzomib dose.

6.3.5.7 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare, neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension. The diagnosis is confirmed by neuroradiological imaging. If diagnosed early and treated, the symptoms of PRES may be reversed. Cases of PRES have been reported in patients receiving carfilzomib. Discontinue carfilzomib if PRES is suspected. The safety of reinitiating carfilzomib therapy in patients previously experiencing PRES in not known.

6.3.5.8 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Carfilzomib does not need to be held in the following cases:

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

Neither Carfilzomib nor Irinotecan need to be held in the following cases:

- Alopecia
- ≥ Grade 3 hyperglycemia attributed to dexamethasone

6.3.5.9 Other Grade 3 or 4 Non-hematologic toxicities

Hold all treatment until toxicities resolve to < Grade 2. Upon resolution resume treatment and decrease irinotecan one dose level. If toxicities do not resolve within three weeks, subject shall be removed from study

6.3.5.10 Other

Any other dose modifications in study treatment that are not described above may be performed at the discretion of the treating investigator, provided that criteria for subject withdrawal from study treatment have not been met.

6.3.5.11 <u>For treatment modification questions, please contact Dr. Susanne Arnold at 859-257-5522 or email at: smarno0@uky.edu.</u>

6.3.6 MISSED DOSES

Missed doses will not be replaced during a cycle.

6.3.7 CHANGES IN BODY SURFACE AREA (BSA)

Dose adjustments for carfilzomib or irinotecan do not need to be made for weight gains/losses of ≤ 10%. Subjects with a Body Surface Area (BSA) of greater than 2.2 m^2 will receive a capped dose of carfilzomib based upon a 2.2 m^2 BSA. Subjects with BSA greater than 2.2 m^2 will receive the prescribed dose of irinotecan without a cap.

6.4 SAFETY CONSIDERATIONS

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, in approximately 700 subjects, the following observations are noted:

- A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequellae of rapid tumor lysis and/or cytokine release.
- Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.
- Dexamethasone 8 mg PO/IV will be administered prior to all carfilzomib doses during the first cycle and after that as per section 6.5.1. Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been completed.
- Subjects should have anemia corrected in accordance with the Institutional guidelines.

Carfilzomib and Irinotecan treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration. Subjects should be advised about diarrhea caused by Irinotecan and should have loperamide readily available at home.

6.5 CONCOMITANT MEDICATIONS

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

6.5.1 REQUIRED CONCOMITANT MEDICATIONS

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

Dexamethasone 8 mg PO/IV will be administered prior to all carfilzomib doses during the first cycle.. A higher dose of dexamethasone may be used per institutional standard. If treatment-related fever, rigors, chills, and/or dyspnea are observed following any dose of carfilzomib after dexamethasone has been discontinued, the subject should receive treatment for infusion reaction per the investigator's institutional standard and dexamethasone (8 mg PO/IV) should be re-instituted and administered prior to all subsequent doses.

All subjects must receive prophylaxis with hydration (see Section 6.1).

6.5.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Subjects may receive RBC or platelet transfusions if clinically indicated in accordance with institutional guidelines. FDA approved bisphosphonates are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically in cycle 1 of therapy.

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

6.5.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with other investigative anticancer therapies or other investigational agents is not allowed.

7 STUDY TESTS AND OBSERVATIONS:

Phase Ib Study Calendar:

Required Studies		***Cycle 1***						***Cycle 2,4,6***							***Cycle 3, 5***							
		Day						***Day***														
	Screen within 2weeks unless specified	*1*	*2*	*8*	*9*	*15*	*16*	*1*	*2*	*8*	*9*	*15*	*16*	*22*	*1*	*2*	*8*	*9*	*15*	*16*	*Off study*	*Follow-up@*
PHYSICAL																						
Informed Consent	*X*																					
Medical History	*X*																					
Physical Examination	*X*							*X*							*X*						*X*	*X*
Performance Status and Weight	*X*							*X*							*X*						*X*	*X*
Toxicity Assessment								*X*							*X*						*X*	*X*
Disease Assessment	*X*							*X*							*X*							
RADIOLOGY																						
CT/MRI scan ¶	*X*													*X*							*X*	*X*
Brain CT/MRI #	*X*																					
ECG#	*X*																					
LABORATORY																						
CBC w/differential	*X**	*X*		*X*		*X*		*X*		*X*		*X*			*X*		*X*		*X*		*X*	*X*
Serum chemistries §	*X**	*X*		*X*		*X*		*X*		*X*		*X*			*X*		*X*		*X*		*X*	*X*
Serum Magnesium	*X**	*X*						*X*							*X*						*X*	*X*
Serum or urine Pregnancy Test	*X**																					
TREATMENT																						
Irinotecan √		*X*		*X*		*X*		*X*		*X*		*X*			*X*		*X*		*X*			
Carfilzomib √ (study provided)		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*	*X*	*X*	*X*	*X*	*X*		
Dexamethasone 8 mg+		*X*	*X*	*X*	*X*	*X*	*X*															
PD/Correlative																						
Pharmcodynamic blood tests £		*X*	*X*																			
Tissue Submission &	*X*																					

¶ CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.3) must be repeated every8 weeks until disease progression. Once off study, the frequency of this scan may be reduced to every 3 months until disease progression.

#Prestudy, and then as clinically indicated

** This test is required prestudy within 2 weeks of starting study medication.*

§ Sodium, potassium, calcium, chloride, creatinine, magnesium, SGOT, SGPT, alkaline phosphatase, total bilirubin prior to treatment on Day 1 of each cycle (at most 2 days prior to Day 1 of the next cycle); Sodium, potassium, chloride, creatinine, prior to treatment on Day 8 & 15

√ After completion of Cycle 6 and if the subject has not met criteria for disease progression, carfilzomib and irinotecan may be continued at the discretion of the sponsor and treating physician.

+ Dexamethasone 8 mg prior to all carfilzomib doses during the first cycle and after that as per section 6.5.1.

