CLINICAL STUDY PROTOCOL

NCT number: NCT01816971

PROTOCOL INFORMATION

Protocol Number: MMRC-043, University of Chicago IRB #12-1725

Study Title: Open-label, Single-arm, Phase 2 Study of the Initial and Post-Transplant Treatment with Carfilzomib, Lenalidomide and Low dose Dexamethasone (CRd) in Transplant Candidates with Newly Diagnosed, Multiple Myeloma Requiring Systemic Chemotherapy

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A Multi-institutional Study Done In Collaboration with The Multiple Myeloma Research Consortium. Participating sites include institutional members of the University of Chicago Personalized Cancer Care Consortium.

Statistician: Kent Griffith, MPH, MS

Investigational Products:
Drug Company Supplied: Carfilzomib (Onyx) IND# 105821
Commercial Agents: Dexamethasone, Revlimid

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Version 5.2	May 20, 2015
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Version 6.2	July 6, 2016
Version 7	October 5, 2016

PROTOCOL SYNOPSIS

Title: **Open-Label, Single-arm, Phase 2 Study of the Initial and Post-Transplant Treatment with Carfilzomib, Lenalidomide and Low dose Dexamethasone (CRd) in Transplant Candidates with Newly Diagnosed Multiple Myeloma (MM) Requiring Systemic Chemotherapy**

Objectives:

Primary Objectives:
To determine the rate of stringent CR (sCR) after 8 cycles of CRd (4 cycles of induction + ASCT + 4 cycles of CRd consolidation).

Secondary Objectives:
Overall response rate defined as partial response or better (≥PR) including the rate of VGPR or better (≥VGPR) and near complete response or better (sCR/CR/nCR) across entire treatment in high risk and low risk patients

Duration of response (DOR), Progression free survival (PFS), Time to progression (TTP), and Overall Survival (OS)

Exploratory Objectives:
Determination of the rate of minimal residual disease in patients who achieved CR

Prospective evaluation of candidate markers of response to CRd established in the completed CRd trial

Evaluation of markers of response and duration of response to treatment strategy using CRd with or without transplant

Study Design:	This is a multi-center, open-label, Phase 2 study in which transplant candidates with newly diagnosed MM requiring systemic chemotherapy will receive initial induction with CRd followed by autologous stem cell transplant (ASCT) followed by CRd consolidation followed by CRd maintenance. The study will determine the efficacy of the treatment strategy by determining the rate of sCR after completion of a total 8 cycles of CRd (4 cycles of induction, followed by ASCT followed by 4 cycles of CRd consolidation). Carfilzomib will be administered at 20 mg/m^2 as an IV infusion on Days 1, 2 and then at 36 mg/m^2 on Days 8, 9, 15, and 16 in cycle 1 of a 28-day cycle and at 36 mg/m^2 for the remaining cycles. Cycles 1 - 4 represent induction. Lenalidomide will be administered PO at 25 mg per dose on Days 1- 21 of the 28-day cycle for pre-ASCT induction Cycles 1 – 4 and Dexamethasone will be administered PO or IV between 30 minutes and 4 hours preceding the carfilzomib dose at 40 mg per dose on Days 1, 8, 15, and 22 in cycle 1-4. After Cycle 4, subjects will proceed into stem cell harvest (SCC) with use of growth factors or as per current standards of care and then to single ASCT. In the CRd consolidation phase, which will be initiated after 3 months post-ASCT evaluation (days 70-90 but not more than day 120), Carfilzomib will be used IV at the last tolerated dose on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle for CRd consolidation cycles (overall CRd Cycles 5-8) and in the CRd maintenance phase at last tolerated dose as an IV infusion on Days 1, 2, 15, and 16 of a 28-day cycle for CRd maintenance (overall Cycles 9-18). Lenalidomide will be used at the last tolerated dose but not higher than 15 mg per dose as initial dose in the CRd consolidation phase and at the last tolerated dose in the CRd maintenance phase on days 1-21 in 28 day cycles. In discussion with the Lead Principal Investigator and on a case-by-case basis, provisions may be made to start at a lower than 15 mg dose of lenalidomide for participants with adequate hematologic parameters following ASCT and/or to escalate lenalidomide dose up to 25 mg per dose after completion of 1 cycle of CRd consolidation for participants with adequate hematologic parameters. Dexamethasone will be administered PO or IV between 30 minutes and 4 hours preceding the carfilzomib dose at 20 mg per dose on Days 1, 8, 15, and 22 in the consolidation phase at last tolerated dose in CRd Cycles 5-8, and at 20 mg (or last tolerated dose) per dose on days 1, 8, 15, and 22 in the CRd maintenance phase (overall CRd cycle 9-18).

Study Population:	Newly diagnosed multiple myeloma, autologous stem cell transplant candidates
Inclusion Criteria:	*Disease-related*: 1. Newly diagnosed, myeloma requiring systemic chemotherapy as per IMWG uniform criteria (see Appendix B) • Prior treatment of hypercalcemia or spinal cord compression or active and/or aggressively progressing myeloma with corticosteroids or lenalidomide or bortezomib-based regimens does not disqualify the patient (the treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period or not more than 1 cycle) • Bisphosphonates are permitted 2. Suitable and interested to proceed to ASCT. (Refer to 6.4) 3. Measurable disease, prior to initial treatment as indicated by one or more of the following: • Serum M-protein ≥ 0.5 g/dL • Urine M-protein ≥ 200 mg/24 hours • If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative immunoglobulin levels are acceptable *Demographic* 4. Males and females ≥ 18 years of age 5. Life expectancy of more than 3 months 6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (See Appendix C) *Laboratory* 7. Adequate hepatic function, with bilirubin < 1.5 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times ULN 8. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L, hemoglobin ≥ 8 g/dL, platelet count ≥ 75 x 10^9/L. Subjects may receive RBC transfusions or platelet transfusions, if clinically indicated in accordance with institutional guidelines. However, screening platelet count should be independent of platelet transfusions for at least 2 weeks. 9. Calculated or measured creatinine clearance of ≥ 50 mL/minute, calculated using the following formula of Cockcroft and Gault:

$$\frac{(140 - \text{age}) \times \text{mass (kg)}}{72 \times \text{creatinine (mg/dL)}} \times 0.85 \text{ (if female)}$$

Or creatinine below 2 g/dl

Ethical/Other

10. Written informed consent in accordance with federal, local, and institutional guidelines
11. Females of childbearing potential (FCBP) [defined as sexually mature females who: 1) have not undergone a hysterectomy or bilateral oophorectomy; or 2) have not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months)] must agree to ongoing pregnancy testing.
12. FCBP must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to initiating lenalidomide. The first pregnancy test must be performed within 10-14 days before Day 1 Cycle 1 and the second pregnancy test must be performed within 24 hours of Day 1 Cycle 1. The subject may not receive lenalidomide until the Treating Investigator has verified that the results of these pregnancy tests are negative, and must agree to ongoing pregnancy tests as outlined in the protocol. *For patients already on Revlimid, continuation of current testing schedule is permitted as long as it is not interrupted during the transition to CRd therapy.*
13. FCBP must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The 2 methods of reliable contraception must include a highly effective method (ie, intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and an additional effective (barrier) method (ie, latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.
14. Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

15. Male subjects must agree to inform his physician if he has had unprotected sexual contact with a female who can become pregnant or if he thinks for any reason that his sexual partner may be pregnant.
16. Male subjects must agree not to donate semen or sperm while taking lenalidomide and/or carfilzomib and 28 days after the last Lenalidomide/Carfilzomib dose.
17. All study participants must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of Revlimid REMS®.
18. The ability to take aspirin or other appropriate VTE prophylaxis
19. Subjects must agree to adhere to all study requirements, including birth control measures and pregnancy testing, visit schedule, outpatient treatment, required concomitant medications, and laboratory monitoring

Exclusion Criteria:

Disease-related

1. Non-secretory or hyposecretory multiple myeloma, prior to initial treatment defined as <0.5 g/dL M-protein in serum, <200 mg/24 hr urine M-protein, or disease only measured by serum free light chain
2. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
3. Waldenström's macroglobulinemia or IgM myeloma
4. Radiotherapy to multiple sites or immunotherapy within 4 weeks before start of protocol treatment (localized radiotherapy to a single site at least 1 week before start is permissible)
5. Participation in an investigational therapeutic study for other reasons than symptomatic myeloma within 3 weeks or within 5 drug half-lives (t1/2) prior to first dose, whichever time is greater
6. Participation in another clinical trial unless approved by the Lead Principal Investigator

Concurrent Conditions

7. Pregnant or lactating females
8. History of allergy to mannitol
9. Major surgery within 3 weeks prior to first dose
10. Myocardial infarction within 6 months prior to enrollment, NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities

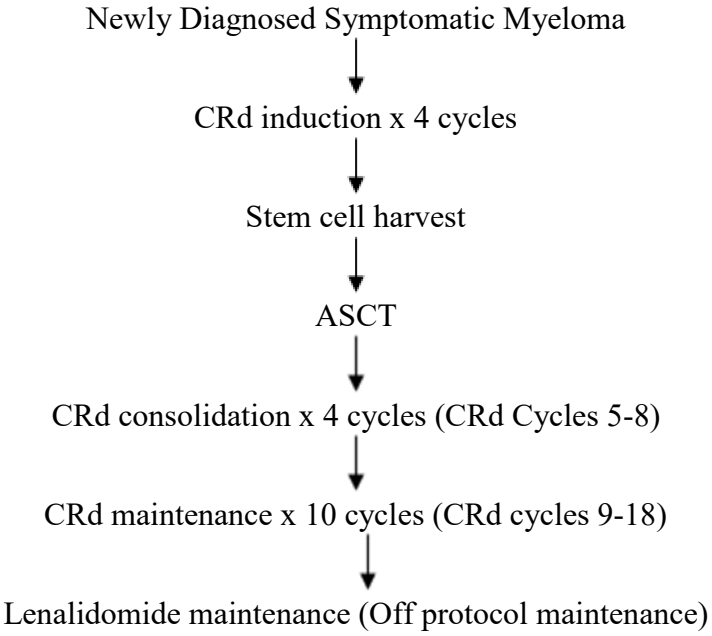
11. Uncontrolled hypertension or diabetes
12. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose
13. Known or suspected HIV infection, known HIV seropositivity
14. Active hepatitis A, B, or C infection
15. Non-hematologic malignancy within the past 3 years except a) adequately treated basal cell, squamous cell skin cancer, thyroid cancer, carcinoma in situ of the cervix, or prostate cancer < Gleason Grade 6 with stable prostate specific antigen levels or cancer considered cured by surgical resection alone
16. Any clinically significant medical disease or condition that, in the Treating Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
17. Significant neuropathy (Grades 3-4, or Grade 2 with pain) at the time of the first dose and/or within 14 days before enrollment
18. Contraindication to any of the required concomitant drugs, including proton-pump inhibitor (eg, lansoprazole), enteric-coated aspirin, allopurinol or if a history of prior thrombotic disease, warfarin or low molecular weight heparin
19. Subjects in whom the required program of PO and IV fluid hydration is contraindicated, eg, due to pre-existing pulmonary, cardiac, or renal impairment
20. Subjects with known or suspected amyloidosis of any organ
21. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis.
22. No coverage or not-acceptable by patient co-pay for Lenalidomide.

Study Treatment:

Subjects will receive carfilzomib, lenalidomide, and dexamethasone. All subjects are planned to receive 4 cycles of CRd induction. After completion of induction, all eligible patients will proceed to stem cells harvest followed by ASCT. Patients who recover from ASCT toxicities will resume protocol treatment starting at 70-90 days post stem cell infusion (not later than 120) in the consolidation and the maintenance portion of the protocol. No toxicities will be recorded from the ASCT period.

	An individual subject will be considered off-treatment following a 30-day safety follow-up period after the last cycle of CRd treatment. Subjects who have not progressed upon completion or discontinuation of the study will be followed for up to 5 years from the safety follow-up visit for disease progression or the start of a new treatment regimen.
Primary Endpoint:	To determine the rate of stringent CR (sCR) after 8 cycles of CRd (4 cycles of induction + ASCT + 4 cycles of CRd consolidation).
Secondary Endpoints:	Overall response rate defined as partial response or better ($\geq$PR) including the rate of VGPR or better ($\geq$VGPR) and near complete response or better (sCR/CR/nCR) across entire treatment in high risk and low risk patients Duration of response (DOR), Progression free survival (PFS), Time to progression (TTP), and Overall Survival (OS)
Exploratory Endpoints:	Determination of the rate of minimal residual disease in patients who achieved CR Prospective evaluation of candidate markers of response to CRd established in the completed CRd trial Evaluation of markers of response and duration of response to treatment strategy using CRd with or without transplant
Statistical Methods:	A total of 70 patients will be enrolled in a single-stage Phase II design. Patients who decline transplant for other reasons than toxicities will be replaced. It is anticipated that most will resume post-transplant CRd at the consolidation phase but those who do not, will not be replaced.

SCHEMA


Newly Diagnosed Symptomatic Myeloma
CRd induction x 4 cycles
Stem cell harvest
ASCT
CRd consolidation x 4 cycles (CRd Cycles 5-8)
CRd maintenance x 10 cycles (CRd cycles 9-18)
Lenalidomide maintenance (Off protocol maintenance)

CONFIDENTIALITY STATEMENT
This document contains confidential information. It is provided for the sole use of the Principal Investigator, Sub-investigators, Staff, Institutional Review Board or Independent Ethics Committee, and Regulatory Authorities. By accepting this document, you agree to maintain the information as confidential and to use it only for the purpose of conducting the study.

Open-label, Single-arm, Phase 2 Study of the Initial and Post-Transplant Treatment with Carfilzomib, Lenalidomide and Low dose Dexamethasone (CRd) in Transplant Candidates with Newly Diagnosed, Multiple Myeloma Requiring Systemic Chemotherapy

Protocol Acceptance Form

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complying with the obligations and requirements of clinical Investigators and all other requirements listed in 21 CFR part 312.

Investigator Signature Date

Print Investigator Name and Title Date

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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
ASCT	Autologous Stem Cell Transplant
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
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
MRD	minimum residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute

NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PCCC	Personal Cancer Care Consortium (of the University of Chicago)
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCC	Stem Cell Collection
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
UCM	University of Chicago Medicine
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood count

1 INTRODUCTION

1.1 MULTIPLE MYELOMA

Multiple myeloma is a clonal neoplastic proliferation of plasma cells affecting 19,900 US patients each year.[1] Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia and increased susceptibility to infections. The disease is systemic, and chemotherapy is indicated for management of symptomatic myeloma. Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide (Revlimid®) and their combinations with and without corticosteroids. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with autologous stem cell transplantation (ASCT). Although improvements in progression free survival and overall survival have occurred in the past 5 years, even with the best available approved agents, 10-30% of patients fail to respond to the primary therapy, and almost all subjects eventually relapse, with a median overall survival of 44.8 months.[2]

1.2 COMBINATIONS OF PROTEASOME INHIBITORS AND IMMUNOMODULATORY AGENTS

Proteasome inhibitors (bortezomib, carfilzomib) and immunomodulatory agents (thalidomide and lenalidomide) are both highly effective agents in multiple myeloma. Lenalidomide is an immunomodulatory derivative of thalidomide and has both immunomodulatory and anti-angiogenic properties which are considered to confer anti-tumor effects. Two pivotal randomized Phase 3 trials established that lenalidomide in combination with high-dose dexamethasone produced a significant improvement in overall response rate and time to tumor progression (TTP) vs. high-dose dexamethasone alone in relapsed multiple myeloma patients with up to 3 prior therapies.[3,4]

Preclinical studies show that lenalidomide sensitizes multiple myeloma to the proteasome inhibitor bortezomib, suggesting combination therapy may enhance clinical activity. The combination of a proteasome inhibitor and immunomodulatory agent is attractive, as the expected overlapping toxicities would be manageable. A Phase 1 dose-escalation study was conducted to determine the maximum tolerated dose (MTD) and activity of the bortezomib, lenalidomide, and dexamethasone

combination in subjects with heavily pre-treated relapsed and/or refractory multiple myeloma.[5] The MTD was established as lenalidomide 15 mg and bortezomib 1.0 mg/m^2 with 20 to 40 mg dexamethasone. In 36 evaluable subjects, the overall response rate (CR+PR+MR) was 58%, including 6% CR. Although the regimen is active, the requirement for dose reductions of both agents to achieve a tolerable combination may have resulted in suboptimal complete response rates.

A phase 2 study followed to evaluate the efficacy and safety of lenalidomide, bortezomib, dexamethasone (RVD) at the phase 1 MTD.[17] In 63 response-evaluable patients, the overall response rate (CR/nCR+VGPR+ PR+ MR) is currently 86%, including 24% CR/nCR and 67% CR/nCR/VGPR/PR. Response rates according to baseline cytogenetics, disease stage, and prior therapies showed no significant differences according to adverse risk. Toxicities were manageable, consisting primarily of grade (G) 1-2 myelosuppression. Attributable non-hematologic toxicities included deep vein thrombosis (two patients; attributed to lenalidomide), and two episodes of atrial fibrillation (G3) prompting Dex dose reduction. G3 polyneuropathy was reported in one pt attributed to bortezomib and leading to treatment discontinuation despite bortezomib dose reduction. Dose reductions were required for: lenalidomide (13 pts); bortezomib (9 pts) and dexamethasone (26 pts).

Lenalidomide and high-dose dexamethasone without a proteasome inhibitor has shown impressive activity in untreated disease. In a Phase 2 study of 34 subjects with newly diagnosed myeloma, subjects received lenalidomide (25 mg Days 1 to 21 of a 28-day cycle) and high-dose dexamethasone (40 mg Days 1 to 4, 9 to 12, and 17-20). The objective response rate was 91%, with 6% CR, 32% near CR plus VGPR, and 53% PR.[12] However, when this regimen was compared with a more conventional delivery of dexamethasone (40 mg Days 1, 8, 15, and 22) in a 445-subject study, the more intensive dexamethasone schedule was associated with significantly shorter overall survival relative to the less intensive regimen (1-year survival rates 86% vs. 96.5%, respectively).[13] The dexamethasone-intensive regimen was associated with higher incidences of thromboembolism, hyperglycemia, and higher incidences of Grades 3 and 4 toxicities overall. Clearly, better and safer combination regimens for newly diagnosed disease are warranted.

A recently completed phase 1/2 study of bortezomib in combination with lenalidomide and dexamethasone (RVD) in newly diagnosed subjects with multiple myeloma has yielded promising results.[9,10] Patients (N=66) received median 10 cycles of combination treatment and achieved 39% and 67% across all dose levels had achieved a CR or VGPR, and at MTD 57% and 74%, respectively. The regimen overall was well tolerated; however, dose reductions due to bortezomib were common and 80% of patients developed peripheral neuropathy.

In summary, the combination of proteasome inhibitors and immunomodulatory agents seems to be very active and well tolerated in patients with relapsed and/or refractory MM, including patients who have received prior lenalidomide, bortezomib, thalidomide, and SCT. Further investigations with combination therapy with these agents in newly diagnosed disease are warranted.

1.3 CARFILZOMIB BACKGROUND

Carfilzomib (PR-171) is a tetrapeptideketoepoxide-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.[11,12]

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 for five days with nine days rest[13] 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.[13] 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.[14,15] DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to related 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 achieveable 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.[11, 16] 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.[11,16]

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.[11]

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.[17] 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 patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m^2 dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m^2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were rechallenged with 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 patients enrolled in PX-171-002, 20 had MM.[17] Four MM patients achieved a partial response (PR), one of two at the 15 mg/m^2 dose, one of six at the 20 mg/m^2 dose, and two of five at the 27 mg/m^2 dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m^2 wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. 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 patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM. In both studies, patients 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 patients 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 increased 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 patients had Grade 1/2 neuropathy upon study entry[8].

The response rate in PX-171-003-A0 was 18% PR, 7% MR and 41% SD in these patients 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).[18]

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. Patients receive 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. The study completed enrollment of 266 patients 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.[17] An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients 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.[18] 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.[18]

In PX-171-004, a first cohort of patients received 20 mg/m2. The subset of patients (N=54) that had not seen bortezomib had an ORR of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR).[19, 20] 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 patients who have not previously been treated with bortezomib and, even in bortezomib-treated patients, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients 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 patients 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.

1.4 DOSE RATIONALE

Preliminary data suggest 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 is ongoing but appears to be 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 patients being treated for >10 cycles without cumulative toxicities.

By the end of 2009, 269 patients 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.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 min 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 min 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 min 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 pharmacologicaltarget of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD of carfilzomib has not been reached in the multiple myeloma (MM) setting, particularly when administered as a 30' infusion. 27mg/m2 of carfilzomib (bolus administration over 2-10') is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities.

A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib administered is ongoing and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m2 (bolus administration over 2-10'). A review of the tolerability of 36 mg/m2 carfilzomib in these patients 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/m2 carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m2 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 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 patients have been treated with carfilzomib given as a 30-minute infusion in order to potentially minimize C_{max}-related infusion events. The protocol was amended and does of 20/36 (20 mg/m2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m2 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 patients with advanced MM and advanced solid tumors; the lower doses were well tolerated. Preliminary tolerability information at this dose level (20/56 mg/m2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m2, dexamethasone was increased from 4mg/dose to 8mg with the 56mg/m2 doses in order to reduce fevers and hypotension. As of March 20, 2010, seven patients have received 20/56mg/m2 and are tolerating it. Patients with advanced, refractory MM being treated at 36mg/m2 and 45mg/m2 have shown very good tolerability (>6

months in some cases) with documented minimal and partial responses in these heavily pretreated patients. 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/m2 carfilzomib are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of carfilzomib in patients 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 patients with substantial renal impairment (CrCl< 30, including patients on dialysis) without dose adjustment.[21] 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.

1.5 LENALIDOMIDE BACKGROUND

Lenalidomide (Revlimid®) is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[22] In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.[22] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[23]

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[24] In addition, lenalidomide has direct activity against multiple

myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.[25]

Indications and Usage: Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

Adverse Events: Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

1.6 EXPERIENCE WITH CARFILZOMIB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE

PX-171-006 is an ongoing Phase 1b study in patients with relapsed multiple myeloma in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and dexamethasone. "Low-dose" dexamethasone 40 mg/day is given on Days 1, 8, 15, and 22 in all cases. Carfilzomib is administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide is administered PO on Days 1 through 21.

Enrollment has closed in this study, and no MTD was reached. The maximum per protocol doses of carfilzomib (27mg/m^2) with lenalidomide 25mg and low dose dexamethasone are being used.[26] After 8 patients tolerated these doses well, an additional 44 patients were enrolled in an

"expansion" cohort at this level, and this regimen is being taken into Phase III in study PX-171-009.

To date, 40 patients were treated in cohorts 1-6 and 44 in the cohort 6 expansion. 27/32 patients in cohorts 1–5 are evaluable for safety and 29/32 for response. Patients were heavily pre-treated; 72% received prior BTZ and 87.5% received prior LEN or thalidomide (Thal). 47% of patients were refractory to their last therapy (typically lenalidomide + high dose dexamethasone; > 84% of patients had a history of neuropathy with 67% BTZ- or Thal-related. No treatment emergent fatigue, neuropathy, or thrombotic events ≥ Grade (G) 3 were observed. Hematological AEs ≥G3 (thrombocytopenia [n=6], anemia [n=4], and neutropenia [n=6]) were reversible. 4 patients had drug-related SAEs as follows: transient G3 sinus bradycardia, G3 upper respiratory tract infection, febrile neutropenia, and G3 diarrhea + G3 urinary infection. ORR and CBR for the 29 evaluable patients are 59% and 72%, respectively. Response data is shown in the table below. Initial responses improved with continued therapy, (up to 18 cycles). Median duration of response has not been reached (median follow-up 5.2 months). No dose-limiting toxicities or deaths attributed to study treatment have been observed. Several patients have completed the study (in the lower dose cohorts) after 18 cycles and are continuing in an extension study. Updated efficacy data are presented in the following table:

	CRd: Cohorts 1–5 (CFZ: 15 to 20 mg/m2; LEN: 10 to 25 mg)		
Response	**Relapsed (n=16)**	**Refractory (n=13)**	**Overall (n=29)**
≥ CR/nCR	5 (31)	1 (8)	6 (21)
≥ VGPR	7 (44)	4 (31)	11 (38)
≥ PR	9 (56)	8 (62)	17 (59)
≥ MR	11 (67)	10 (77)	21 (72)

In the Investigator Initiated CRd study in newly diagnosed MM, the regimen was well tolerated in phase I portion of the study up to maximum planned dose (MPD) of carfilzomib 36 mg/m2, lenalidomide 25 mg and dexamethasone 40 mg without reaching MTD, and highly active with ≥PR 96%, ≥VGPR 70%, and 55% CR/nCR as best response for all dose levels.[27] Furthermore, the

lack of overlapping toxicity have allowed for the use of these agents at full doses and for extended periods and the study proceeded to Phase II at MPD and completed enrollment (total 53 patients). On both phase I and II, patients receive 8 initial 28-day cycles, with carfilzomib at 20 mg/m^2, 27 mg/m^2 (Phase I), and 36 mg/m^2 (Phase I and II, given IV on days 1, 2, 8, 9, 15, and 16, lenalidomide at 25 mg PO (days 1–21), and dexamethasone at 40/20 mg PO weekly (cycles 1–4/5-8). Patients achieving ≥PR could proceed to stem cell collection (SCC) and autologous stem cell transplant (ASCT) after 4 cycles. Per protocol design, ASCT candidates were offered the option to continue CRd treatment after SCC. After 8 cycles, pts received 28-day maintenance cycles of carfilzomib (days 1, 2 15, 16), lenalidomide days 1–21, and dexamethasone weekly at the doses tolerated at the end of 8 cycles. Responses are assessed by IMWG criteria with the addition of nCR. In the phase I, 4 patients were enrolled at carfilzomib 20 mg/m^2, 13 at carflizomib 27 mg/m^2 and 36 at CFZ 36 mg/m^2 (18 in Phase I and 18 in Phase II). Median age was 59 years (range 35-81; including 23 patients 65 or older), 74% were men, 60% ISS stage II/III, 33% of 49 with available data any of del 13 or hypodiploidy by metaphase, or t(4;14), t (14;16), del17 by FISH. As of cut-off date (June 30, 2011), 51 evaluable pts received a median of 8 cycles. Toxicity data (cycles 1-8) were available for 51 pt who have completed at least the first cycle. Hematologic toxicities were reversible and included Grade (G) 3/4 neutropenia in 10%, G3/4 thrombocytopenia in 10%, and G3/4 anemia in 9%. The most common non-hematologic toxicities (all grades) were hyperglycemia (76%), hypophosphatemia (61%), and infection (53 %). G3/4 non-hematologic AEs included DVT/PE while on ASA prophylaxis (10%), mood alteration (2%) and glucose elevations (24%); the last 2 AEs were related to Dexamethasone. Peripheral neuropathy was limited to G1/2 sensory (24%) Forty-five pts continue treatment (2 proceeded to transplant, 1 discontinued for toxicities, 3 for events not related to treatment or per pt wish), and 22 pts continue on treatment in the maintenance phase. The majority of pts did not require any dose modifications, neither in the initial nor in the maintenance phase (31% and 25%, respectively). Responses were rapid with 42 of 49 pts achieving at least PR after 1 cycle. After a median of 8 cycles for all pts (range 1–20), the best response rates per IMWG criteria in 49 evaluable pts who completed at least 1 cycle are shown in Table. Response rates improved with the duration of treatment and reached PR 100%, ≥VGPR 100%, and CR/nCR 79%. Responses were deep even at lowest dose levels with the majority of pts at level 3 still early in treatment. Responses by ISS stage or cytogenetic status were similar in specific subgroups to overall response results. 24 patients proceeded to stem cell

collection after a median of 5 cycles of CRd (range 4-9), using growth factors only in 23 patients and cyclophosphamide and growth factors in 1 pt, with a median 6.55 x 10^6 CD34+ cells/kg collected (range 3.75-9.6); all resumed CRd treatment. After a median of 9.5 months of follow-up, only 1 evaluable patient has progressed, and all are alive. More recent analysis, showed continued improvement of the depth of response with the duration of treatment (median 13 months) and an unprecedented rate of stringent responses (sCR) which at the completion of 8 cycles reached 43% [28]

	ORR (%)	CR/nCR (%)	VGPR(%)
Tx cycles			
1+ (n=49)	94	53	65
4+ (n=35)	100	71	89
8+ (n=28)	100	75	89
12+ (n=19)	100	79	100
CFZ dose, mg/m^2			
20 (n=4)	100	75	100
27 (n=13)	100	85	100
36 (n=32)	91	38	47
ISS stage			
I (n=20)	90	50	65
II (n=16)	94	44	56
III (n=13)	100	69	77
Cytogenetics n=49			
Normal/favorable (n=33)	91	52	61
Unfavorable (n=16)	100	56	75

It was concluded that CRd is highly active and well tolerated allowing the use of full doses for an extended time in patients with newly-diagnosed MM with limited need for dose modification. Responses are rapid and improve over time reaching 100% ≥VGPR. Efficacy results were comparable across ISS stage and cytogenetic status and early time-to-event data are very encouraging. This study is the first to report the frontline treatment of myeloma with CRd to date, and provides additional support for the ongoing phase 3 ASPIRE trial of CRd vs. Rd in patients with relapsed and/or refractory MM.[29]

Together, these results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in combination are active and well tolerated and that there are no significant overlapping

toxicities (in the dose ranges tested). Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with carfilzomib, suggesting that carfilzomib will combine well with other anti-cancer agents.

1.7 STUDY RATIONALE

Considering that autologous stem cell transplant (ASCT) improves the depth of response of even the most active regimens and that post ASCT consolidation further improves this effect,[3,4], the current study will investigate whether a combination of initial treatment with 4 cycles of CRd (pre-ASCT induction) followed by ASCT followed by 4 cycles of CRd consolidation improves the rate of sCR compared to the historical rate of sCR determined in the recently completed frontline CRd study with delayed transplant, with comparisons made at the completion of the equivalent duration of treatment without transplant, i.e. after 8 cycles of CRd without transplant.[28,30] In addition, the study design will provide an estimate of an impact of ASCT on an overall response, DOR, PFS, and OS in comparison to treatment with CRd induction and CRd maintenance of similar patient population but without transplant. Therefore, this study's results help to answer whether or not we can build upon the already established high activity of the CRd regimen adding of the most active treatment in myeloma, i.e. high dose of melphalan and ASCT to the CRd treatment strategy and further improve sCR rate.