£ PD: Carfilzomib proteasome chymotrypsin-like activity in PBMC (LMP7 and b5 activity) and gamma-H2AX and Topoisomerase-I expression Day 1: The sampling times relative to the start of irinotecan infusion: Pre-irinotecan, 90 min, 2 hours, 5.5 hours; Day 2: pre-carfilzomib infusion

& Submit tumor block or 10 unstained slides of pre-existing tumor

@ Follow-up will be for 30 days after last treatment or until all drug-associated (possible, probably or definite) toxicities have resolved to Grade 1 or less

Phase II Study Calendar:

Required Studies		**Cycle 1**						**Cycle 2,4,6**							**Cycle 3, 5**							
		Day						**Day**														
	Screen within 2 weeks unless specified	1	2	8	9	15	16	1	2	8	9	15	16	22	1	2	8	9	15	16	Off study	Follow-up@
PHYSICAL																						
Informed Consent	X																					
Medical History	X																					
Physical Examination	X							X							X						X	X
Performance Status and Weight	X							X							X						X	X
Toxicity Assessment								X							X						X	X
Disease Assessment	X							X							X							
RADIOLOGY																						
CT/MRI scan ¶	X													X							X	X
Brain CT/MRI #	X																					
ECG#	X																					
LABORATORY																						
CBC w/differential	X*	X		X		X		X		X		X			X		X		X		X	X
Serum chemistries §	X*	X		X		X		X		X		X			X		X		X		X	X
Serum Magnesium	X*	X						X							X						X	X
Serum or urine Pregnancy Test	X*																					
TREATMENT																						
Irinotecan √		X		X		X		X		X		X			X		X		X			
Carfilzomib √ (study provided)		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		
Dexamethasone 8 mg		X	X	X	X	X	X															
PK/PD/Correlative																						
Pharmcodynamic blood tests £		X	X																			
Tissue Submission &	X																					

¶ CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.3) must be repeated after ever two cycles of treatment until disease progression. Once off study, the frequency of this scan may be reduced to every 3 months until disease progression.
#Prestudy, and then as clinically indicated
* This test is required prestudy within 2 weeks of starting study medication.
§ Sodium, potassium, calcium, chloride, , creatinine, magnesium, SGOT, , alkaline phosphatase, total bilirubin prior to treatment on Day 1 of each cycle (at most 2 days prior to Day 1 of the next cycle); Sodium, potassium, chloride, creatinine, prior to treatment on Day 8 & 15
√ After completion of Cycle 6 and if the subject has not met criteria for disease progression, carfilzomib and irinotecan may be continued at the discretion of the investigator-sponsor and treating physician.
+ Dexamethasone 8 mg prior to all carfilzomib doses during the first cycle and after that as per section 6.5.1.
£ PD: **In first 15 subjects in each stratum:** Carfilzomib proteasome chymotrypsin-like activity in PBMC (LMP7 and b5 activity), Gamma-H2AX and Topoisomerase-I in PBMC Day 1: The sampling times relative to the start of irinotecan infusion: Pre-irinotecan, 90 min, 2 hours, 5.5 hours; Day 2: pre-carfilzomib infusion
& **All subjects:** Submit tumor block or 10 unstained slides of pre-existing tumor
@ Follow-up will be every 3 months for up to 2 years

8 STUDY DISCONTINUATION

8.1 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT:

a. Completion of 6 cycles of chemotherapy.

b. Progression of disease or symptomatic deterioration (as defined in Appendix B-Section 2).

c. Unacceptable toxicity.

d. Treatment delay for any reason for greater than 3 weeks

e. At the discretion of the treating physician

f. The subject may withdraw from the study at any time for any reason.

Subjects will receive up to 6 cycles of therapy. Subjects who are deemed to be clinically benefitting from this therapy by the treating physician, may be considered for further treatment at the discretion of the sponsor, Amgen, the treating physician and the study PI.

ALL REASONS FOR DISCONTINUATION OF TREATMENT MUST BE DOCUMENTED IN THE OFF TREATMENT NOTICE ECRF

8.2 POST TREATMENT FOLLOW-UP

Phase Ib: All subjects will be followed for 30 days after last treatment and until all drug-associated (possible, probably or definite) toxicities have resolved to Grade 1 or less.

Phase II: All subjects will be followed every 3 months until death or for 2 years after initial registration, or until death, or until study closure whichever occurs first.

9 ADVERSE EVENTS

9.1 ADVERSE EVENTS DEFINITIONS

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

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

A suspected adverse reaction means any AE for which there is reasonable possibility that the drug caused the AE. *'Reasonable possibility'* means there is evidence to suggest a causal relationship between the drug and the AE. An adverse reaction means any AE caused by a drug. This means there is reason to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current Investigators Brochure (IB) or prescribing information for a marketed compound or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. In addition, AEs or suspected adverse reactions that are mentioned in the IB 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 particular study drug is considered "unexpected."

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 to describe the event and for assessing the severity of AEs (see Appendix D). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.

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

9.2 CAUSALITY

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

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

9.3 ADVERSE EVENTS REPORTING PROCEDURES

All AEs, any new event with an onset date after the subject signs consent for study participation or changes to any pre-existing abnormalities that occur after initiation of treatment must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the Adverse Events and SAE eCRFs, as part of the CRAB CTC Electronic Data Capture (EDC) system.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
Attribution of the AE:

Definite – The AE is clearly related to the study treatment.

Probable – The AE is likely related to the study treatment.

Possible – The AE may be related to the study treatment.

Unlikely – The AE is doubtfully related to the study treatment.
Unrelated – The AE is clearly NOT related to the study treatment.

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

Baseline abnormalities will be captured as part of the medical history as described in section 9.1. AEs should be reported from the time of consent through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever occurs first. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject is randomized but discontinues study prior to receiving any study drug, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source. AEs continuing at 30 days post-last dose should have a comment in the source by the Investigator that the event has stabilized or is not expected to improve.

The site Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate.

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

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

9.3.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS FOR CARFILZOMIB (CAEPR)

The following side effects and conditions to watch for have been observed and may be due to carfilzomib.

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
Blood	Low red blood cell count, which may cause tiredness and fatigue; Low platelets, which may cause easy bruising or bleeding; Low white blood cell count, which may decrease your ability to fight infection	Low white blood cell count, which may be associated with fever;	Hemolytic uremic syndrome (HUS) (see 'Conditions you need to look out for')	Thrombotic thrombocytopenic purpura (TTP) (see 'Conditions you need to look out for'); Thrombotic microangiopathy (see 'Conditions you need to look out for')
Heart		Heart failure*, and heart problems including rapid, strong or irregular heartbeat	Heart attack; Reduced blood flow to the heart; Abnormal amount of fluid between the heart and the lining around the heart; Swelling and irritation of the lining around the heart	
Lung	Shortness of breath; Cough, cough with phlegm	Blood clot in the lungs; Fluid in the lungs; Nose bleed; Change in voice or hoarseness; Pain in throat; Wheezing; Pulmonary hypertension (see 'Conditions you	Lung problems see 'Conditions you need to look out for'); Bleeding in the lungs	