The CRd combination shows very high activity without transplant in new myeloma (100% PR rate, up to 82% VGPR, and 67% CR/nCR rate)[1] and is well tolerated in both new myeloma[1] as well is in relapsed myeloma.[2] At the completion of 8 cycles of CRd, 67% of patients achieved nCR/CR and 43% sCR. While the role of autologous stem cell transplant (ASCT) in the era of novel active therapies is currently being evaluated, ASCT remains a standard of care for transplant candidates and still commonly used. Initial therapy with active novel regimens (ie RVD, RVDD, VDT) followed by autotransplant produced excellent post-ASCT response rates with evidence that transplant improves further pre-transplant level of disease cytoerduction.[3,4] We hypothesized that given the superior activity seen in the CRd combination, this combination will likely improve the depth of response achieved with other regimens prior to transplant, and therefore subsequently at 3 months post-ASCT. Using similar strategy, pre-ASCT and at 3 months post-ASCT patients initially treated with VDT achieved 31% and 52% nCR/CR, respectively (sCR not reported).[31]

Since at least VGPR (including CR/nCR) prior to ASCT and post-ASCT improves progression free survival and overall survival,[5,6] we will use information gained from this study to evaluate if ASCT incorporated into the CRd treatment is a better treatment strategy for initial therapy of patients starting treatment with CRd than an extended treatment with CRd without transplant. Therefore, this study can influence the design of future randomized studies with CRd as initial treatment of newly diagnosed myeloma. The study population for the current protocol, i.e. newly diagnosed multiple myeloma subjects, is expected to have similar characteristics as the study population enrolled in the recently completed CRd study and is expected to tolerate therapy very well, based on our frontline CRd experience, as detailed in Section 1.5 above. Since we established tolerable CRd doses in the recently completed frontline CRd trial, there is no need for Phase 1b study. This study will allow for an assessment of the role of ASCT for patients initially induced with CRd as the results from this study could be compared to the results from the recently completed clinical trial in which all patients, including ASCT candidates continue CRd treatment with a deferred transplant for later. The current standard of care for patients who completed ASCT is lenalidomide maintenance based on the results of 2 randomized studies, which showed superior PFS versus placebo for all patient groups including patient in CR post ASCT (Attal et al ASH 2010, McCarthy et al. ASH 2010), and superior OS (McCarthy et al., IMW 2011). But there is also evidence of benefit of bortezomib-based consolidation (Cavo et al, ASH 2010 and ASH 2011) and maintenance with proteasome inhibitor (bortezomib, the first approved proteasome inhibitor; Sonnefeld et al, ASH 2011) and appearance of superior maintenance when both IMiD and bortezomib are combined (Palumbo et al, ASH 2010, Mateos et al, Lancet Oncology 2011). Based on excellent tolerance of CRd for extended periods of time in the recently completed frontline CRd study (Jakubowiak et al, ASH 2011) we hypothesized that a course of post-ASCT CRd consolidation and CRd maintenance will improve depth of response and progression-free survival in post transplant setting compared to post-ASCT lenalidomide alone. Therefore, PFS from this study—which is one of the study secondary endpoints—will provide an estimate whether this strategy is superior to the initial therapy with any regimen followed by transplant followed by lenalidomide maintenance reported earlier (Attal et al ASH 2010, McCarthy et al. ASH 2010), therefore further enhancing our ability to design future randomized studies with CRd in transplant candidates.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine the rate of stringent CR (sCR) after 8 cycles of CRd (4 cycles of induction + ASCT + 4 cycles of CRd consolidation).

2.2 SECONDARY OBJECTIVES

Secondary objectives include characterization of additional efficacy variables:

- Overall response rate defined as partial response or better (≥PR) including the rate of VGPR or better (≥VGPR) and near complete response or better (sCR/CR/nCR) across entire treatment in high risk and low risk patients
- Duration of response (DOR), Progression free survival (PFS), Time to progression (TTP), and Overall Survival (OS)

2.3 EXPLORATORY OBJECTIVES

Exploratory objective include characterization of following variables:

- To determine the rate of minimal residual disease by multiparameter-flow cytometry in patients who achieved CR after 4 cycles, transplant, 8 cycles and end of treatment
- Evaluation of MRD by gene sequencing method using the Sequenta platform (LymphoSIGHT®) in parallel with multi-parameter flow cytometry (MFC)
- Prospective evaluation of candidate markers of response to CRd established in the completed CRd trial
- Evaluation of markers of response and duration of response to treatment strategy using CRd with or without transplant

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This study is a multi-center, open-label, Phase 2 study in which transplant candidates with newly diagnosed MM requiring systemic chemotherapy will receive induction treatment with

carfilzomib, lenalidomide, and dexamethasone and post autologous stem cell transplant CRd consolidation/maintenance therapy.

The study will determine the efficacy of the treatment strategy. The primary endpoint is to determine the response rate (sCR) after completion of a total of 8 cycles of CRd (4 cycles of CRd induction followed by ASCT followed by 4 cycles of CRd consolidation). Definitions of these primary endpoints plus a list of secondary endpoints are given in Section 2.1. Protocol treatment (CRd) will last for a total of 18 cycles (4 cycles prior to ASCT + 4 cycles post ASCT consolidation + 10 cycles of maintenance).

This study will enroll 70 patients in the pre-ASCT induction portion of the study and anticipate that most of these will resume protocol treatment at the consolidation/maintenance therapy post ASCT. Patients who complete the CRd induction but who become not eligible for ASCT can be considered to continue protocol treatment after discussion with the Lead Principal Investigator with an additional 4 cycles of CRd as in consolidation regimen followed by 10 cycles of CRd maintenance as in CRd maintenance regimen. Patients who decline transplant for reasons other than toxicities will be replaced. After completion of CRd treatment, it will be recommended that patients continue single-agent lenalidomide maintenance therapy off protocol at the last tolerated dose of lenalidomide, provided the dose is tolerated and there is no evidence of progressive disease.

Carfilzomib will be administered at 20 mg/m^2 as an IV infusion on Days 1 and 2 of Cycle 1 followed by 36 mg/m^2 as an IV infusion on Days 8, 9, 15, and 16 for the remainder of Cycle 1 and on Days 1, 2, 8, 9, 15, 16 of a 28-day cycle for the remaining Cycles 2-4 (Cycles 1- 4 represent induction) and at dose last tolerated prior to ASCT on Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle for Cycles 5-8 (CRd consolidation). During CRd maintenance (Cycles 9-18), carfilzomib will be administered at the last tolerated dose as an IV infusion on Days 1, 2, 15, and 16 of a 28-day cycle. Lenalidomide will be administered PO daily at 25 mg on Days 1-21 of the 28 day cycle for pre-ASCT induction Cycles 1-4 (induction) and at the last tolerated dose prior to ASCT on Days 1-21 of the 28 day cycle for Cycles 5-8 (CRd consolidation) and Cycles 9-18 (CRd maintenance). The first cycle of consolidation post-transplant must start at a lenalidomide dose no higher than 15 mg. In discussion with the Lead Principal Investigator and on a case-by-case basis, provisions may be made to start CRd consolidation with a lower than 15 mg dose of lenalidomide for participants

with inadequate hematologic parameters at 70-90 days following stem cell reinfusion (not later than 120) and/or to escalate lenalidomide dose up to 25 mg per dose after completion of 1 cycle of CRd consolidation for participants with adequate hematologic parameters. Patients that do not complete ASCT but continue on CRd maintenance will follow the same CRd consolidation treatment for 4 cycles followed by 10 cycles of CRd maintenance.

Dexamethasone will be administered PO or IV between 30 minutes and 4 hours preceding carfilzomib infusion as follows:

- Cycles 1-4 (induction): 40 mg per dose on Days 1, 8, 15, and 22
- Cycles 5-8 (CRd consolidation): 20 mg (or last tolerated dose) per dose on days 1, 8, 15, and 22
- Cycles 9-18 (CRd maintenance): 20 mg (or last tolerated dose) on days 1, 8, 15 and 22

Individual subjects should receive 4 cycles of pre-ASCT CRd induction treatment. After cycle 4, subjects will proceed to stem cell harvest with the use of growth factors or as per current standards of care as described in section 6.4. Patients who achieve confirmed CR/nCR prior to completion of 4 cycles of CRd can proceed to stem cell collection (SCC) earlier but then resume treatment for a total of 4 induction CRd cycles. Patients who achieve less than optimal response (≤PR) may be eligible to receive up to two more cycles of induction CRd prior to transplant after approval from the Lead Principle Investigator. The number of post-transplant consolidation cycles will be adjusted accordingly so that the total number of cycles (induction + consolidation) remains at 8.

3.2 NUMBER OF CENTERS

A total of 5 MMRC centers will participate in this study.

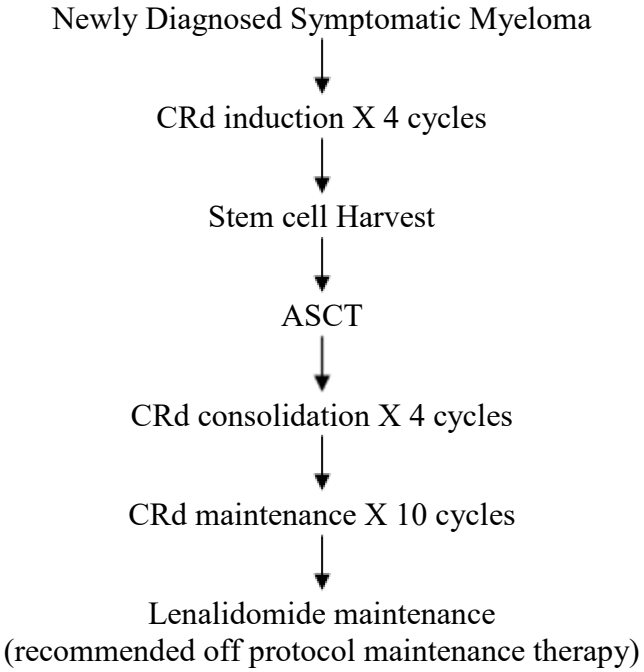
3.3 NUMBER OF SUBJECTS

This study will enroll 70 patients in the induction portion of the study. Those who do not have ASCT will be replaced.

3.4 ESTIMATED STUDY DURATION

The total study enrollment period is expected to be 18-24 months. A subject is considered to have completed the treatment phase of the study 4 weeks (28 days) after the end of the last treatment cycle. Excluding long-term follow-up, the treatment phase of the study will be completed once the last subject completes the 28-day safety follow-up visit (30 days for resolution of toxicity). Subjects who have not progressed will be followed for progression for up to 5 years from the completion of the safety follow-up visit. All subjects will be followed for survival and development of new cancers at least every 3 months for 5 years.

3.5 TREATMENT SCHEMA



3.6 INCLUSION CRITERIA

Disease-related:

1. Newly diagnosed, myeloma requiring systemic chemotherapy as per IMWG uniform criteria (see Appendix B):
   - Prior treatment of hypercalcemia or spinal cord compression or active and/or aggressively progressing myeloma with corticosteroids or lenalidomide or bortezomib-

based regimens does not disqualify the patient (the treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period or not more than 1 cycle)

- Bisphosphonates are permitted

2. Suitable and interested to proceed to ASCT. (Refer to section 6.4)
3. Measurable disease, prior to initial treatment as indicated by one or more of the following:
   - Serum M-protein ≥ 0.5 g/dL
   - Urine M-protein ≥ 200 mg/24 hours
   - If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative immunoglobulin levels are acceptable

Demographic:

4. Males and females ≥ 18 years of age
5. Life expectancy of more than 3 months
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix C)

Laboratory

7. Adequate hepatic function, with bilirubin < 1.5 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times ULN
8. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L, hemoglobin ≥ 8 g/dL, platelet count ≥ 75 x 10^9/L. Screening platelet count should be independent of platelet transfusions for at least 2 weeks.
9. Calculated or measured creatinine clearance of ≥ 50 mL/minute, calculated using the following formula of Cockcroft and Gault:

   $$\frac{(140 - \text{age}) \times \text{mass (kg)}}{72 \times \text{creatinine (mg/dL)}} \times 0.85 \text{ (if female)}$$

   Or creatinine below 2 g/dl

Ethical/Other

10. Written informed consent in accordance with federal, local, and institutional guidelines
11. Females of childbearing potential (FCBP) [defined as sexually mature females who: 1) have not undergone a hysterectomy or bilateral oophorectomy; or 2) have not been

naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months)] must agree to ongoing pregnancy testing.

12. FCBP must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to initiating lenalidomide. The first pregnancy test must be performed within 10-14 days before Day 1 Cycle 1 and the second pregnancy test must be performed within 24 hours of Day 1 Cycle 1. The subject may not receive lenalidomide until the Treating Investigator has verified that the results of these pregnancy tests are negative, and must agree to ongoing pregnancy tests as outlined in the protocol. *For patients already on Revlimid, continuation of current testing schedule is permitted as long as it is not interrupted during the transition to CRd therapy.*
13. FCBP must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The 2 methods of reliable contraception must include a highly effective method (ie, intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and an additional effective (barrier) method (ie, latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.
14. Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
15. Male subjects must agree to inform his physician if he has had unprotected sexual contact with a female who can become pregnant or if he thinks for any reason that his sexual partner may be pregnant.
16. Male subjects must agree not to donate semen or sperm while taking lenalidomide and/or carfilzomib and 28 days after the last Lenalidomide/Carfilzomib dose.
17. All study participants enrolled in the United States must be registered into the mandatory REVLIMID Rems ® program and be willing and able to comply with the requirements of REVLIMID Rems®.
18. The ability to take aspirin or other appropriate VTE prophylaxis

19. Subjects must agree to adhere to all study requirements, including birth control measures and pregnancy testing, visit schedule, outpatient treatment, required concomitant medications, and laboratory monitoring.

3.7 EXCLUSION CRITERIA

Disease-related

1. Non-secretory or hyposecretory multiple myeloma, prior to initial treatment defined as <0.5 g/dL M-protein in serum, <200 mg/24 hr urine M-protein, or disease only measured by serum free light chain
2. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
3. Waldenström's macroglobulinemia or IgM myeloma
4. Radiotherapy to multiple sites or immunotherapy within 4 weeks before start of protocol treatment (localized radiotherapy to a single site at least 1 week before start is permissible)
5. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives (t1/2) prior to first dose, whichever time is greater
6. Participation in another clinical trial unless approved by the Lead Principal Investigator

Concurrent Conditions

7. Pregnant or lactating females
8. History of allergy to mannitol
9. Major surgery within 3 weeks prior to first dose
10. Myocardial infarction within 6 months prior to enrollment, NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities
11. Uncontrolled hypertension or diabetes
12. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose
13. Known or suspected HIV infection, known HIV seropositivity
14. Active hepatitis A, B, or C infection

15. Non-hematologic malignancy within the past 3 years except a) adequately treated basal cell, squamous cell skin cancer, thyroid cancer, carcinoma in situ of the cervix, or prostate cancer < Gleason Grade 6 with stable prostate specific antigen levels or cancer considered cured by surgical resection alone
16. Any clinically significant medical disease or condition that, in the Treating Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
17. Significant neuropathy (Grades 3-4, or Grade 2 with pain) at the time of the first dose and/or within 14 days before enrollment
18. Contraindication to any of the required concomitant drugs, including proton-pump inhibitor (eg, lansoprazole), enteric-coated aspirin, allopurinol or if a history of prior thrombotic disease, warfarin or low molecular weight heparin
19. Subjects in whom the required program of PO and IV fluid hydration is contraindicated, eg, due to pre-existing pulmonary, cardiac, or renal impairment
20. Subjects with known or suspected amyloidosis of any organ
21. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis.
22. For subjects enrolled in the United States, no coverage or not-acceptable by patient co-pay for Lenalidomide.

4 SUBJECT ENROLLMENT

4.1 PATIENT ENROLLMENT AND REGISTRATION

Patient registration for this trial will be centrally managed by the designated University of Chicago Clinical Research Associate (CRA). A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the University of Chicago.

It is the responsibility of the site Treating Investigator to determine patient eligibility prior to submitting a patient registration request to the lead site. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent source documents will be submitted by the requesting site to the University of Chicago CRA, either by fax or by email between the hours of 9 am and 5 pm CST.

The University of Chicago CRA, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the CRA of a potential registration by 5 p.m. Central Time at least 72 hours prior to the anticipated Cycle 1 Day 1. Same day registrations cannot be guaranteed.

Subsequently, an email will be sent by the University of Chicago CRA to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed eligibility worksheet signed and dated by the registrar, will be faxed back to the requesting site registrar.

Following completion of the induction therapy, patients proceeding to ASCT will be considered "off study." Prior to beginning consolidation, subjects must meet treatment parameters including ANC $\geq 1.0 \times 10^9$/L, Platelet count $\geq 50 \times 10^9$/L, serum uric acid and creatinine levels returned to baseline and resolution of all transplant-related toxicities (Section 5.3).

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5 TREATMENT

5.1 GENERAL PROCEDURES

Individual Subject Treatment

After screening, eligibility determination, and enrollment, subjects will receive carfilzomib, lenalidomide, and dexamethasone. All subjects are planned to receive 4 cycles of CRd induction. Patients who achieve confirmed CR/nCR prior to completion of 4 cycles can proceed to SCC earlier but then resume treatment for a total of 4 induction cycles. After completion of induction, all patients will proceed to stem cells harvest followed by ASCT.

Following ASCT (3 months post-AST; 70-90 days but not more than 120), subjects will continue with CRd consolidation (cycles 5-8). Of note, 30 days following the last dose of CRd, (i.e. Cycle 4 Day 22), or at the start of stem cell collection (whichever occurs first), and during ASCT period, patients will be considered to be off-study so no toxicities will be recorded for this period unless

considered directly related to treatment with CRd. The CRd maintenance phase will commence at the start of cycle 9 and continue through cycle 18.

For patients enrolled into CRd induction, consolidation, and maintenance the protocol treatment will last for a total of 18 cycles (4 cycles prior to ASCT + 4 cycles post ASCT consolidation + 10 cycles of CRd maintenance). After completion of CRd treatment, patients will then move to a recommended single-agent lenalidomide maintenance therapy off protocol, as long as it is tolerated and there is no evidence of progressive disease.

An individual subject will be considered off-treatment following a 30-day safety follow-up period after the last CRd cycle of treatment. Subjects who have not progressed upon completion or discontinuation of the study will be followed for up to 5 years from the safety follow-up visit for disease progression. All subjects will be followed for survival and development of new cancers at least every 3 months.

5.2 DRUG ADMINISTRATION

5.2.1 PRETREATMENT PREPARATION

Two days before Day 1 of Cycle 1, the following **required** concomitant medication should be started:

- **Oral hydration** 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) and before each dose of carfilzomib. Compliance must be assessed before initiating treatment; treatment is to be delayed if PO hydration is not adequate.

The following required treatments will be started on Cycle 1 Day 1 or up to 24 hours prior to Cycle 1 Day 1:

- **Valacyclovir** 500 mg PO QD or equivalent HZV prophylaxis, continuing for the duration of treatment. Additional prophylaxis is at the Treating Investigator's discretion.
- **Aspirin** (enteric-coated) 325 mg PO QD for the duration of treatment. (Subjects with known high thrombotic risk, eg, prior thrombosis, DVT, etc) should receive full anticoagulation at the Treating Investigator's discretion.)

The following may be given at Treating Investigator’s discretion

- **Lansoprazole** (Prevacid) 15 mg PO QD, or other PO proton-pump inhibitor or H1 blocker to prevent peptic disease for the duration of treatment
- **Mycostatin** or Nystatinto prevent oral thrush

Serum chemistries and hematology must be obtained and reviewed prior to carfilzomib dosing on Days 1, 8, 15 during Cycle 1-8 and on Days 1 and 15 of Cycles 9-18. Clinically significant electrolyte abnormalities (ie, ≥ Grade 2) should be corrected before carfilzomib dosing. Serum chemistries on Day 2, 9, 16 are optional if Tumor Lysis Syndrome is suspected or at the discretion of the treating investigator.

- **On Day 1:**
    - Dexamethasone (IV or PO) is given between 30 minutes and 4 hours before carfilzomib.
    - IV hydration will be given immediately before each carfilzomib dose during Cycle 1. This will consist of 125 to 500 mL normal saline or other appropriate IV fluid. If LDH or uric acid is elevated (and/or in subjects considered still at risk for tumor lysis syndrome) 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 (comparable to fluid intake). Subjects should be monitored closely during this period for evidence of fluid overload and diuretics should be used if patients have positive fluid balance of more than 1litre or weight gain of more than 1 kg.
    - Subjects should have a dedicated line for carfilzomib administration. Before and after administration, the line must be flushed with 20 mL of normal saline. If a dedicated line is not possible, the existing line must be flushed with a minimum of 20 mL of normal saline before and after drug administration.

5.2.2 DEXAMETHASONE

Dexamethasone will be administered between 30 minutes and 4 hours preceding the carfilzomib (on days that they coincide), as follows:

• Cycles 1 – 4 (induction): 40 mg PO or IV per dose Days 1, 8, 15 and 22

• Cycles 5 – 8 (consolidation): 20 mg (or last tolerated dose) PO or IV per dose Days 1, 8, 15 and 22

• Cycles 9 – 18 (maintenance): 20 mg (or last tolerated dose) PO or IV per dose Days 1, 8, 15 and 22

During Cycle 1, dexamethasone may administered as a split schedule PO or IV pre-Carfilzomib on days 1, 2, 8, 9, 15, 16 as well as Day 22, 23 in patients with high tumor burden or risk for cytokine release syndrome. This means that a patient assigned 40mg dexamethasone on days 1, 8, 15, 22 may receive 20 mg on days 1,2, 8, 9, 15, 16, 22, 23 (20/20) or 36 mg on Day 1, 8, 15, 22 and 4 mg on Days 2, 9, 16, 23 (36/4). It is recommended that patients should return to one dose of 40mg/week in Cycle 2+ however a split schedule may be implemented after discussion with the Lead Principle Investigator.

Dexamethasone given on days without carfilzomib (on Days 22 of Cycles 1-8) may be self-administered by the subject on an outpatient basis.

Missed doses of dexamethasone will not be made up. Procedures for dose reductions and delays are summarized in Section 5.4 (Table 5.3)

5.2.3 CARFILZOMIB

Carfilzomib will be administered after dexamethasone as follows:

- Cycle 1 Days 1 and 2: 20 mg/m^2 IV over 10 minutes but may be administered over 30 minutes according to institutional guidelines
    - For patients at high risk for Tumor Lysis Syndrome, step-up dosing to 27 mg/m^2 on Day 8, 9 and to 36 mg/m^2 on Days 15, 16 may be used.
- Induction Cycles 1-4 (starting with Cycle 1 Day 8) 36 mg/m^2 IV as a 30 minute infusion Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle
- CRd Consolidation Cycles 5-8: Last tolerated dose prior to ASCT as IV infusion Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle

- CRd Maintenance Cycles 9-18: Last tolerated dose as IV infusion Days 1, 2, 15, and 16 of a 28-day cycle

The dose will be calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. For weight changes >10%, carfilzomib dose should be recalculated.

Carfilzomib for Injection will be given as an IV infusion. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic for at least 1 hour following each dose of carfilzomib for clinical observation during each dose in Cycle 1 and for Day 1 of Cycle 2.

Doses of carfilzomib may be rescheduled by up to 2 days, In the event that there is a one day break in between Carfilzomib dosing (i.e. Carfilzomib administered on Day 1 and 3, for example, due to a holiday) then 4mg of dexamethasone should be administered prior to the second day of dosing. Anticipated delays of carfilzomib dosing should be discussed with the Lead Principal Investigator. Missed doses will not be replaced during a cycle.

Procedures for carfilzomib dose reductions and delays are summarized in Section 5.4, along with the criteria that must be met for re-treatment with study drug.

Carfilzomib for Injection is supplied both as a lyophilized parenteral product in single-use vials; the lyophilized product is supplied in 25-mg and 60-mg vials. Prior to use, the lyophilized product is reconstituted with Water for Injection. See Section 10.1 for details on carfilzomib description, formulation, preparation, storage, and accountability.

5.2.4 LENALIDOMIDE

Subjects will receive lenalidomide as follows:

- Induction Cycles 1-4: Lenalidomide 25 mg PO once daily on Days 1-21 of each 28-day cycle.
- CRd Consolidation Cycles 5-8 and CRd maintenance Cycles 9-18: Last tolerated dose prior to ASCT on Days 1-21 of each 28-day cycle. The first cycle of consolidation, Cycle 5, must start at last tolerated dose prior to ASCT but not higher than 15 mg per dose.

In discussion with the Lead Principal Investigator and on a case-by-case basis, provisions may be made to start at a lower than 15 mg dose of lenalidomide for participants with inadequate hematologic parameters following ASCT. The dose of lenalidomide should be re-escalated up to 25 mg per dose (or best tolerated dose prior to transplant) after completion of 1 cycle of CRd consolidation for participants with adequate hematologic parameters. On days coinciding with carfilzomib administration, lenalidomide should be taken at least 4 hours after the carfilzomib dose and may be self-administered at home by the subject. On days on which carfilzomib is not administered, lenalidomide should be taken at approximately the same time each day. Missed doses of lenalidomide will not be made up. Subjects should be instructed to never take lenalidomide past Day 21 of each cycle.

Lenalidomide is taken with water on a full or empty stomach. Subjects should not break, chew or open capsules. Late doses of lenalidomide should if possible be taken on the assigned day but should not be made up the next day. Vomited doses will not be made up.

No intra-subject dose escalation of lenalidomide will be permitted.

For all subjects enrolled in the United States, Lenalidomide (Revlimid®) will be used as commercial drug covered by patients insurance in accordance with the Revlimid REMS® program of Celgene Corporation. In accordance with Revlimid REMS® requirements, all participating investigators and subjects must be registered in and must comply with all requirements of the program. Prescriptions must be filled within 7 days and will only be filled for one cycle at a time, for 21 days of treatment. All subjects and investigators must comply with lenalidomide prescribing requirements.

Procedures for dose reductions and delays are summarized in Section 5.4. Information on lenalidomide description, formulation, storage, and accountability may be found in Section 10.2.

5.2.5 TREATMENT COMPLIANCE

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

5.3 INSTRUCTIONS FOR INITIATION OF A NEW CYCLE

NOTE: to initiate consolidation therapy following ASCT, the patient must be recovered from all transplant-related toxicities as well as meet the treatment parameters described below:

The following guidelines refer to a new course of treatment following cycle 1 induction or after the first consolidation cycle. Patients who do not proceed to ASCT and continue on CRd therapy may proceed as noted below.

A new course of treatment may begin on the scheduled Day 1 of a new cycle if all of the following are met:

• ANC $\geq 1.0 \times 10^9$/L

• Platelet count $\geq 50 \times 10^9$/L, unless attributed to myeloma involvement of > 50% in the bone marrow, in which case platelets must be $> 30 \times 10^9$/L to initiate the next cycle

• Any other study drug-related adverse event must have resolved to grades as specified in protocol (see Section 5.4)

• Serum uric acid and creatinine levels must return to baseline prior to carfilzomib doses during Cycles 1 and 2

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly, and a new treatment cycle will not be initiated until the toxicity has resolved, as described above.

If either lenalidomide or carfilzomib are held for the remainder of the previous cycle or the new cycle is delayed due to residual toxicity on the planned Day 1 of the next cycle, then the new cycle will be started at 1 dose decrement. (see Section 5.4)

5.4 DOSE MODIFICATION GUIDELINES

The following sections and tables summarize dosing modifications of carfilzomib, lenalidomide, and dexamethasone to manage possible toxicity. Dose modifications different from those stated in the protocol should be discussed with the Lead Principal Investigator. Administration of

carfilzomib and lenalidomide will be discontinued in the event of any other toxicity that, in the opinion of the Lead or Treating Investigator, warrants discontinuation.

Dose reduction levels of carfilzomib and lenalidomide for toxicity management of individual subjects are provided below:

Table 5-1. Dose Reductions for Carfilzomib

Nominal Carfilzomib Dose	Reduced Carfilzomib Doses			
	Dose -1	Dose -2	Dose -3	Dose -4
36 mg/m^2	27 mg/m^2	20 mg/m^2	15 mg/m^2	11 mg/m^2

Table 5-2. Dose Reductions for Lenalidomide

Nominal Lenalidomide Dose	Reduced Lenalidomide Doses			
	Dose -1	Dose -2	Dose -3	Dose -4
25 mg	20 mg	15 mg	10 mg	5 mg

In addition to dose reductions, administration of carfilzomib and lenalidomide will be held temporarily in the event of a treatment-related toxicity at the Treating Investigator's discretion. Study treatment may be reintroduced if resolution of the event to the baseline value or to ≤ Grade 1 within 21 days; otherwise study drug will be permanently discontinued, unless approved by the Lead Principal Investigator.

Two dose reduction levels of dexamethasone are defined for the 2 protocol-stipulated dose levels (40 mg for Cycles 1-4 and 20 mg for Cycles 5-18), as illustrated in Table 5-3. Dexamethasone delay should be performed as clinically indicated at the discretion of the treating investigator however the dexamethasone dose must be administered as part of the premedication for carfilzomib on Days 1, 8, 15.Refer to section 5.5.2 for further guidance on dexamethasone administration.

Table 5-3. Dose Reductions for Dexamethasone

Nominal Dexamethasone Dose	Reduced Dexamethasone Doses			
	Dose -1	Dose -2	Dose -3	Dose -4

40 mg	30 mg	20 mg	15 mg	10 mg
20 mg	15 mg	10 mg	N/A	N/A

5.4.1 HEMATOLOGIC TOXICITY

Guidelines for the management of hematologic toxicities (thrombocytopenia and neutropenia) are summarized in Table 5-4.

5.4.2 NON-HEMATOLOGIC TOXICITY

Guidelines for the management of non-hematologic toxicities are summarized in Table 5-5.

Table 5-4. Dose Reduction Guidelines for Hematologic Toxicity

***Thrombocytopenia*[1]**

	Recommended Action	
When Platelets:	**Lenalidomide**	**Carfilzomib**
Fall to < 30 x 10^9/L	Hold lenalidomide, follow CBC weekly. Hold prophylactic ant-coagulation until platelets return to 30 x 10^9/L	Hold carfilzomib, follow CBC weekly. Hold prophylactic anti-coagulation until platelets return to 30 x 10^9/L
Return to ≥ 30 x 10^9/L	Resume lenalidomide at full dose	Resume carfilzomib at full dose.
Subsequently drop to < 30 x 10^9/L	Hold lenalidomide and follow CBC weekly	Hold carfilzomib and follow CBC weekly
Return to ≥ 30 x 10^9/L	Resume lenalidomide at 1 dose decrement	Resume carfilzomib at one dose decrement if cyclical thrombocytopenia is still below levels considered safe by the Treating Investigator at one dose decrement (i.e., dose decrease only if Treating Investigator judgment is that Carfilzomib contributed to thrombocytopenia)

[1]Platelet transfusions should also be considered for the management of thrombocytopenia as clinically indicated

Neutropenia

	Recommended Action	
When ANC	**Lenalidomide**	**Carfilzomib**
Falls to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold lenalidomide, add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly	Hold carfilzomib, add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly

Returns to 1.0 x 10^9/L (if neutropenia was the only toxicity noted)	Resume lenalidomide at full dose	Resume carfilzomib at full dose
Return to 1.0 x 10^9/L (if other toxicity noted)	Resume lenalidomide at 1 dose decrement	Resume carfilzomib at full dose unless marked cyclical thrombocytopenia is present, then reduce by 1 dose decrement
Subsequently drops to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold lenalidomide treatments	Hold carfilzomib treatments
Returns to 1.0 x 10^9/L	Resume lenalidomide at 1 dose decrement	Resume carfilzomib previous dose at 1 dose decrement (dose decrease required only if treating investigator judgment is that Carfilzomib contributed to neutropenia)

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	**Recommended Action**	
	Lenalidomide	**Carfilzomib**
Non-Blistering Rash		
Grade 3	Hold lenalidomide dose; follow weekly If the toxicity resolves to ≤ Grade 1 prior to Day 21 of the current cycle, restart at 1 dose decrement and continue the cycle until Day 21 of the current cycle.	Hold (if Treating Investigator's opinion is possibly related to Carfilzomib) until ≤ Grade 1, reinstitute at current dose
Grade 4	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Desquamating (blistering) rash – any grade	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Sinus bradycardia/ other cardiac arrhythmia		

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
≤ Grade 2	Hold lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	Hold until ≤ Grade 1, reinstitute at current dose.
≥ Grade 3	Discontinue lenalidomide study drug	Hold until ≤ Grade 1, reinstitute at current dose.
Allergic reaction/hypersensitivity		
Grade 2 – 3	Hold lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	Hold until ≤ Grade 1, reinstitute at current dose.
Grade 4	Discontinue	Discontinue
Tumor lysis syndrome (≥ 3 of the following: ≥ 50% increase in creatinine, uric acid, or phosphate;≥ 30% increase in potassium;≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold lenalidomide until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection Grade 3 or 4	Hold lenalidomide until systemic treatment for infection is completed. If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.	Hold carfilzomib until systemic treatment for infection is completed If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex of any grade	Hold lenalidomide until lesions are dry. Reinstitute at full doses.	Hold carfilzomib until lesions are dry. Reinstitute at full doses.