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
		need to look out for')		
Eye		Blurred vision; Cataract		
Intestine	Diarrhea; Nausea; Constipation; Vomiting; Stomach Pain	Indigestion; Toothache	Perforation in stomach, small intestine, or large bowel; Bleeding in the stomach and bowels	
General	Tiredness (fatigue); Fever; Swelling of the hands, feet or ankles; Chills; General weakness;	Pain; Feeling too hot; Pain, swelling, irritation or discomfort where you received the injection into your vein; Infusion reactions (see 'Conditions you need to look out for')	Multi-organ failure	
Liver		Liver problems including an increase in your liver enzyme in the blood	Liver failure; Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)	
Infections	Respiratory tract infection; Pneumonia	Sore throat; Bronchitis; Runny nose or nasal congestion; Urinary tract infection; Inflammation of the nose and throat;		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
		Flu-like symptoms (influenza); Serious infection in the blood (sepsis); Viral infection; Infection and/or irritation of your stomach and bowels; Lung infection		
Metabolism	Decreased appetite	Dehydration	Tumor lysis syndrome (TLS) (see “Conditions you need to look out for’)	
Bone and Muscle	Back pain; Joint pain; Pain in limbs, hands or feet; Muscle spasms	Bone and muscle pain; Chest pain; Muscle weakness; Aching muscles		
Nervous System	Headache; Dizziness; Numbness	Abnormal sensation such as tingling or decreased sensation in arms and/or legs	Bleeding in the brain	Posterior reversible encephalopathy syndrome (PRES) (see ‘Conditions you need to look out for’)
Psychiatric	Insomnia (difficulty sleeping)	Anxiety		
Kidney		Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure needing dialysis		
Skin		Rash;		

Body System	Very Common (may affect more than 1 in 10 people)	Common (may affect up to 1 in 10 people)	Uncommon (may affect up to 1 in 100 people)	Rare (may affect up to 1 in 1000 people)
		Itchy skin; Redness of the skin; Increased sweating		
Tests	Changes to blood tests (decreased blood levels of potassium, increased blood levels of sugar and/or creatinine)	Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin, or c-reactive protein)		
Immune System			Allergy to carfilzomib	
Blood Vessels	High blood pressure (hypertension)	Low blood pressure (hypotension); Blood clots in the veins; Flushing	Stroke; Bleeding; Extremely high blood pressure (see 'Conditions you need to look out for')	
Ear and labyrinth		Ringing in the ears		

*The risk of developing heart failure when receiving carfilzomib is higher if you are 75 years of age or older. This risk is also higher if you are Asian.

Subjects will be advised to inform the study staff if they develop any of the following:

- Chest pains, shortness of breath, or if there is swelling of your ankles and feet, which may be symptoms of heart problems.
- Difficulty breathing, including shortness of breath (dyspnea) at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung problems.

- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis.
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension.
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure.
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells.
- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain.
- Unusual bruising or bleeding, such as a cut that does not stop bleeding in a normal amount of time or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools.
- Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs).
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be signs of liver problems, including liver failure.
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS).
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as Posterior Reversible Encephalopathy Syndrome (PRES).

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib:

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML).
- Tenderness of pain in the abdomen that gets more intense with motion or touch, abdominal

bloating or distention, nausea and vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs.

Driving and Using Machines

Subjects may experience fatigue, dizziness, fainting, and/or a drop in blood pressure after treatment with carfilzomib. This may impair your ability to drive or operate machinery. If you have these symptoms, you should not drive a car or operate machinery.

Hydration Risks

There may be risks associated with over hydrating so it is important to follow the study physician's instructions regarding how much water or other fluids you should drink. Over hydration can cause side effect to your heart, lungs, and kidneys.

9.3.2 ADVERSE EVENTS AND POTENTIAL RISKS FOR IRINOTECAN

Irinotecan is FDA approved for all cancers treated in this clinical trial. Please refer to the package insert for a full adverse event listing. Risks and side effects related to Irinotecan include those which are:

Likely Side Effects: those occurring in more than 20% of subjects (or more than 20 out of 100 persons) who received Irinotecan:

- Thrombocytopenia that could result in bleeding including serious and life-threatening bleeding
- Anemia
- Changes in liver function. These changes are usually detected by blood test only and are not associated with any symptoms. These changes usually do not require treatment.
- Fatigue
- Constipation
- Nausea or vomiting
- Leukopenia and neutropenia that could lead to the risk of infection including serious and life-threatening infection
- Diarrhea
- Abdominal cramping, gas and bloating
- Constipation
- Shortness of breath
- Cough or runny nose

- Mouth sores
- Anorexia
- Weight loss
- Alopecia
- Rash
- Fever and chills
- Dizziness
- Pain
- Increased salivation
- Excessive tearing
- Flushing
- Sweating
- Infection

Less Likely Side Effects: those occurring in 5-20% of subjects (or 5 to 20 out of 100 persons) who received Irinotecan

- Allergic reactions (including hives, rash, itching, collapse, low blood pressure)
- Decrease in proteins in the blood stream and/or Malnutrition
- Rash
- Mouth sores
- Hair loss (scalp or body)
- Vomiting
- Weight loss
- Shortness of breath
- Dehydration
- Hypotension
- Neuropathy
- Flushing
- Changes in electrolytes.
- Changes in liver function.
- Taste alterations or loss of appetite
- Difficulty walking

- Dizziness
- Severe Thrombocytopenia bleeding including serious and life-threatening bleeding
- Severe Anemia
- Reversible difficulty speaking

Rare and/or Potentially Serious Side Effects: those occurring in less than 5% of subjects (or in less than 5 out of 100 persons) who received carfilzomib; side effects can be serious enough to be life-threatening or even fatal in rare cases:

- Muscle weakness
- Severe anorexia
- Fever with or without neutropenia
- Liver damage
- Life threatening infection
- Arterial/venous (artery/vein) blood clotting
- Myocardial ischemia
- Colitis, bowel obstruction
- Pulmonary fibrosis which includes symptoms such as- difficulty breathing, including shortness of breath (dyspnea) at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, or wheezing, which can be signs of lung problems
-
- Death

Reproductive risks:

Subjects should not become pregnant or father a baby while on this study because the drug in this study could affect an unborn child. It is not known if carfilzomib is transferred to breast milk. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment with carfilzomib and for an additional 30 days following their last treatment with carfilzomib.

Irinotecan may cause fetal harm when administered to pregnant women. Animal studies have revealed evidence of harm to an unborn baby as well as birth defects. Potential risks could include complications such as miscarriage or birth defects. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment with irinotecan and for an additional 30 days following their last treatment with irinotecan.

If you are of childbearing potential, you must use contraception during and for 30 days after the last dose of carfilzomib and irinotecan. Examples of contraceptive methods with a failure rate of less than 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of less than 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

Male subjects who have had a vasectomy and testing has shown that there is no sperm present in the semen, the use of birth control method in this study is not required. Otherwise, male subjects must:

- Let their female partner know he is participating in this study.
- Practice abstinence or use a condom during treatment in addition to 30 following final treatment with carfilzomib.

Male subjects must not donate sperm during treat and for an additional 30 days following their last treatment with carfilzomib. To prevent exposure of the unborn child to carfilzomib through semen, the male subject must agree to the use of a condom during vaginal sex.

9.4 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is one that meets the following criteria:

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

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

9.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

The Investigator-sponsor must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. All SAEs occurring from the time of subject consent through 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

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

The Investigator-sponsor is responsible for notifying the appropriate health authorities (HAs), ethics committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations.