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Grade 2 neuropathy with pain or any Grade 3 neuropathy	Hold until ≤ Grade 2. Then restart lenalidomide at 1 dose decrement	Hold until resolved to ≤ Grade 2. Then restart carfilzomib at 1 dose decrement
Grade 4 neuropathy	Discontinue	Discontinue
Renal dysfunction		
Serum creatinine > 2 mg/dL	Base dose reduction on calculated GFR (below)	Base dose reduction on calculated GFR (below)
CrCl>50 mL/min	Full dose	Full dose
CrCl <50 mL/min > 30 mL/min	Reduce lenalidomide to 10 mg every 24 h; may reinstate prior dose if, after 2 cycles, CrCl normalizes	Full dose
CrCl< 30 mL/min	Reduce lenalidomide to 15 mg every 48 h	Hold carfilzomib until CrCl> 30 mL/min; restart at 1 dose decrement
CrCl< 30 mL/min requiring dialysis	5 mg. Once daily. On dialysis days the dose should be administered following dialysis.	Hold until resolved to ≤ Grade 2. Then restart carfilzomib at 1 dose decrement

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Venous thrombosis/embolism ≥ Grade 3	Hold lenalidomide dose and adjust anticoagulation regimen; re-start at Treating Investigator's discretion at full dose	No adjustment required
Hyperthyroidism or hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate, and initiate appropriate therapy. Restart lenalidomide next cycle at 1 dose decrement	No adjustment required
Congestive heart failure (CHF)	Any subject with symptoms of CHF, whether or not lenalidomide related, must have the dose held until resolution or return to baseline. If CHF was felt to be lenalidomide related, reinstate by one dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.	Any subject with symptoms of CHF, whether or not carfilzomib related, must have the dose held until resolution or return to baseline. If CHF was felt to be carfilzomib related, reinstate by one dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.
Hypertension including Hypertensive Crises	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 2. Resume at one level dose reduction
Heart problems, including rapid, strong, or irregular heartbeat Heart attack, reduced blood flow to the heart, abnormal amount of fluid between the heart and lining around the heart, and swelling/irritation of the lining around the heart	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction
Pericardial Effusion	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction
Pericarditis	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Pulmonary Hypertension	NA	= Grade 2: Carfilzomib attribution, Reduce drug: one level dose reduction ≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤Grade 2. Resume at one level dose reduction
Pulmonary Toxicities: Interstitial Lung Disease (inc. pneumonitis), Acute Respiratory Failure, and Adult Respiratory Distress Syndrome (ARDS), cough and cough with phlegm	NA	≥ Grade 2 for Pneumonitis ≥ Grade 3 for ARDS ≥ Grade 4 for Respiratory Failure Carfilzomib attribution, hold drug until resolved to ≤Grade 1. Resume at one level dose reduction
Blood clot in the lungs, fluid in the lungs, bleeding in the lungs	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction
Gastrointestinal Perforation	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction
Hepatic Toxicities (≥ Grade 3 elevation of AST or ALT, Bilirrubin, or other ≥ Grade 3 liver abnormalities)	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented.	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented.
Other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3	Hold lenalidomide dose. Follow at least weekly. If the toxicity ≤ Grade 1 before Day 21 of the current cycle, restart at 1 dose decrement and continue until Day 21 of the current cycle	Full dose

Table 5-5. Dose Modifications for Non-hematologic Toxicity

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Full dose	Hold carfilzomib dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement
Other non-hematologic toxicity assessed as drug-related ≥ Grade 3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline

Table 5-6. Treatment Guidelines for Toxicity Related to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or PO hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.

5.4.3 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 more than 3 days with adequate treatment of antiemetics or antidiarrheal agents)
- Grade 3 dexamethasone-related hyperglycemia
- Grade 1-3 lenalidomide-induced rash

- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia

5.4.4 TREATMENT DISCONTINUATION

Administration of Carfilzomib, lenalidomide and dexamethasone can be discontinued permanently in the event of a treatment-related toxicity at the Treating Investigator's discretion.

If a delay of starting a new cycle is greater than 21 days, the subject should be discontinued from treatment, unless continuing treatment is mutually agreed upon by the Treating Investigator and the Lead Principal Investigator.

If either carfilzomib or lenalidomide requires permanent discontinuation before Cycle 4 induction, the subject's treatment will be discontinued at the end of Cycle 4 induction. If either carfilzomib or lenalidomide requires permanent discontinuation during consolidation or maintenance cycles, the subject may remain on study with the remaining drug(s).

Dexamethasone may be discontinued without the subject discontinuing study treatment.

5.5 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications must be recorded on the concomitant medications case report form from 21 days before Day 1 through 30 days following the last dose of study drugs.

5.5.1 REQUIRED CONCOMITANT MEDICATIONS

- Valacyclovir or similar anti-varicella (anti-herpes) agent HZV prophylaxis
- Aspirin for VTE prophylaxis.

Instructions for their administration are found in Section 5.2.1.

Note: If a subject is allergic to aspirin, low-molecular-weight heparin or clopidogrel may be used. In subjects with a prior history of venous thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (target INR 2-3) are required.

5.5.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

In view of emerging data that pneumocystis pneumonia (PCP) is unlikely in patients treated with low dose dexamethasone, the use of Pentamidine or Bactrim will be optional in CRd.

Of these medications, use of Pentamidine is recommended as the PCP prophylaxis of choice for CRd patients.

Use of Dapsone for PCP prophylaxis will require approval of the Lead Principal Investigator, in view of the potential for hemolysis in this subset of patients.

Mycostatin and lansoprazole or other proton pump inhibitor or an H2 antagonist are recommended but NOT required and considered optional medications.

Marketed bisphosphonates are allowed.

Subjects may receive anti-emetics and antidiarrheal agents as necessary.

Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

Subjects may receive RBC or platelet transfusions if clinically indicated in accordance with institutional guidelines, however screening platelet count must be independent of platelet transfusions for at least 2 weeks (Section 3.6). Subjects who require repeated platelet transfusion support should be discussed with the Lead Principal Investigator.

Allopurinol (for use only in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Treating Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol and are at risk for TLS should be discussed with the Lead Principal Investigator in order to discuss alternatives.

If signs of tumor flare are present, split dosing of dexamethasone may be implemented so that subjects may be given 4 mg dexamethasone PO or IV on Days 2, 9 and 16 in Cycles 1 and 2 prior to carfilzomib infusion. The total dose of dexamethasone prior to carfilzomib should not exceed 40 mg weekly therefore it is recommended that the dose is split between days of carfilzomib administration, for example 36mg Day 1 and 4mg Day 2.. This will be prescribed at the Treating Investigator's discretion. Subjects believed to be at high risk for bacterial infection may receive antibiotic prophylaxis as per institutional guidelines.

Radiation therapy to a localized mass for subjects on CRd therapy is acceptable with prior approval of the Lead Principal Investigator.

Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose ≤ 4 mg/day or prednisone ≤ 20 mg/day are permitted

5.5.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with a marketed or investigational anticancer therapeutic is not allowed.

Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4 mg/day or prednisone > 20 mg/day are not permitted.

Other investigational agents are not to be used during the study.

5.6 SAFETY GUIDANCE FOR INVESTIGATORS

5.6.1 "FIRST-DOSE EFFECT"

A "first dose" effect has been encountered early in carfilzomib treatment, characterized by fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a "first dose" effect occur, treatment with glucocorticoids is recommended. In addition IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted as medically indicated.

5.6.2 TUMOR LYSIS SYNDROME

Tumor lysis syndrome, which may be associated with multi-organ failure, has been observed in Cycles 1 and 2 of some subjects with multiple myeloma treated with carfilzomib. In addition, multiple myeloma subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (GFR < 50 mL/min) should be considered to be at particularly high risk. All such subjects should be identified at screening.

During Cycles 1 and 2, serum electrolytes and chemistries are closely monitored as outlined in Section 7.2. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated as clinically indicated. The Lead Principal Investigator should be consulted if there are further delays.

Subjects should be informed of signs and symptoms that may be indicative of tumor lysis syndrome, such as fevers, chills/rigors, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output; subjects should be instructed to report such symptoms immediately and seek medical attention.

In the event tumor lysis syndrome manifests, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of tumor lysis syndrome must be reported to The University of Chicago as a Serious Adverse Event (SAE) as outlined in Section 8.5.

5.6.3 RENAL FUNCTION

Carfilzomib has not been fully characterized in subjects with creatinine clearance < 30 mL/min. It is critical that the subject's renal function is known at the time of dosing. Renal function, serum creatinine, and serum uric acid should be monitored closely as outlined in Section 6. See Section

5.4.2 and Table 5-5 for guidance regarding dose reduction in subjects with compromised renal function.

5.6.4 HYDRATION

All subjects should be well-hydrated. However, over-hydration without matching output should be avoided with use of diuretics as needed. Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheal agents. Fluid and electrolyte replacement should be administered as outlined in Section 5.2.1

6 STUDY TESTS AND OBSERVATIONS

All protocol-required tests and observations along with their chronology are summarized in Appendix A.

6.1 SCREENING (DAYS -21 TO -1)

Written informed consent must be obtained before any protocol-specific tests or procedures may be conducted. The consent may be obtained within 30-days of Cycle 1 Day 1 however the following screening assessments will be performed between Days -21 and –1 unless otherwise stated:

General

- Medical history (review of systems, prior treatments for all significant conditions including neuropathy)
- Complete physical examination (including vital signs [systolic and diastolic blood pressure, respiration, pulse, oral temperature], height, weight, calculation of body surface area [BSA], and ECOG score). Height outside of the 21-day window is acceptable.
- Skeletal survey (lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri). May be within 30 days of planned Day 1 of Cycle 1. Skeletal surveys performed outside of the 30 day window may be considered for inclusion. Please contact the Lead Principal Investigator on a case-by-case basis.

- 12-lead ECG, including QTc interval
- Neurologic assessment, consisting of neurologic exam (to detect peripheral neuropathy and/or changes in pre-existing neuropathy) and completion of the neurologic questionnaire by the subject.
- Record all concomitant medications starting 21 days before planned Day 1 of Cycle 1.

Laboratory

- Pregnancy test (FCBP must have a negative serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL, within 10-14 days before and again within 24 hours before lenalidomide is prescribed for Day 1 of Cycle 1). See also Appendix F.
- Urinalysis
- Serum chemistries (see Section 6.2 for list of analytes). Creatinine clearance calculated by Cockroft-Gault (See Appendix G)
- Hematology (hemoglobin, hematocrit, WBC with complete differential, RBC, platelets)
- Coagulation tests (prothrombin time, activated partial thromboplastin time, and international normalized ratio)

Disease-related

- M-protein determination using both of the following procedures:
  - Serum protein electrophoresis (SPEP) and serum protein immunofixation
    - Pre-treatment serum M-protein baseline level from outside institution must be well documented and recorded and required for eligibility
  - Urine protein electrophoresis (UPEP), urine protein immunofixation (using 24-hour urine collection above) and total protein in urine. SPEP will be used serially during the study if the baseline value for M-protein is > 0.5 g/dL. UPEP will be used if the baseline value is

> 200 mg per 24 hours. If both tests are positive at baseline, both will be performed at each required time point.

    - Pre-treatment urine M-protein baseline level from outside institution (light chain 24 hr quantitation) must be well documented and recorded. If not available but the patient has pre-treatment measurable serum M-protein, lack of pre-treatment 24 hr urine results is not an exclusion

- Plasmacytoma evaluation (either physical exam or imaging where applicable and at treating investigator's discretion)

- Serum quantitative immunoglobulins

- Serum β2 microglobulin

- Serum free light chains (SFLC)

- Bone marrow aspirate and biopsy – quantify percent myeloma cell involvement, and obtain bone marrow aspirate for cytogenetics [i.e. diploidy, del 13] and fluorescent in situ hybridization (FISH) studies [i.e. t(4:14); t(11:14); del 17p]. Cytogenetics is only required at screening.

    - All patients are required to have two samples for MRD analysis centrally (by Flow cytometry at the University of Chicago and by Next Generation Sequencing (NGS) at Adaptive Biotechnologies) collected at 1) Screening (for calibration for MRD by gene sequencing), 2) Pre-transplant (end of cycle 4), 3) Post-transplant (pre-consolidation), 4) End of Cycle 8, 5) End of Treatment, 6) 1, 2, 3, and 5 years after EOT. In the event that a superfluous bone marrow aspirate (BMA) sample from screening was not available, slides of BMA smear or clot from a time prior to enrollment can be used.

- CT-PET – Performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked.

- CRP levels

- If pre-treatment serum β2 microglobulin, serum free light chains (SFLC), and cytogenetics are missing, this is not an exclusion.

6.2 TREATMENT CYCLES 1 THROUGH 4 (INDUCTION), CYCLES 5-8 (CONSOLIDATION), AND CYCLES 9-18 (MAINTENANCE)

- Complete physical examination (including vital signs [systolic and diastolic blood pressure, respiration, pulse, oral temperature], weight, calculation of body surface area [BSA]) and ECOG score) on Day 1 of each cycle. Abbreviated (i.e., symptom-directed) exams may be performed on Days 8 and 15 if indicated. For Cycle 1, the screening physical may be used if it was within 7 days before Day 1.

- Vital signs within 1 hour before the dose of carfilzomib on Days 1, 2, 8, 9, 15, and 16 during Cycles 1-8 and on Days 1, 2, 15, and 16 during Cycles 9-18.

- Hematology Days 1 and 15 of each cycle during Cycles 1-8 and on Day 8 of Cycles 1 and 2 only. On cycles 9-18 hematology should be done on day 1 only. Results must be available before the dose of carfilzomib is given (hence may be performed the day before planned dosing).

- Full serum chemistry panel on Days 1, 8, and 15 of Cycles 1 through 8 and on Day 1 of Cycles 9-18, plus abbreviated panel (see below) on Days 2, 9, and 16 of Cycles 1 and 2 only and only if clinically indicated as per institutional standards of care (i.e., subject at risk for tumor lysis syndrome).

  Results must be available before the dose of carfilzomib is given (hence may be performed the day before planned dosing). Results must be consistent with eligibility criteria prior to dosing on Cycle 1 Day 1.

Full Chemistry Panel		Abbreviated Chemistry Panel
sodium potassium chloride bicarbonate BUN creatinine glucose uric acid total protein albumin	calcium Phosphorus Magnesium total bilirubin alkaline phosphatase ALT AST LDH	sodium potassium chloride bicarbonate BUN creatinine glucose uric acid

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and 14 and 28 days after discontinuation from the study. Patients already on lenalidomide at the initiation of CRd therapy, may continue with the regularly scheduled pregnancy testing schedule as long as there has been no interruption in the testing schedule and use of birth control measures, rather that repeating the cycle 1 weekly testing.

  In addition to the above, at each visit the Treating Investigator must confirm that FCBP are continuing to use 2 reliable methods of birth control. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her cycle is abnormal. See also Appendix F.

- Disease-related tests (M-protein by SPEP and/or UPEP [requires 24-hour urine collection] as appropriate, quantitative immunoglobulins, and plasmacytoma as appropriate) on Day 1 of each cycle. For cycle 1, screening values may be used if within 7 days of Day 1. In Cycle 1 only, these tests are repeated on Day 15 to assess possible onset of early response.

- Neurologic assessment as before on Day 1 of every cycle. This includes subject completion of the neurologic questionnaire.

- All patients are required to have two samples for MRD analysis centrally (by Flow cytometry at the University of Chicago and by Next Generation Sequencing (NGS) at Adaptive Biotechnologies) collected at 1) Screening (for calibration for MRD by gene sequencing), 2) Pre-transplant (end of cycle 4), 3) Post-transplant (pre-consolidation), 4) End of Cycle 8, 5) End of Treatment, 6) 1, 2, 3, and 5 years after EOT. In the event that a superfluous bone marrow aspirate (BMA) sample from screening was not available, slides of BMA smear or clot from a time prior to enrollment can be used.
- CT-PET – Performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked.

6.3 END OF CYCLE 4

After 4 cycles of induction treatment, disease status including bone marrow for pre-transplant assessment will be assessed as described in Section 6.8.Bone marrow biopsy and aspirate must include two research samples for MRD by flow and by NGS. Also at this point of the study, subjects will proceed to stem cell collection and then ASCT. A CT-PET must be performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked.

6.4 STEM CELL COLLECTION AND AUTOLOGOUS STEM CELL TRANSPLANT

Thirty days after the last dose of CRd treatment, or at the start of stem cell collection (whichever occurs first), subjects will no longer be followed for adverse events and will be considered off-treatment for the remainder of the transplant period. Treating Investigators should follow their institution's standard practice for SCC and mobilization however section 6.4.1 should be referenced for guidance and recommendations. Section 6.4.2 should be followed for autologous stem cell transplant along with standard practice.

6.4.1 MOBILIZATION AND COLLECTION OF AUTOLOGOUS PERIPHERAL BLOOD STEM CELLS

Mobilization with G-CSF should start 2-4 weeks from the last dose of lenalidomide (i.e., 2-4 weeks after Cycle 4 Day 21). In general, scheduling of stem cell collection should assure as limited break as possible between the last dose of CRd treatment and ASCT, which should not exceed 6 weeks.

Neupogen (G-CSF) should be used for stem cell mobilization according to standard practice. If G-CSF alone is not sufficient for mobilization, the addition of plerixafor (Mozibil) should be used or as per the institution's standard.

During the apheresis procedure, correction of cytopenias and electrolyte abnormalities will be performed as per standard unit policy.

6.4.2 AUTOLOGOUS STEM CELL TRANSPLANT PROCEDURE

Patients will be admitted to the inpatient stem cell transplant unit at the treating institution. Conditioning chemotherapy will consist of melphalan 200mg/m^2 IV. If melphalan at 200mg/m^2 cannot be administered because it is not tolerated or it is against institutional guidelines for reasons such as the patient's age, than the patient is not considered suitable for transplant per protocol and should not be enrolled to the trial. Sites should follow their standard protocol for hydration and antiemetic prophylaxis prior to melphalan infusion, antibiotic prophylaxis, platelet and packed red blood cell transfusions, and standard laboratory testing. Administration of autologous peripheral stem cells will take place on day 0 according to standard unit protocol. Patients will be monitored inpatient per standard protocol until criteria for discharge are met.

6.5 3 MONTHS POST TRANSPLANT

After recovery from ASCT toxicities (day 70-90 but not more than 120 and prior to initiation of CRd consolidation), disease status will be assessed as described in section 6.8 and Appendix E and bone marrow biopsy and aspirate must include two samples for MRD by flow and by NGS. Patients who have established sCR earlier with negative MRD can have bone marrow biopsy waived after discussion with study Lead Principal Investigator. A CT-PET must be performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked.

6.6 END OF CYCLE 8 (END OF CYCLE 4 CRD CONSOLIDATION)

After completion of 8 cycles, disease status will be assessed as described in section 6.8 and Appendix E and bone marrow biopsy and aspirate including two samples for MRD by flow and by NGS. Patients who have established sCR earlier with negative MRD can have bone marrow biopsy waived after discussion with study Lead Principal Investigator. A CT-PET must be performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked.

6.7 LONG-TERM FOLLOW-UP

Subjects who did not progress while on study, including subjects on lenalidomide maintenance, will be followed every 3 months for 5 years from the safety follow-up visit (28 days post last dose of study treatment) to document progression-free survival and development of any new cancers. Progression-free survival (PFS) and overall survival (OS) will be calculated every 6 months. When the median PFS/OS is reached, follow-up can be stopped.

For subjects who are in CR or better at the end of 18 cycles (± 30 days), a repeat bone marrow aspirate and biopsy should be collected for Minimal Residual Disease (MRD) at the end of study treatment visit done in central labs. One sample will be analyzed by Flow cytometry at the University of Chicago and the other by Next Generation Sequencing (NGS) at Adaptive Biotechnologies). A bone marrow aspirate and biopsy with two aspirates for MRD analysis should be collected 1, 2, 3, and 5 years after EOT for central analysis at UC and at Adaptive Biotechnologies.

Fresh Bone Marrow aspirate for MRD analysis by **flow cytometry** will be shipped at ambient temperature on the same day of the procedure directly to the University of Chicago **Hematology lab**. Please refer to the lab manual for shipping details.

On the other hand, fresh Bone Marrow aspirate MRD analysis by **NGS by Adaptive Biotechnologies,** will be shipped at ambient temperature on the same day of the procedure directly to the University of Chicago **Multiple Myeloma lab** for processing and later batched shipping. Please refer to the lab manual for shipping details.

6.8 TUMOR RESPONSE ASSESSMENT

Subjects will be evaluated under Treating Investigator review for disease response according to the International Myeloma Working Group (IMWG) uniform response criteria Appendix E. Response categories include sCR, CR, nCR, VGPR, PR, SD, and progressive disease (PD).In addition, minimal response (MR) will be evaluated as an alternate response following EBMT modified criteria (Appendix E).

For subjects in whom achievement of a sCR, CR, or nCR is suspected, a repeat bone marrow biopsy and aspirate (showing < 5% myeloma cells in the marrow, in addition to the other criteria in Appendix E) will be required to document the initial response. For confirmation of response, an aspirate but not a biopsy is required. All response categories (sCR, CR, nCR, and VGPR) require 2 consecutive assessments made after baseline and before the start of new therapy. If a subject is being followed by serum M-protein only, a response must be confirmed by a negative UPEP even if negative at baseline. SFLC will be repeated to confirm an MR or better.

PD requires 2 consecutive assessments made at any time before classification as relapse or progression and/or the institution of new therapy when clinically possible.

6.9 OPTIONAL CORRELATIVE STUDIES

In addition to the required bone marrow aspirate samples for MRD analysis [1) Screening 2) Pre-transplant, 3) Post-transplant), 4) End of Cycle 8, 5) End of Treatment, 6) 1, 2, 3, and 5 years after EOT], for patients who consent additional samples will be collected including bone marrow aspirate, peripheral blood, and buccal swabs. As a companion study to the proposed clinical trial, studies will be conducted aimed at identifying markers of response to the CRd regimen. The correlative studies will focus on the (1) evaluations of markers of response, and (2) pre-treatment myeloma cell characteristics. Briefly, we will collect samples prior to treatment and at indicated time points. The first objective is to determine tumor characteristics, which predict at least very good partial response (VGPR). VGPR has been associated with longer progression survival and overall survival.[25,26] The results will complement ongoing efforts to identify markers of VGPR using samples already collected from VDD, RVD, RVDD, and CRd frontline clinical trials, with a broader goal to provide rationale for individualized therapy as a method of improving VGPR or CR/nCR. In addition to global assessment of pretreatment profiling and genetic variants, which

will be correlated with a response, we will prospectively evaluate selected characteristics and markers of response identified in our proteomics studies to date, and other emerging markers of response including Cereblon.

If the subject provides additional consent, please obtain research samples (peripheral blood and bone marrow aspirates) at the time points below. In the event that adequate sample cannot be obtained, these studies may be run using any superfluous sample obtained from the required samples for MRD analysis for patients who have given consent

- Screening*
- Pre-transplant/Post-transplant
- End of C8
- Time of response (to confirm complete response), and/or

End of Treatment visit
*Please also obtain a buccal mucosa swab at screening.
Assays may include:

1. Proteomics
2. Tumor cell
   - Gene micro array
   - SNP analysis
   - Analysis of genetic variants
2. Additional Biomarker Studies
   - Cereblon expression

Specimen Collection Instructions:
- BM aspirate)
- Peripheral blood Serum
- Buccal swab

Please note that supplies for correlative sample collection will not be provided

Please refer to the Laboratory Manual for detailed collection, processing and shipping instructions.

Label all specimens with the following:
1. Subject initials
2. Subject study number (will include protocol number)
3. Visit at which sample was drawn (i.e. C1D4)
4. Date sample drawn (i.e. mm/dd/yyyy)
5. Time sample drawn (24 hour clock)

6. Sample type (eg. plasma, serum, bone marrow cells, tumor cells)

Shipping Instructions:

1. An inventory sheet provided in the lab manual including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment.
2. An electronic copy (Word or Excel) of the sample list must also be sent via email. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment. They should sign and date the form.
3. Please email the Myeloma Lab at the University of Chicago (myeloma-lab@bsd.uchicago.edu) as notification of an incoming shipment.
4. Please ship Monday, Tuesday, Wednesday or Thursday, as shipments cannot be received on weekends and/or on holidays.

Please note that collection and processing supplies will not be provided however a FedEx account number will be provided for shipments.

Andrzej J Jakubowiak, MD, PhD
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Note: Please follow your institution's policy regarding destruction of patient samples upon withdrawal of informed consent.

7 STUDY DISCONTINUATION

Subjects may withdraw from the study at any time. Subjects who withdraw will be monitored for AEs, as described in Section 8.3. The Lead Principal Investigator may elect to discontinue the study at any time.

The Treating Investigator may remove a subject from the study for the following reasons:

- Disease progression
- Noncompliance with study procedures
- Requirement for alternative therapy
- Subject no longer consents to participate in the study

- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs that indicates a potential health hazard to the subject
- Suspected pregnancy or positive pregnancy
- Death
    - Reports of any death should include date of death and specific cause (disease under study of specific other cause) and information about autopsy if the cause of death was unknown

The Lead Principal Investigator must be contacted to discuss any impending discontinuation of a study subject/patient prior to withdrawal from the study. If withdrawal occurs prior to discussion with the Lead Principal Investigator, they must be notified within 24 hours via email with a copy to the University of Chicago CRA.

If the reason for withdrawal is the occurrence of an AE, the subject will be followed until such events resolve, stabilize, and, according to the Treating Investigator's judgment, there is no need of further follow-up. The reason for withdrawal from the study will be documented in the case report form.

8 ADVERSE EVENTS

8.1 ADVERSE EVENTS DEFINITIONS

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

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

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

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs (see Appendix 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. For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Table 5-7

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

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

8.2 CAUSALITY

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows: Definite, Probable, Possible, Unlikely, Unrelated.

8.3 ADVERSE EVENTS REPORTING PROCEDURES

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory tests or other means, will be collected and recorded and followed as appropriate.

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date on or after Cycle 1 Day 1 of treatment must be documented on the appropriate CRF. Adverse Events which occur after consent but prior to the start of treatment must be reported if they are considered related to study procedures. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate SAE form. All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.

AEs should be reported from Day 1 of treatment through 30 days post-last dose of study drug (Carfilzomib) or initiation of a new anti-cancer therapy, whichever occurs first. For subjects who continue to ASCT, AEs will be recorded for 30 days post last dose of Cycle 4 or until the start of stem cell collection if earlier. AEs will not be recorded during the transplant period (stem cell collection through start of consolidation) but should be collected again starting at Cycle 5 Day 1 or the first cycle of consolidation following ASCT. In addition, the Treating 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 enrolled but discontinues study prior to receiving any study drug, only SAEs that are considered related to study procedures 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 Treating Investigator that the event has stabilized or is not expected to improve.

The Treating Investigator is responsible for evaluating all AEs for relationship to study drug and for seriousness, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI-CTCAE grading scale

v4.0. The treating investigator must assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the treating investigator must provide details about the action taken with respect to the test drug and about the patient's outcome. 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 Treating Investigator.

The Site or Lead Principal Investigator may delegate these duties to Sub-investigators and must ensure that these Sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572 and delegation log.

8.4 SERIOUS ADVERSE EVENTS

Information about all serious adverse events (SAE) will be collected and recorded on the appropriate SAE form. To ensure patient safety, each serious adverse event must be reported to the Lead Investigator and the University of Chicago Comprehensive Cancer Center (via paper SAE form and electronic submission in Velos) within 24 hours of learning of its occurrence.

8.4.1 SERIOUS ADVERSE EVENT DEFINITION

An SAE is one that meets any the following criteria:

- Death
- Life threatening experience defined as any adverse experience that places the subject, in the view of the Treating 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 Lead Investigator/ University of Chicago Comprehensive Cancer Center as an SAE.

8.4.2 SERIOUS AND UNEXPECTED SUSPECTED ADVERSE REACTION (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there is evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens Johnson Syndrome), one or more occurrence of an event otherwise uncommon in the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, FDA approved package insert, or elsewhere in the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent. **ALL serious and unexpected suspected adverse reactions (SUSARs) occurring on this clinical trial must be reported to the FDA. Refer to section 8.5 for reporting guidelines.**

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

ALL Serious Adverse Events, whether or not they are considered related to the study agent MUST be reported to the Lead Principal Investigator and to the University of Chicago Comprehensive Cancer Center (via entry on the SAE form in Velos). Refer to Section 8.5 for reporting guidelines.

8.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

All SAEs (except those that occur during ASCT more than 30 days after the last dose of CRd at cycle 4 unless considered to be related to CRd treatment) from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug must be reported to the Lead Principal Investigator and to the University of Chicago Comprehensive Cancer Center via paper submission. The SAE should also be entered electronically as soon as possible. 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.

A copy of the SAE form (found in Velos) should be sent via fax or via email to the University of Chicago Cancer Clinical Trials Office (fax number 773-702-1561 or email to qaccto@bsd.uchicago.edu) according to the timeframe in section 8.6.1.

All MedWatch Form 3500A SAE forms must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to study drug(s) (e.g. probably related, unknown relationship, definitely not related), date and time of administration of study drug(s) and all concomitant medications and medical treatment provided. The Treating Investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" as defined above are present. 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 form as well as the Study Discontinuation report form.

The appropriate University of Chicago coordinator will be responsible for notifying the Regulatory Agencies as required.

8.5.1 EXPEDITED REPORTING BY LEAD PRINCIPAL INVESTIGATOR TO ONYX

The University of Chicago CRA will inform Onyx in writing by email or facsimile of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on a MedWatch Form 3500A. This form will be supplied to Onyx

within 24 hours/1 business day or at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up FDA MedWatch Form 3500A. A final report to document resolution of the SAE is required.

The Onyx protocol number **(IST-CAR-578)** and the institutional protocol number should be included on SAE reports to Onyx. A copy of the fax transmission or email confirmation of the SAE report (or on the fax cover letter) sent to Onyx should be attached to the SAE and retained with the patient records

Onyx Drug Safety and Pharmacovigilance Contact Information:
Fax: 800-783-7954 or 650-266-0501
SAE Hotline: 650-266-2501
Email: adverse.events@onyx.com

8.5.2 INVESTIGATOR REPORTING RESPONSIBILITES

The conduct of the study will comply with all applicable safety reporting requirements.