The Investigator is also responsible for notifying the local ECs in accordance with local regulations. Reporting will be coordinated through the CRAB CTC Operations Office. Generally, Expedited Safety Reports are all SAEs **that are assessed to be unexpected and possibly, probably or definitely related** to study drug(s), as specified in ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports. However, certain Regulatory Agencies may have additional requirements for expedited safety report submissions.

Any safety report submission will cross reference the Amgen investigational new drug (IND) or clinical trial approval (CTA) number.at the time of submission.

Expedited Reporting by Investigator to Amgen

The Investigator-sponsor must inform Amgen by fax at the contact information listed below for all SUSARs that are judged as reasonably related to the Amgen study drug. Site will transmit the final MedWatch of that event to Amgen within twenty-four (24) hours of

submitting the report to the applicable regulatory authority. CRAB is responsible for facilitating communication with the Investigator-Sponsor and Amgen.

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Amgen in English. The Individual Case Safety Report (ICSR) may be referred to as an individual safety report or SAE Report, including Pregnancy Exposure Reports and Follow up Reports. The ICSR must be as complete as possible, at a minimum including event reference number, protocol name and number, investigator contact information, specific patient identifiers (e.g., initials, patient number, date of birth or age, or gender), the name of the suspect Study Drug, the date and dosage(s) of exposure, event, the date(s) of event, country of event, "Serious" Criteria, Relationship/causality of Study Drug, Hospitalization history for the event, Event status/outcome, Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment, and narrative summary.

Sponsor shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports and will exercise commercially reasonable due diligence to obtain follow-up information on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the Company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, Company will not contact non-party investigators directly, but will route all such inquiries through Site for forwarding to such investigator(s). Site will be responsible to ensure such inquiries are completed and timely provided to Company.

The Principal Investigator (Sponsor) will ensure the site investigator's initial report (FDA 3500A MedWatch is as complete as possible, and at a minimum includes the serious adverse event term (s), subject identifier, date of event awareness, an assessment of the causal relationship between the event and each investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented by the site investigator on a follow-up MedWatch form,

The Principal Investigator (Sponsor) will submit information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant

laboratory values, scan data and autopsy reports) which are received after the initial report and must be documented on a follow-up form, and submitted to Amgen in the same timelines as outlined above. Sponsor shall be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as documented in the appropriate case report forms per the Institution's guidelines. The Amgen protocol number (**CAR-IST-553**) and the institutional protocol number should be included on all reports to Amgen.

Other aggregate analysis including reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. Final study report including unblinding data when applicable and reports of unauthorized use of a marketed product to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. but not later than one calendar year of study completion

Sponsor will provide an annual IND report to Amgen. Reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. Sponsor will support reconciliation of all ICSRs at the end of the study at a minimum.

Amgen Drug Safety and Pharmacovigilance Contact Information (Safety Reports will be submitted to Amgen by CRAB CTC Operations Office, on behalf of the site investigator and sponsor):

Amgen Global Safety Contact Information:

- Drug Safety Reporting Fax
- Toll-free US 888-814-8653

Email (Only for sponsors with a secure email connection with Amgen):

- svc-ags-in-us@amgen.com

Drug Safety Reporting by secure e-mail can be established upon request.

9.5.1 Instructions for Rapid Notification of Serious Adverse Events

The site principal investigator has the obligation to report all serious adverse events to the CRAB CTC Operations Office and to the governing IRB. The CRAB CTC Operations Office will further report the SAE to the FDA and to Amgen Global Safety

All events reported to the CRAB CTC Operations Office by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch) Form.

All events must be reported, by phone at 206-342-1692. Supporting documents are to be sent via FAX at 206-342-1688, to the CRAB CTC Operations Office within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the subject has been enrolled and until 30 days after the subject has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 30 days after study discontinuation need only be reported if a relationship to the Amgen study drug is suspected.

GUIDELINES FOR EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS (SAEs)

1. **Within 24 hours of the event, call the CRAB Operations Office at 206-342-1692. In addition, investigators are asked to complete the SAE Preliminary Report Form and FAX to CRAB at 206-342-1688. The form can be accessed through the study website.**
2. **Within 2 calendar days, send the following to the CRAB CTC Operations Office:**
    a. SAE Reporting Coversheet

b. A copy of the FDA Form 3500A, including investigator's attribution[1] of the event

c. IRB notification documentation, as applicable

d. Other data as requested during the telephonic report

3. **Within 7 calendar days of discharge, if the subject was hospitalized:** A copy of the hospital discharge summary

4. **In addition, the following guidelines apply:**

These guidelines apply to subjects accrued to FDA research protocols which use investigational anticancer agents. The following events, when attributed as possibly, probably, or definitely related to the agent(s), must be reported in an expedited fashion:

a. Any AE/SAE which is life threatening (Grade 4) or fatal (Grade 5) and unexpected (is not listed as a known toxicity, or is of greater severity or specificity than listed toxicity).[2,3,4]

b. Any AE/SAE which is fatal (Grade 5), even if it is an expected toxicity. [4]

c. Any SAE occurring in a subject after providing informed consent, while receiving study drug, and until four weeks after stopping study drug, within 24 hours of learning of its occurrence, even if not felt to be drug related.

The SAE report, documented on FDA Form 3500A, must be sent **within 7 calendar days** to the CRAB CTC Operations Office as indicated below:

send copies of items listed under "2" above to:

Cancer Research And Biostatistics
Attn: CRAB CTC/SAE Program
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
OR fax to: 206-342-1688

[1] Attribution: Whether the event was *definitely not, unlikely, possibly, probably, or definitely* related to protocol treatment.
[2] For grading events, please use the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.
[3] Known toxicities are listed in the Drug Information, Introduction, and Informed Consent Form sections of the protocol.
[4] A report shall be submitted if the adverse event is *definitely, probably, or possibly* related to the agent(s). Events judged definitely not treatment related should not be reported, except that all deaths while on treatment or within 30 days after treatment must be reported. Any death more than 30 days after treatment which is felt to be treatment-related must also be reported.

9.6 PREGNANCY

It is not known if carfilzomib is harmful to an unborn or breastfed baby. If a subject or their partner becomes pregnant while receiveing this drug, potential risks could include complications such as miscarriage or birth defects. It is not known if carfilzomib is transferred to breast milk. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment with carfilzomib and for an additional 30 days following their last treatment with carfilzomib.

The FDA has assigned Irinotecan to pregnancy category D. It may cause fetal harm when administered to pregnant women. Animal studies have revealed evidence of embryotoxicity and teratogenicity. There are no controlled data in human pregnancy. If the subject or her partner becomes pregnant while receiving this drug, potential risks could include complications such as miscarriage or birth defects. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment with irinotecan and for an additional 30 days following their last treatment with irinotecan.

Pregnant or breastfeeding women and women planning to become pregnant should not participate in this study. If a female subject or the female partner of a male subject is unable to become pregnant because her healthcare provider has determined that she is postmenopausal or she has had her uterus, ovaries, or both fallopian tubes removed, the use of birth control is not required during this study. If a female subject or the female partner of a male subject could become pregnant, she must let her partner know she is in the study. She must agree to discuss acceptable pregnancy prevention methods with the study physician and practice abstinence or use an acceptable method of birth control.

Patient of childbearing potential must use contraception during and for 30 days after the last dose of carfilzomib and irinotecan. Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

If a male subject has had a vasectomy and testing has shown that there is no sperm present in the semen, the use of birth control method in this study is not required. Otherwise, male subjects must:

- Let his female partner know he is participating in this study.
- Practice abstinence or use a condom during treatment in addition to 30 following final treatment with carfilzomib.

Male subjects must not donate sperm during treat and for an additional 30 days following their last treatment with carfilzomib. To prevent exposure of the unborn child to carfilzomib through semen, the male subject must agree to the use of a condom during vaginal sex.

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of Carfilzomib or irinotecan, they must inform the study staff right away. The CRAB CTC Operations Office must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy. Instructions are provided below.

Pregnancy Reporting by Investigator-sponsor to Amgen

Report Pregnancy and potential infant exposure including Lactation, within ten (10) calendar days of Sponsor awareness. Provide to Amgen the SAE reports associated with pregnancy. SUSARs are to be reported within twenty-four (24) hours of submitting the report to the applicable regulatory authority. (See Amgen Drug Safety and Pharmacovigilance Contact information above).

If the subject is pregnant, carfilzomib and irinotecan must be withheld.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to report the results to the CRAB CTC Operations Office who will inform both the study sponsor as well as Amgen Drug Safety.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be

documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

Any pregnancy that occurs during study participation must be reported using the Pregnancy Report Forms (please see the instructions below). To ensure subject safety, each pregnancy must be reported to the CRAB Operations Office within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications and their relation to study drug. Initial and Follow-up Pregnancy Report Forms are accessible online through the study website. The CRAB CTC Operations Office will report the pregnancy and outcome to Amgen Drug Safety.

The pregnancy, breastfeeding, and birth control information in this protocol is specific to carfilzomib. There may be additional risks to an unborn child or breastfed baby from irinotecan, which is also used in this protocol. This may require study subjects to change the type and/or length of time they use birth control. The length of time breastfeeding must be avoided may also change. Subjects must be instructed to discuss this with their study physician.

Instructions for Rapid Notification of Pregnancies

Each pregnancy commencing during the study must be reported by telephone to the CRAB CTC Operations Office at 206-342-1692 within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported as directed during the call. Any serious adverse event experienced during pregnancy must be reported as outlined in Section 9.5.1. Pregnancy follow-up must describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to the study drug.

10 CORRELATIVE STUDIES

Pharmacodynamics/Biomarkers (Phase-Ib and Phase-II): The dose dependent proteasome inhibition on LMP7 and b5 proteasome subunits will be determined in purified PBMC to ensure that the intended effect is achieved in this surrogate tissue. Correlative PD biomarkers will be collected from all Phase 1b subjects (up to 24) and **the first 15 subjects from each stratum of the Phase 2 portion**. If a patient is registered as one of the first 15 patients in each stratum, the site will receive notice of for pharmacokinetic sampling via an auto-email. The response to irinotecan depends on the expression of topoisomerase-I (topo-I). Here, we will determine the expression of topo-I in banked tissues to determine if response correlates with Topo-I expression. Furthermore, to determine the effect of irinotecan and carfilzomib, we will measure the time dependent expression of gamma-H2AX and Topoisomerase-I in purified PBMC. We expect that irinotecan/SN-38 mediated DNA damage will increase the expression of gamma-H2AX. As topoisomerase-I undergoes proteasome mediated degradation, the expression of gamma H2AX declines. We expect that the combination with carfilzomib will increase Topo-I stability and sustained gamma-H2AX expression.

10.1 LABORATORY CORRELATIVE STUDIES

Pharmacodynamics (Phase-Ib and Phase-II):

- Carfilzomib proteasome chymotrypsin-like activity in PBMC (LMP7 and b5 activity) in all subjects in phase Ib and in 15 subjects in each cohort from phase II study.
- Expression of gamma-H2AX and Topoisomerase-I in PBMC in all subjects in all subjects in phase Ib and in 15 subjects in each cohort from phase II study.
- Expression of Topoisomerase-I in banked tissues in all subjects. Ten unstained slides on charged glass slides are preferable.

Carfilzomib mediated proteasome inhibition will be measured in purified PBMC using commercially available reagents. Irinotecan mediated DNA damage and the effect of carfilzomib in this process will be determined by time dependent changes in gamma-H2AX and Topoisomerase-I expression in purified PBMC. Blood samples for isolation of monocytes will be collected in BD Vacutainer CPT Mononuclear Cell Preparation Tubes (8mL) on Day 1

and 2 of Cycle 1. When available, tumor tissues will be obtained from participating sites to assess the expression of Topoisomerase-I using immunohistochemistry in all subjects.

Collection of Specimen(s)

Day 01: Sampling times are relative to the start of irinotecan infusion time: Pre-irinotecan, 90 min., 2 hr, and 5.5 hr.

Day 02: Pre-carfilzomib infusion.

Handling of Specimens(s)

1. Process each sample (both CPT tubes) individually within 5 minutes following sample collection. **Samples should not be placed on ice**.
2. Gently invert the tube 8 to 10 times to mix the anticoagulant with the whole blood. Do not shake the tube.
3. Keep sample tube at room temperature in the upright position at all times before and after blood collection and while waiting for centrifugation.
4. Centrifuge the CPT® tubes containing blood sample at room temperature (18-25°C) in a horizontal rotor (swing-out head) for 20 minutes at 1800xG.
5. Gently inverted 5-10 times to re-suspend cells (whitish layer)
6. Using a disposable transfer pipet transfer the plasma/PBMC suspension from the two CPT® 4mL tubes into a single, 15 mL centrifuge tube
7. Centrifuge the 15 mL tube at 1800xG, for 2 minutes at room temperature (18-25°C). Carefully pipette and discard all the plasma supernatant.
8. Allow samples to stand upright for 2 minutes on ice and carefully aspirate and discard any additional supernatant. NOTE: Please use care so that the cell pellet is not disturbed
9. Store tubes on dry ice or transfer to -80°C for storage until shipping. Record the time the sample was placed on dry ice or into -80°C as the "time processed" on the eCRF.
10. Send a hard copy of the eCRF "Specimen Collection Form" with this package

Samples should be shipped on Monday, Tuesday or Wednesday only. Please send notification of shipping via email to Dr. Leggas on the day of shipment.