All adverse experience reports must include the patient number, age, sex, weight, event diagnosis (if known) or signs/symptoms, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The Treating Investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present.

Participating sites are responsible for reporting all SAEs to the Lead Principal Investigator. The Lead Principal Investigator will be responsible for reporting SAEs to Onyx (as outlined above) and the FDA.

The Treating Investigator is responsible for notifying their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations of all SAEs. Events occurring at a participating site should be reported to the local IRB of record according to

their policies and procedures and may be reported to the University of Chicago IRB if they meet current reporting criteria.

It is the responsibility of the University of Chicago coordinator on behalf of the Lead Principal Investigator to notify all participating sites of all serious unexpected suspected adverse reactions that occur on this clinical trial and which are reported to the FDA as an IND Safety Report (21 CFR 312.32). A copy of the completed Form 3500A (MedWatch) and/or IND Safety Report Narrative will be provided to the responsible Regulatory Manager by the IND coordinator for distribution to all participating sites.

8.5.3 FDA REPORTING BY THE LEAD PRINCIPAL INVESTIGATOR

This study will be conducted under an IND held by Andrzej Jakubowiak at the University of Chicago.

Current FDA regulations require that all SUSARs (see definition in section 8.4.1) occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report.

In order to meet these requirements, the lead principal investigator will review all reported serious adverse events as they occur to determine if FDA reporting is required and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

Individual Event Reports: FDA Form 3500A (MedWatch) will be completed for all SAEs that require FDA reporting. This will be completed by the designated research staff at each site. The completed MedWatch form for fatal or life-threatening events must be returned to the Lead Investigator/ University of Chicago CRA within 4 calendar days. All other events must be received within 10 calendar days.

Other findings that suggest significant risks to the subject: A narrative description summarizing all relevant findings will be provided by the lead principal investigator along with a copy of any relevant publications (if applicable).

Clinically Significant Increase in Frequency of Events: A narrative description summarizing all relevant findings will be provided by the lead principal investigator along with details of individual cases (if applicable).

All MedWatch reports are due to the designated University of Chicago CRA (and will be forwarded to the University of Chicago Clinical Trials Office IND coordinator) according to the specified timeline regardless of whether or not all information regarding this event is available. If applicable, a follow-up report should be provided to the University of Chicago CRA/ IND coordinator once additional information on the event is available.

The completed MedWatch form and/or safety narrative will be forwarded to the FDA by the University of Chicago Comprehensive Cancer Center – Cancer Clinical Trials Office (CCTO) on behalf of the IND Holder within the appropriate timeframes as designated in 21 CRF 312.32.

8.5.4 ADVERSE EVENT UPDATES/IND SAFETY REPORTS

Onyx shall notify the Treating Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of the drug in this study or other studies that is both serious and unexpected
- Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity or carcinogenicity.

The Treating Investigator shall notify his/her IRB/IEC promptly of these new serious and unexpected AEs or significant risks to subjects in accordance with their policies.

The Lead Principal Investigator must keep copies of all AE information, including correspondence with Onyx and the IRB/IEC on file (see Section 12.2.3 for records retention information).

8.6 PREGNANCY

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on treatment or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. Study drugs—both lenalidomide and carfilzomib—are to be discontinued immediately and the subject instructed to return any unused lenalidomide to the Treating Investigator. The pregnancy must be reported within 24 hours of the Treating Investigator's knowledge of the pregnancy by phone and facsimile using the SAE form (Velos

SAE form as well as FDA MedWatch 3500A) to the University of Chicago CRA either by fax or by email. The Treating Investigator must inform the University of Chicago in writing by email or facsimile of any pregnancy within 24 hours / 1 business day at the latest on the following workday of being aware of the event. The University of Chicago must report pregnancy as an SAE directly to Onyx Drug Safety as well, using expedited reporting procedures listed in Section 8.5.

The Treating Investigator will follow the pregnant female until completion of the pregnancy, and must notify the Lead Principal Investigator at the University of Chicago. It is the responsibility of the coordinator on behalf of the Lead Principal Investigator to notify Onyx Drug Safety of the outcome as specified below. The Treating Investigator will provide this information as a follow-up to the initial SAE.

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 Treating Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

Any suspected fetal exposure to lenalidomide must be reported to Celgene and Onyx within 24 hours of the Lead Principal Investigator being made aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Treating Investigator suspects may be related to the in utero exposure to lenalidomide should also be reported to the Lead Principal Investigator and subsequently to Celgene and Onyx by the University of Chicago coordinator.

In the event of a live "normal" birth, Celgene and Onyx Drug Safety should be advised as soon as the information is available.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 OBJECTIVES

9.1.1 PRIMARY OBJECTIVES

The primary objective of this Phase 2 trial is to determine the efficacy of the CRd combination regimen as measured by response, defined as the rate of stringent CR (sCR) after 8 cycles of CRd (4 cycles of induction + ASCT + 4 cycles of CRd consolidation).

9.1.2 SECONDARY OBJECTIVES

Secondary objectives include determining the best objective overall response rate (ORR) defined as partial response or better (>PR), the rate of VGPR or better, near complete response or better (sCR/CR/nCR), the time to progressive disease, duration of response, and progression-free and overall patient survival distributions.

9.1.3 EXPLORATORY OBJECTIVES

Additional exploratory objective include evaluation of the status of minimal residual disease in patients who achieve a CR 1) after induction (first 4 cycles), 2) post-transplant, 3) after 8 cycles, 4) end of CRd treatment (cycle 18) 5) or any point that bone marrow is performed for assessment of CR response on CRd therapy. Additional prospective evaluation of candidate markers of response to CRd established in ongoing frontline CRd trial in newly diagnosed myeloma will be completed (Jakubowiak et al, ASH 2011, ASCO 2012, Blood 2012). In addition, we will ask patients to consent to provide research samples for additional evaluations of prognostic markers with a goal to established marker-based individualized therapy with CRd with or without transplant.

Bone marrow biopsies are optional with patient consent for research purposes at the end induction, post-transplant, end of 8 cycles of CRd (end of cycle 4 CRd consolidation), and end of treatment, per section 6.6. In order to accrue an adequate sample size for MRD assessment in patients who are suspected of having a sCR, CR, or nCR at this time given other disease-related tests, we will over-accrue above the original sample size, N = 53, to N=70. Given this additional sample size, we hypothesize a 65-70% consent rate for the necessary optional marrow biopsies. A 65-70% consent rate would afford a total sample size of approximately 45-49 patients, which would afford interrogation of the hypothesis that this regimen will

improve the rate of MRD after 4 CRD induction cycles, ASCT, and 4 cycles of CRD consolidation from 25% estimated MRD rate in the CRD trial without transplant to 45% with transplant, with approximately 80% power with 5% type II error.

9.2 POPULATION FOR ANALYSIS

The Intent-to-Treat (ITT) population of patients will be defined as all patients who receive at least one dose of carfilzomib and lenalidomide. If a patient fails to receive these drugs, the patient will be replaced. The primary efficacy results in the study will be based on data from this population. Patients in this population who have inadequate data to assess efficacy according to the criteria for response in section 8 will be considered treatment failures for this analysis. Patients in this population will be analyzed according to the treatment they were actually scheduled to receive, regardless of any errors of dosing or dose modifications. Analysis of safety will be performed on the set of patients who receive any study drug, formally the same group as comprises the ITT population.

9.3 STUDY DESIGN AND SAMPLE SIZE

This is single-arm, open label phase II study to determine the rate of sCR after a total of 8 cycles of CRd (i.e. 4 cycles of CRd induction and 4 cycles post ASCT consolidation) in patients who were enrolled into initial treatment with CRd and received at least one dose of carfilzomib and/or lenalidomide. The historical comparison population is the recently completed CRd phase I/II frontline therapy study which incorporated a deferred transplant design. The response rate determined in the current trial will be compared to, and be expected to exceed, the rate of sCR after the same duration of CRd therapy, 8 cycles. Mature data from the recently completed CRd phase I/II trial indicates that 13 of 44 (30%) patient attained a sCR when receiving 8 cycles of CRd frontline therapy.

For primary objective of the study, at least 53 and up to 70 patients will be enrolled to the CRd induction phase of this trial, with the expectation that the patients will receive ASCT, CRd consolidation, CRd maintenance, and recommended lenalidomide maintenance off protocol if able. To minimize the sample size, the study was originally designed as a Simon 2-stage study design with interim analysis after the enrollment of the first 27 patients, with the trial to continue enrollment if 12 of the first 27 patients achieved sCR at the end of 4 cycles of consolidation (or

after a total of 4 cycles before and 4 cycles post-transplant). This design did not take into account that it takes approximately 1 year for each subject to reach the primary end-point evaluation, which would require either extended study delay or the study would complete enrollment by the time 27 patients were evaluable for this interim primary end-point. Therefore, the study is revised to a single-stage. The sample size was increased to 53 patients, and further to 70 for MRD assessment, based upon the updated mature results of our prior CRd trial for patient at the completion of 8 cycles of frontline therapy without transplant and the consent rate for optional bone marrow biopsy for MRD assessment in the early portion of conducting this trial, respectively.. The sample size of 53 minimally necessary to test whether the rate of sCR would be 50% or greater in the current trial after 8 cycles of CRd ((i.e. 4 cycles of CRd induction and 4 cycles post ASCT consolidation) versus 30%, the sCR rate after 8 induction cycles in the historical comparison population. This trial will have 5% type I error (1-sided) and 10% type II error (90% power) to interrogate the stated hypothesis. With 70 patients, this trial will have 10% type II error (90% power) with 5% type I error (2-sided) to interrogate the stated hypothesis.

ANALYSIS PLAN

9.3.1 PRIMARY OBJECTIVE

The study's primary endpoint, attainment of sCR will be assessed at the completion of the 8 cycle of CRd (at the conclusion of the 4th consolidation cycle). All patients enrolled and receiving any CRd treatment will be evaluable for this endpoint, with the exception of patients that decline to receive transplant for reasons unrelated to toxicity and/or efficacy. Patients in that category will be replaced. All other patients who discontinue treatment before receiving 4 cycles of CRd induction and transplantation will be considered treatment failures for assessment of the study's primary endpoint. Patients who receive less than 4 cycles of consolidation will be evaluable for primary end point provided that they received at least lenalidomide and/or carfilzomib in post-transplant period for at least 4 months at the completion of 4 months of post-transplant treatment. Patients not meeting the minimum consolidation therapy as just described will be considered treatment failures for the study's primary endpoint.

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9.3.2 SECONDARY OBJECTIVES

Secondary objectives include the overall response rate, defined as at least a partial response to therapy (>PR), at least VGPR and at least nCR rate, time to progression, duration of response, and progression-free and overall survival. The rate of overall response will be reported along with its exact 95% binomial confidence interval. Time to event endpoints will be estimated using the product-limit method of Kaplan and Meier. Follow-up time for these endpoints will be calculated from the date of first treatment (D1C1 of CRd induction). For time to progression, patients that do not experience progression during follow-up will be censored on the date of their last clinical examination. Duration of response will be assessed conditional upon achieving at least a partial response. Follow-up time for this endpoint will be calculated from the date of the clinical examination which confirmed the response, until the date of disease progression, or censoring at the date of last clinical follow-up. For progression-free survival, follow-up time will continue from the date of first therapy until the date of documented disease progression or death. Patients not reach either milestone during follow-up will be censored on their date of last clinical assessment.

9.3.3 EXPLORATORY OBJECTIVES

Patients first enrolled onto this trial who achieve suspected CR will be evaluated for minimal residual disease using multicolor flow cytometry and gene sequencing (Sequenta, Inc). Patients with marker characteristics determined to predict response to CRd will be evaluated for time to events. The rate of MRD in those with at least a CR after 8 cycles of CRD (4 induction cycles, ASCT, and 4 consolidation cycles) will be estimated along with 95% confidence intervals.The proportion of patients alive and free of disease progression at 2 years post ASCT, will be estimated using the product limit method of Kaplan and Meier.

9.3.4 SAFETY ANALYSIS

Safety analysis will be based on the incidence, intensity, and type of adverse events, and clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients in the study. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

All adverse events occurring on study will be listed in by-patient data listings. Treatment emergent events will be tabulated, where treatment emergent is defined as any adverse event that occurs after administration of the first dose of study drug and through the End of Study visit or up through 30 days after the last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered drug-related by the Treating investigator and/or Lead Principal Investigator. Events that are considered related to treatment (possibly, probably or definitely drug-related) will also be tabulated. Deaths, serious adverse events and events resulting in study discontinuation will be tabulated. Of note 30 days following the last dose of CRd, during ASCT period patients will be considered to be off-study so no toxicities will be recorded from that period.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Similarly, changes in vital sign parameters will be summarized over time, and any abnormal values will be tabulated.

10 INVESTIGATIONAL PRODUCT

10.1 CARFILZOMIB DESCRIPTION

Please refer to the Carfilzomib manual provided by Onyx for detailed information. 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.

10.1.1 FORMULATION

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

10.1.2 STORAGE

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

10.1.3 ACCOUNTABILITY

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

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

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

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

10.1.4 CARFILZOMIB ORDERING

Carfilzomib will be provided at no cost by Onyx Pharmaceuticals. Drug orders will be made by the institution's investigational drug services. After full IRB approval and study activation including site initiation, the following documents need to be submitted to Onyx Clinical Research:

- 1572 (including investigational pharmacy shipping address as identification in section 7)
- Principal Investigator's current CV and license
- IRB letter of approval for protocol and consent

- Onyx Site Contact Information Sheet

After the site receives approval for drug shipment, drug orders can be placed directly using the Onyx Pharmaceuticals Carfilzomib Drug order form for IST-CAR-578.

10.2 LENALIDOMIDE

10.2.1 DESCRIPTION

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic and anti-neoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/ water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/mL. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero. Lenalidomide is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for PO administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink.

10.2.2 SUPPLY

Commercially available REVLIMID® (lenalidomide) capsules are supplied through the Revlimid REMS® program as the drug is approved for indications in this study. Lenalidomide is for PO (oral) administration only.

10.2.3 STORAGE CONDITIONS

Store lenalidomide at 25°C (77 °F) away from direct sunlight; excursions permitted to 15-30°C (59-86 °F).

10.2.4 ACCOUNTABILITY

Bottles of lenalidomide will contain a sufficient number of capsules to last for one cycle of dosing. Sites will be required to record and document subject compliance regarding lenalidomide dosing.

10.2.5 PRESCRIBING INFORMATION

Lenalidomide will be provided in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial must be registered in must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. Unused Revlimid will be counted and documented by each site. Unused Revlimid will be returned to Celgene by the site using instructions provided by Celgene.

10.2.6 SPECIAL HANDLING INSTRUCTIONS

Females of child-bearing potential should not handle or administer lenalidomide unless they are wearing gloves.

10.3 DEXAMETHASONE

Dexamethasone may be given IV or PO

10.3.1 DESCRIPTION

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

10.3.2 FORMULATION

Dexamethasone is a commercially available PO drug, supplied as 2 and 4 mg tablets.

10.3.3 STORAGE CONDITIONS

Store dexamethasone at controlled room temperature 20 to 25ºC (68 to 77ºF)

10.3.4 ACCOUNTIBILITY

Sites will be required to record and document subject compliance regarding dexamethasone dosing.

11 REGULATORY OBLIGATIONS

11.1 INFORMED CONSENT

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.

The University of Chicago will provide the Treating Investigator with a sample consent form developed by the University of Chicago. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the University of Chicago for approval, prior to submission to the participating site IRB/IEC. The participating site IRB/IEC will review the consent form for approval. A copy of the IRB/IEC approval form must be submitted to the University of Chicago prior to initiation of the study at the participating site.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the Lead and Site Principal Investigator and available for inspection by the designated University of Chicago coordinator at any time.