Shipping of Specimen(s)

Samples should be shipped on dry ice to:

Dr. Mark Leggas
Department of Pharmaceutical Sciences
College of Pharmacy
University of Kentucky
789 South Limestone, Room 323
Lexington, KY 40536-0596
E-mail: mark.leggas @uky.edu
(859) 257-2633 Office
(859) 257-4550 Fax

11 STATISTICAL ANALYSIS

The accrual rate for the phase I component is anticipated to be approximately 2-3 subjects per month, with a completion time of 6-9 months. The accrual rate for the phase II component is anticipated to be 3-5 subjects per month and will proceed separately in two strata (platinum-sensitive vs. platinum-refractory subjects).

The primary endpoint for the phase II trial is the percent of subjects alive at six months. We will consider the combination of Carfilzomib and Irinotecan to be of interest in *platinum sensitive* subjects if the proportion of subjects alive at six months is 60% or greater, compared to a benchmark six-month survival rate of 40%. With a total of 40 eligible subjects treated at the RP2D in the platinum sensitive stratum, we will be able to test the null hypothesis that the true survival rate at six months is at most 40% versus the alternative that the true survival rate at six months is 60% or greater with a power of 79% and a one sided significance level, alpha of .04. According to this design, if at least 22 subjects out of 40 are alive at six months, we can reject the null hypothesis of a 40% six-month survival rate. This will be considered adequate evidence of promising activity for this regimen, and it may be recommended for further testing in subsequent studies. If fewer than 22 subjects are alive at 6 months, we will consider the regimen insufficiently active in this subject population. We will consider the combination of Carfilzomib and Irinotecan to be of interest in *platinum refractory* subjects if the proportion of subjects alive at six months is 45% or greater, compared to a benchmark six-month survival rate of 25%. For the platinum refractory stratum, 40 evaluable subjects will enable us to test the null hypothesis that the true survival rate at six months is at most 25% versus the alternative that the true survival rate at six months is 45% or greater with a power of 86% and a one-sided significance level of .054. If at least 15 subjects out of 40 are alive at six months, this will be considered adequate evidence of promising activity, and the regimen may be recommended for further testing in subsequent studies. If fewer than 15 subjects are alive at 6 months, we will consider the regimen insufficiently active in this subject population.

Secondary endpoints for both phases include response rates, safety/tolerability and the rates of specific adverse events, progression-free survival and biomarker endpoints as described in sections 10.1 and 10.2. With 40 eligible subjects in each stratum, the 6 month survival rate,

and the rates of individual adverse events, can be calculated to within at most +/-16% (95% confidence interval) for each individual stratum. Due to the limited sample size in a Phase II setting, correlative studies will be considered exploratory in nature and will be used to formulate hypotheses that can be tested using correlative data from a Phase III setting.

11.1 ADDITIONAL SAMPLE SIZE CONSIDERATIONS

Based on a standard 3+3 design, the phase I portion of the study will accrue *at most* 24 subjects. An additional 80 evaluable subjects will be needed for phase II. Because some subjects are subsequently found to be ineligible after central review, or inevaluable due to receiving no treatment after enrollment, accrual beyond 80 subjects is anticipated in order to ensure that 80 eligible, evaluable subjects, are available for analysis. The anticipated number of registrations for phase II is therefore approximately 88 subjects.

11.2 INTERIM ANALYSIS

Interim analyses will be performed separately for each stratum after 30 subjects have been accrued. Evaluable subjects that have been on study for 6 months or more will be included in the interim analysis, a projected 24 subjects within each stratum. At this time, if a test of the alternative hypothesis (six-month survival rate of at least 60% in the platinum sensitive stratum or at least 45% in the platinum refractory stratum) is rejected at the .005 level, this will be evidence in favor of closing the stratum to further accrual. The power to reject the alternative hypotheses (and exact alpha) will depend on the exact number of subjects analyzed. For example, on the platinum sensitive stratum, if the true survival rate is 40% and 24 subjects are available for analysis, then the power to reject the alternative of 60% would be 19% (alpha=.0022). For the platinum refractory stratum, if 24 subjects are available, the power to reject the alternative of at least 45% survival at 6 months would be 25% given a true survival rate of 25% (alpha=.0036).

11.3 PLANNED METHODS OF ANALYSIS

Six month survival and progression free survival rates, as well as response to treatment, will be calculated based on all subjects who receive the recommended Phase II dose of the drug

combination. All eligible subjects accrued to phase II who have received at least one dose of each drug in the regimen will be considered as evaluable in the phase II analysis.

Survival will be estimated using the Kaplan-Meier method, separately for each stratum. Response and progression will be determined according to RECIST criteria. Overall survival is defined as the time between registration and death due to any cause. Subjects last known to be alive are censored at date of last contact. Progression free survival is defined as the date of registration to the date of first documentation of progression, or death due to any cause. Subjects last known to be alive and progression free are censored at the date of last contact. Due to the limited sample size in a Phase II setting, correlative studies will be considered exploratory in nature and will be used to formulate hypotheses that can be tested using correlative data from a Phase III setting.

12 INVESTIGATIONAL PRODUCT

12.1 CARFILZOMIB DESCRIPTION

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

12.1.1 FORMULATION

Carfilzomib for Injection is supplied as an individually cartooned single-use vial containing a dose of 60 mg of Carfilzomib as a white to off-white lyophilized cake or powder. When reconstituted, Carfilzomib contains 2 mg/mL isotonic solution of carfilzomib, 100 mg/mL sulfobutylether-beta-cyclodextrin, and 1.9 mg/mL citrate buffer (pH 3 to 4). Each mL of reconstituted drug product contains 0.3 mmol (7 mg) of sodium.

12.1.2 STORAGE

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

12.1.3 RECONSTITUTION AND ADMINISTRATION

Aseptically reconstitute each vial of carfilzomib by slowly injecting 29 ml Sterile Water for Injection, USP, directing the solution onto the inside wall of the vial to minimize foaming. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. Do not shake to avoid foam generation. If foaming occurs, allow solution to rest in the vial for about 2 to 5 minutes, until foaming subsides. After reconstitution, carfilzomib is ready for intravenous administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product.

When administering in an intravenous back, withdraw the calculated dose from the vial and dilute into 50 ml to 100 mL 5% Dextrose Injection, USP intravenous bag. Immediately discard the vial containing the unused portion. The reconstituted solution contains carfilzomib at a concentration of 2 mg/ml and is stable at room temperature for four hours (or 24 hours at 2ºC – to 8ºC) following reconstitution.

The IV administration line should be flushed with normal saline or 5% Dextrose Injection, USP immediately before and after carfilzomib administration. **Carfilzomib should not be administered as a bolus.**

12.1.4 ACCOUNTABILITY

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

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

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

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

12.1.5 CARFILZOMIB DRUG ORDERING

Carfilzomib will be provided by Amgen. Investigators must order carfilzomib by accessing a password protected online, secure website. Amgen will provide access information to the system for all appropriate study personnel after the requirements for study activation at the site

have been confirmed. Please see below for requirements prior to submitting the initial drug request.

An initial startup supply for the first cycle may be ordered prior to subject registration.

Prior to submitting the initial drug request, investigators must first do the following:

1. Be aware that investigational new drug regulatory best practices mandate that drug must be shipped to the single designated pharmacy listed in Box 3 of the FDA-1572 Form; further dispensation to satellite pharmacies will be the site Principal Investigator's responsibility. Compliance with Good Clinical Practices for drug accountability, storage, dispensation, and documentation is expected.
2. Prior to the submission of the initial drug request, the site investigator must confirm the required regulatory documents have been submitted to the CRAB CTC Operations Office at the time of site activation. Documents to be submitted include: site/central IRB approved Informed Consent and site/central IRB approval letter for current version of the protocol and informed consent form. Once completed documents have been received, the CRAB CTC Operations Office will forward the documents to Amgen prior to the site's initial drug request.

12.2 IRINOTECAN

12.2.1 IRINOTECAN DESCRIPTION

Irinotecan hydrochloride injection is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11. Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as Mappia foetida and Camptotheca acuminata. The chemical name is (S) - [CPT- 1 1, (4S)-4, 1 1- diethyl-4-hydroxy-9-
[(4-piperidinopiperidino) carbonyloxy] -IHpyroano [3',4':6, 7l indolzino [1 ,2-bl
quino line-3, 14(4H, l2H) dione hydrochloride trihydrate]

12.2.2 FORMULATION

Irinotecan hydrochloride injection is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials containing 40 mg Irinotecan hydrochloride, and 5 mL-fill vials containing 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan hydrochloride injection is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

12.2.3 TOXICOLOGY

Human Toxicity: Virtually all Phase I and II studies of irinotecan have reported neutropenia and diarrhea as the dose-limiting toxicities. It is expected that these toxicities will also be encountered in this trial. Other Grade 2-3 toxicities seen include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss. Sporadic cases of pulmonary toxicity, manifested as shortness of breath and nonproductive cough, have also been reported.

12.2.4 PHARMACOLOGY

Pharmacokinetics: Several studies describing the pharmacokinetic characteristics of irinotecan (CPT-11) and its active metabolite, SN-38, when administered alone or in combination with other agents (including cisplatin) in subjects with small cell or non-small cell lung cancer have been reported in published literature. CPT- 11 is converted by carboxylesterases to its more active metabolite, SN-38. In vitro, SN-38 is 250 to 1,000 fold more potent than CPT-11 in the inhibition of topoisomerase I activity. A reversible, pH-dependent hydrolysis converts the closed lactone E ring form of both CPT-11 and SN-38 to the open, carboxylate form of each

compound. Only the closed ring (lactone) forms of CPT-11 and SN-38 are effective topoisomerase I inhibitors. The mean terminal half-life of SN-38 in plasma is slightly longer than that for CPT-11; 11.5 ± 3.8 hours versus 6.3 ± 2.2 hours for the lactone forms. Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak for SN-38 is highly inter-subject dependent occurring at variable time points 30 to 90 minutes after the end of infusion. Murine studies suggest that the liver may concentrate, convert CPT-11 to SN-38, and eliminate both compounds as well as the glucuronide conjugate of SN-38 (SN-38G) via biliary secretion. In rats, 55% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours, while 21.7% was transformed to SN-38. It recently was demonstrated that plasma concentrations of SN-38G in subjects occur 0.5 to 3 hr after the SN38 peak and plasma levels generally exceeded that of SN-38. Overall, 73% of the radioactivity could be recovered from the feces of rats and 25% from the urine. Bile concentrations of CPT-11 were 10 to 60 fold higher than plasma concentrations in one subject during the first 6 hours following administration, while bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.

12.2.5 STORAGE

Storage and Stability: Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Protect from light. Do not freeze. It is recommended that the vial should remain in the carton until the time of use. It is stable for at least three years at room temperature. Irinotecan is stable for 24 hours in glass bottles or plastic bags after reconstitution with D5W.

Reconstitution and Administration: Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90 minutes, per institutional standards. Nothing else should be added to the bag.

12.2.6 ACCOUNTABILITY

The Investigator will maintain records of each dose of chemotherapeutic drug given. The records will document dose, infusion rate, date given and time given, as per standard of care

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

12.2.7 IRINOTECAN DRUG ORDERING

Irinotecan is commercially available and will be charged to the subject's insurance as per standard of care.

13 REGULATORY OBLIGATIONS

13.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be provided to the CRAB CTC Operations Office before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the study sponsor and Amgen.

13.2 INFORMED CONSENT

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the subject could not read or sign the documents. No subject can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

13.3 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice

(GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

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

The site Investigator or designee will be responsible for obtaining continuing and not less than annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report and other significant protocol updates to the FDA, IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided by the CRAB CTC Operations Office to Amgen via email PRA Health Services:

PRA Contact: Ms. Maria Bloodgood
Manager, Investigator Sponsored Studies
PRA Health Sciences
Email: mbloodgo@amgen.com
Phone: 610-268-5074

The site Investigator is also responsible for notifying the FDA , their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

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

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

13.4 REGULATORY DOCUMENTATION REQUIREMENTS

c. The documents listed below must be submitted to the CRAB CTC Operations Office prior to the site's activation of CTC 11-001. Subject registration will not be permitted until all documents have been received. Documents may be submitted via Fax or email to:

CRAB CTC Operations Office – Regulatory Affairs
Fax: (206) 342-1688
Email: webhelpCRS@crab.org

- Investigator Signature sheet
- IRB protocol and consent form approval letter (s)
- IRB approved consent form
- OHRP Federal Wide Assurance number
- IRB membership list if available
- FDA Form 1572
- Curriculum Vitaes, Financial Disclosure forms, and Medical Licenses for all investigators and sub-investigators listed on the FDA Form 1572
- Laboratory certification and normal ranges

d. Updates to the documents specified above must be submitted to the CRAB CTC Operations Office during the course of the study and will include at the minimum:

- IRB protocol approval letters for annual, continuing, or modification reviews
- IRB approval of modified consent form
- Investigator Signature sheet for each version of the protocol
- Updated Form 1572 to document changes in investigators or sub-investigators

13.5 SUBJECT CONFIDENTIALITY

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

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

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

14 ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 PROTOCOL AMENDMENTS OR CHANGES IN STUDY CONDUCT

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment from the CRAB CTC Operations Office. All amendments must be approved by the Sponsor-Investigator, CRAB CTC, and Amgen before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the central IRB at each study. A copy of the written approval of the IRB must be provided to the CRAB CTC Operations Office. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects;
2. significant changes in the study design (e.g. addition or deletion of a control group);
3. increases in the number of invasive procedures; and
4. addition or deletion of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator, by the CRAB CTC, or by Amgen in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the CRAB CTC Operations Office must be notified and the central IRB must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials, and
2. minor changes in the packaging or labeling of study drug.

14.2 STUDY TERMINATION

Amgen and the CRAB CTC reserve the right to discontinue the study under the conditions specified in the clinical trial agreement.

14.3 STUDY DOCUMENTATION AND ARCHIVE

Records and documents pertaining to the conduct of this study, including CRFs, source documents, consent forms, laboratory test results, and medication inventory records must be maintained by the Investigator or Institution for the following length of time:

- For a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

No study records shall be destroyed without prior authorization from Amgen and the CRAB CTC Operations Office.

14.4 DISCLOSURE AND CONFIDENTIALITY

The participating CTC investigator agrees to keep all information provided by Amgen and/or the CRAB CTC in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Amgen (such as Investigators' Brochures and other materials), and by the CRAB CTC (such as study protocol and other materials) will be stored appropriately to ensure their confidentiality. The information provided by Amgen and/or the CRAB CTC to the investigator may not be disclosed to others without direct written authorization from Amgen and the CRAB CTC Operations Office, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

14.5 PUBLICATION OF RESULTS

Any formal presentation or publication of data from this trial may be considered as a joint publication by the Sponsor-Investigator, participating CRAB CTC Investigators, Cancer Research And Biostatistics, and Amgen. For multicenter studies, it is mandatory that the first publication be based on data from all study sites, analyzed as stipulated in the protocol, and not by investigators acting solely on their own or their institution’s behalf. Investigators participating on multicenter studies agree not to present data gathered from one study site or from a subset of study sites before the full, joint initial publication, unless formally agreed to by the Sponsor-Investigator, the CRAB CTC Operations Office, and Amgen.

The CRAB CTC Operations Office and Amgen must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge CRAB's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. The Sponsor-Investigator and CRAB CTC Operations Office shall have the final authority to determine the scope and content of publications, provided such authority shall be exercised with reasonable regard for the interests of CRAB CTC and Amgen and, in accord with the trial contract and shall not permit disclosure of confidential or proprietary information.

14.6 STUDY MONITORING

14.6.1 PHASE IB ONLY: MANDATORY BI-MONTHLY TELECONFERENCES

A mandatory conference call will take place approximately twice a month during the registration period of the Phase Ib portion of the trial. Less frequent conference calls will be held after Phase Ib has completed. The call will update participating investigators on the current status of the trial and will include representatives from the study team (lead investigators, biostatisticians, and data management personnel), and investigators from all participating institutions. During the calls, adverse events encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, participating investigators will be informed of important study decisions via email and by study announcements posted to the study website.

Institutional participation on the conference calls requires identification of an investigator contact and a CRC contact. Prior to registration of the first subject, each institution must provide contact names, email addresses, and phone numbers to the CRAB CTC Program Manager via email or Clinical Research Services main phone line: 206-342-1692. Institutions will be responsible for keeping this information up-to-date and must notify the CTC Program Manager of any changes. The investigator and the contact CRC will receive e-mail reminders with the conference call information.

14.6.2 PHASE II ONLY: MANDATORY QUARTERLY TELECONFERENCES

A mandatory conference call will take place approximately every three months during the registration period of the Phase II portion of the trial. The call will update participating investigators on the current status of the trial and will include representatives from the study team (lead investigators, biostatisticians, and data management personnel), and investigators from all participating institutions. During the calls, adverse events encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, participating investigators will be informed of important study decisions via email and by study announcements posted to the study website.

Institutional participation on the conference calls requires identification of an investigator contact and a CRC contact. Prior to registration of the first subject, each institution must provide contact names, email addresses, and phone numbers to the CRAB CTC Program Manager via email or Clinical Research Services main phone line: 206-342-1692. Institutions will be responsible for keeping this information up-to-date and must notify the CTC Program Manager of any changes. The investigator and the contact CRC will receive e-mail reminders with the conference call information.

14.6.3 SITE MONITORING

Monitoring procedures will be carried out by the Cancer Research And Biostatistics (CRAB) Study Monitor, and will be performed remotely on a regular basis to comply with Good Clinical Practice guidelines. Data and safety will be monitored by the sponsor-investigator, the biostatistician, and data management personnel. In addition, on-site monitoring visits will occur at least once during the study. Materials to be reviewed include the electronic case report forms (which will be cross-referenced with selected source documentation), study-related regulatory documents, and drug accountability logs.

At the conclusion of the on-site monitoring visits, the CRAB Study Monitor will complete a written monitoring report and forward it to the site Principal Investigator, the Sponsor-Investigator and to the CRAB Clinical Trial Consortium (CTC) Program Manager. The report will include a summary of what the Study Monitor reviewed and statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to the CRAB CTC Program Manager and the CRAB Study Monitor.

A copy of the monitoring materials, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's study file at Cancer Research And Biostatistics for follow-up at the next monitoring session.

14.7 DATA SUBMISSION REQUIREMENTS

Investigators must record the information required by the protocol.

The CTC 11-001 study uses a web based data entry system for data submissions through the data management services of Cancer Research And Biostatistics (CRAB). All study case report forms will be accessed online through the study website at: https://ctc-11-001.crab.org/Login.aspx . The eCRFs on the screening tab should be completed within 5 business days following registration to treatment. All other eCRFs should be completed within 5 business days following the visit date. For questions and assistance using the site, please contact: WebHelpCRS@crab.org.

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APPENDIX A: NCI-CTCAE VERSION 4.0

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

Publish Date: June 14, 2010
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX B: ASSESSMENT OF EFFICACY (RECIST 1.1 CRITERIA)

Criteria for Disease Response Evaluation Using RECIST 1.1 Criteria [33]

1. Measurability of lesions.

a. **Measurable disease**.

1) Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, as ≥ 1.0 cm by CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

2) Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**. All other lesions (or sites of disease), including small lesions (longest diameter <1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to <1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**:

1.) For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2.) The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

3.) PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

4.) Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

5.) Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

6.) If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

2. Objective status at each disease evaluation.

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to subjects with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:
   1. "Appropriate diameters" means short axis for lymph nodes; longest diameters for all other lesions,
   2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
   3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
   4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
   5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
   6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the subject could alter the size of the effusion.
   7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

3. Best Response. This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression at first assessment after registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

4. Performance Status

Subjects will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
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 housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of 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. Progression-Free Survival From the date of registration to first documentation of progression or symptomatic deterioration (as defined in 2.d and 2.e), or death due to any cause. Subjects last known to be alive and progression-free are censored at date of last contact.

6. Overall Survival From the date of registration to the date of death due to any cause. Subjects last known to be alive are censored at date of last contact.

7. Time to Treatment Failure From date of registration to date of first observation of progressive disease (as defined in 2.d) , death due to any cause, symptomatic deterioration (as defined in 2.e), or early discontinuation of treatment.