11.2 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 Lead or Site Principal Investigator, the Lead Investigator or designee will provide Onyx with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

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

Onyx Inc.

Regulatory Department

2100 Powell St.

Emeryville, CA 94608

The Lead and Site Principal Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

Onyx will provide study sites 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 Lead Principal Investigator must provide the IRB or Ethics Committee and Onyx with a summary of the trial's outcome.

11.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Before the start of the study, the following documents must be on file with the University of Chicago:

- A U.S. Form FDA 1572 signed by the Principal Investigator

- Current Curriculum Vitae (CV) for the Principal Investigator and all Sub-Investigators
- Current IRB/IEC membership list and/or Department of Health and Human Services number
- Copies of all appropriate laboratory certifications and laboratory normal ranges
- IRB/IEC approval of the protocol
- IRB/IEC approved informed consent and approval letter
    - The informed consent must also be reviewed and approved by the University of Chicago Cancer Clinical Trials Office
- IRB/IEC approval of any advertising materials to be used for study recruitment, if applicable (also to be approved by the University of Chicago)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Health Insurance Portability and Accountability Act forms, if required

11.4 SUBJECT CONFIDENTIALITY

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

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

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

12 ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

All protocol amendments will be implemented by the University of Chicago and must receive IRB/IEC approval before implementation, except where necessary to eliminate an immediate hazard to subjects. Amendments should only be submitted to the IRB/IEC after consideration of Onyx. Only the Lead Investigator can authorize any modifications, amendments, or termination

of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form to the affiliate institutions electronically for submission to the affiliate institution's IRB. The Site Principal Investigator or designee must send a copy of the approval letter from the IRB for the amendment, along with the revised Informed Consent form (as applicable), to the University of Chicago. The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter (the version date can be found on the footer of every page of the protocol and consent form, and the amendment number can be found on the University of Chicago IRB amendment approval letter sent with the amendment).

The University of Chicago jointly with the study supporters and the Lead Principal Investigator reserves the right to terminate the study according to the study contract. The Site and Lead Principal Investigator or designee should notify jointly the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to the regulatory affairs manager at the University of Chicago Cancer Clinical Trials Office.

12.2 STUDY DOCUMENTATION AND ARCHIVE

12.2.1 SOURCE DOCUMENTS

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site and Lead Principal Investigators will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report forms.

12.2.2 CASE RERPORT FORM COMPLETION

All required data must be recorded in the Velos database in at the completion of each cycle. All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into Velos within 48 hours of enrollment approval.

AEs are to be entered in real time. SAEs are to be entered in Velos on the SAE reporting form within 24 hours of the site's knowledge of the event. All other data to be entered within 30 days of source acquisition.

12.2.3 ARCHIVAL OF RECORDS

According to 21 CFR 312.62I, the Site and Lead Principal Investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Site and Lead Principal Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The Site and Lead Principal Investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

12.2.4 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be remotely monitored by the designated University of Chicago Medicine Clinical Research Associate (CRA).

Prior to subject recruitment, a participating site will undergo site initiation teleconference to be conducted by the designated University of Chicago Medicine CRA and Lead Principal Investigator. The site's principal investigator and his or her study staff should make every effort in attending the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate UCM personnel until they have been answered and resolved.

Monitoring will be conducted to verify the following:

- Adherence to the protocol

- Completeness and accuracy of study data and samples collected
- Compliance with regulations

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the Site Principal Investigator is aware of his/her ongoing responsibilities.

12.2.5 DATA SAFETY AND MONITORING

The University of Chicago Medical Center is responsible for data and safety monitoring for this study, including reviewing and monitoring the study's scientific progress, accrual rate and any serious adverse events. This protocol will undergo weekly review at the University of Chicago multi-institutional data and safety monitoring teleconference as per procedures specified by the UCCCC NCI-approved Data and Safety Monitoring Plan.

Each participating site is responsible for participating in Data Safety Monitoring (DSM), including participating in the teleconference. Prior to study start up, sites will be asked to submit their Data Safety Monitoring procedures for review by the University of Chicago. Drug accountability should be included in the monitoring plan.

The study will conduct teleconferences at a rate determined by the Lead Principal Investigator to review the following:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented within 7 calendar days of awareness of the event using the Protocol Deviation Form in Velos or using a Notice of Protocol Deviation form on paper that is sent to the UCM CRA or appropriate representative at the University of Chicago Medicine.

12.2.6 PROTOCOL DEVIATIONS

Protocol deviations are to be documented using the Notice of Protocol Deviation Form in the Velos clinical trial management system. Deviations that are considered major because they

impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported into the Velos system within 7 days.

12.2.7 QUALITY ASSURANCE AND AUDITING

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan. For institutions who are forma members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

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APPENDIX A. SCHEDULE OF TESTS AND OBSERVATIONS

PROCEDURES	Screen	CRd Induction Cycles 1-4							
DAY	**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**End of Cycle 4**
Informed Consent	X								
Medical/Treatment History	X								
Skeletal Survey[2]	X								
ECG[3]	X								
Physical Exam[5]	X	X[4]							
Vital Signs[6]	X	X	X	X	X	X	X		X
Height, Weight, BSA	X	X							
24-hour urine[7]	X	X[4,7]				X[7]			X[7]
Urinalysis	X								
Coagulation Tests[8]	X								
CRP	X								
Hematology[9]	X	X		(X)[10]		(X)[10]			
Serum Chemistry	X[11]	X[11]	X[12]	X[11]	X[12]	X[11]	X[12]		
Pregnancy Test[13]	X	X		X[14]		X[14]		X[14]	
Disease Assessment									X[15]
β2-microglobulin	X								
SPEP, UPEP[16]	X	X[4]				X[17]			X
Immunofixation – Serum and Urine	X	X[4]				X[17]			X
BM Aspirate/biopsy, cytogenetics, FISH[18]	X								X[18]
Plasmacytoma Evaluation[31]	X								
Quantitative Igs	X	X[4]				X[17]			X

PROCEDURES	Screen	CRd Induction Cycles 1-4							
DAY	**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**End of Cycle 4**
SFLC[19]	X								X[19]
Neurological Assessment[20]	X	X[20]							
Correlative Samples[21]	X								X[21]
Bone marrow aspirate sample for MRD analysis[32]	X								X
CT-PET[33]	X								X
Adverse Events[22]		Ongoing							
Concomitant Medications		Ongoing							
Register Patient into Revlimid REMS® program and prescribe lenalidomide[24]	X								
Carfilzomib[25]		X	X	X	X	X	X		
Revlimid® (Lenalidomide)[26]		X	X	X	X	X	X		
Dexamethasone[27]		X	X[27]	X	X[27]	X	X[27]	X	

***Following cycle 4, subjects will proceed to Stem Cell Collection and Autologous Stem Cell Transplant (section 6.4)**

PROCEDURES	CRd Consolidation Cycles 5-8 (Following ASCT Days 70-90 but not more than 120)								CRd Maintenance Cycles 9-18						End of Tx	LTFU
DAY	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**End of Cycle 8[30]**	**1**	**2**	**8**	**15**	**16**	**22**		
Skeletal Survey															X	

PROCEDURES	CRd Consolidation Cycles 5-8 (Following ASCT Days 70-90 but not more than 120)								CRd Maintenance Cycles 9-18						End of Tx	LTFU
DAY	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**End of Cycle 8[30]**	**1**	**2**	**8**	**15**	**16**	**22**		
ECG[3]															X	
Physical Exam[5]	X								X						X	
Vital Signs	X	X	X	X	X	X			X	X		X	X		X	
Height, Weight, BSA	X								X						X	
24-hour urine[7]	X[7]								X[7]						X[7]	
Urinalysis																
Hematology[9]	X				X				X						X	
Serum Chemistry	X[11]		X[11]		X[11]			X[11]	X[11]						X	
Pregnancy Test[13]	X				X[14]				X[14]			X[14]			X[14]	
Disease Assessment								X[15]						X[15]		X[23]
β2-microglobulin								X								
SPEP, UPEP[16]	X							X	X						X	
Immunofixation – Serum and Urine	X							X	X						X	
BM Aspirate/biopsy, cytogenetics, FISH[18]								X[18]							X[18]	X
Plasmacytoma Evaluation															X	
Quantitative Igs	X							X	X						X	
SFLC[19]								X[19]							X[19]	
Neurological Assessment[20]	X								X						X	
Correlative Samples[21]															X[21]	

PROCEDURES	CRd Consolidation Cycles 5-8 (Following ASCT Days 70-90 but not more than 120)								CRd Maintenance Cycles 9-18						End of Tx	LTFU
DAY	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**End of Cycle 8[30]**	**1**	**2**	**8**	**15**	**16**	**22**		
Bone marrow aspirate sample for MRD analysis[32]	X							X							X	X[32]
CT-PET[33]	X								X						X	X[33]
Adverse Events[22]	Ongoing															
Concomitant Medications	Ongoing															
Carfilzomib[25]	X	X	X	X	X	X			X	X		X	X			
Revlimid® (Lenalidomide)[26,28]	X	X	X	X	X	X			X	X	X	X	X	X		X[28]
Dexamethasone[27]	X		X		X		X		X		X	X		X		
Survival and New Cancer Evaluation [29]																X

* Variations of ± 3 days of the scheduled visit are permitted however doses of carfilzomib may only be rescheduled by up to 2 days (Section 5.2.3).

**The CRd consolidation cycles are cycle 5 – 8. Maintenance cycles are 5-18 for patients that do not proceed to ASCT.

Footnotes for Appendix A

+ Documented informed consent must be obtained within ≤ 30 days prior to initiation of therapy.

1. Includes neuropathy history.
2. May be within 30 days planned treatment start. Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Skeletal surveys performed outside of the 30 day window may be considered for inclusion. Please contact the Lead Principal Investigator and/or/CRA on a case-by-case basis. End of treatment skeletal survey only if clinically indicated.
3. 12-lead ECG, including QTc interval. End of treatment ECG only if clinically indicated.
4. For Day 1 of cycle 1, screening results may be used if within 7 days of treatment start.
5. Complete physical exam (including vital signs [systolic and diastolic blood pressure, respiration, pulse, oral temperature], height, weight, calculation of body surface area [BSA]) and ECOG score) required at screening and Day 1 of each cycle. .
6. Systolic and diastolic blood pressure, pulse, respiration, temperature approximately 1 hour before dosing.

7. 24 hour urine total protein, urine protein electrophoresis (UPEP), and urine protein immunofixation. For subjects whose disease is being monitored through UPEP, additional post baseline 24-hour urine collections are required as indicated.
8. Prothrombintime, activated partial thromboplastin time, and international normalized ratio.
9. Hemoglobin, hematocrit, WBC with complete differential, RBCs, platelet count. Results must be reviewed before dosing.
10. Cycles 1 and 2 only and subsequent cycles as clinically indicated or per institutional standard of care.
11. Full serum chemistry panel at Screening, Days 1, 8, and 15 of Cycles 1-8, and Day 1 of Cycles 9+: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, uric acid, total protein, albumin, calcium, phosphorus, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH. Results must be reviewed before dosing in Cycles 1 and 2.
12. Abbreviated serum chemistry panel on Days 2, 9, and 16 of Cycles 1 and 2 only or as clinically indicated (e.g., risk factors for tumor lysis syndrome): sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, uric acid.
13. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not had a hysterectomy or bilateral oophorectomy; or 2) has not been naturally post-menopausal for at least 24 consecutive months (i.e., menses within the preceding 24 months) See Appendix F of protocol for details.
14. Pregnancy tests must occur within 10-14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
15. After 4 cycles, subjects are evaluated before receiving ASCT. It is anticipated that all patient will proceed to ASCT but if patient becomes not eligible, continuation of CRd treatment as per maintenance schedule can be granted by the Lead Principal Investigator..
16. Serum protein electrophoresis and urine protein electrophoresis (the latter only for those whose disease is being followed by UPEP). Subjects with baseline urine protein greater than 200 mg/24 hours must have a UPEP to confirm VGPR or better. Obtain blood for M-protein levels measured by SPEP or quantitative immunoglobulins for those subjects in whom SPEP/UPEP are felt to be unreliable (IgA type multiple myeloma), depending upon which studies were positive at baseline.
17. Disease assessments on Day 15 of Cycle 1 (only) are only for assessing onset of early response, not for definitive achievement of response.
18. Bone marrow aspirate and biopsy - quantify % myeloma cell involvement; bone marrow sample for cytogenetics and fluorescent in situ hybridization (FISH). Bone marrow aspirate and biopsy should be performed at screening, end of cycle 4 (pre-transplant), 3-months post-transplant, and the end of CRd consolidation (end of cycle 8). See sections 6.3-6.5. Repeat bone marrow biopsy/aspirate if CR is suspected (e.g., end of cycle 4) and as appropriate to confirm achievement of sCR, CR, or nCR (aspirate only—biopsy not required).If institution has established flow-based multi-color study for minimal residual disease (MRD), this evaluation should include MRD evaluation. Bone marrow biopsy/aspirate performed outside of the 30 day window may be considered for inclusion. Please contact the Lead Principal Investigator and/or the CRA on a case-by-case basis. (Cytogenetics is required at screening only. If cytogenetics is completed at a time point other than screening, the results should be captured in eCRF)
19. SFLC repeated only to confirm CR.
20. Screening and Day 1 of every cycle. Includes neurologic exam (to detect peripheral neuropathy and/or changes in pre-existing neuropathy) and examination of clinical AEs indicative of neuropathy. Collect FACT/GOG neurotoxicity questionnaire at each time point above.
21. Peripheral blood and bone marrow aspirate samples collected at screening, time of response (to confirm complete response), and/or end-of-treatment visit. Buccal mucosa swab will be collected at screening only.

22. AEs will be collected from the time of signing informed consent. 30 days following the last dose of CRd, during ASCT period, patients will be considered to be off-study so no toxicities will be recorded for this period. AE tracking will re-commence at the initiation of Cycle 5. All concomitant medications must be recorded on the concomitant medications case report form from 21 days before Day 1 through 30 days following the last dose of study drugs.
23. Assessment for disease progression in subjects who did not progress during treatment. At least every 3 months (+/- 30 days) for 5 years from safety follow-up visit (which must be 28days (+/- 3 days) post-last study treatment).
24. Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMSt® program.
25. Cycles 1-8: Days 1, 2, 8, 9, 15 & 16. Cycles 9-18 Days 1, 2, 15 & 16
26. Daily on Days 1-21 followed by a 7-day rest period every 28 days. On day coinciding with carfilzomib administration, lenalidomide should be taken at least 4 hours after the carfilzomib dose and may be self-administered at home by the subject. On days that carfilzomib is not administered, lenalidomide should be taken at approximately the same time each day.
27. Days 1, 8, 15 and 22. Dexamethasone is given between 30 minutes and 4 hours before carfilzomib on days they coincide. Cycles 5-8 dexamethasone will be reduced down to 20 mg on days 1, 8, 15 and 22. Cycles 9-18 represent the CRd Maintenance Phase of therapy and the dose of dexamethasone will remain 20 mg on days 1, 8, 15 and 22. Subjects may be given 4 mg dexamethasone p.o. or IV on Days 2, 9 and 16 in Cycles 1 and 2 prior to carfilzomib infusion if signs of tumor flare are present. This will be prescribed at the Treating Investigator's discretion.
28. Single-agent Lenalidomide maintenance therapy, is recommended using last tolerated dose of lenalidomide for 21 days in 28 day cycles after CRd protocol treatment (cycles 1-18) is completed.
29. Patients will be followed for survival and development of any new cancers, at least every 3 months. Reports of any death should include date of death and specific cause (disease under study or specify other cause).
30. Evaluations at the end Cycle 8 may be done on Day 1 of the next Cycle 9
31. Plasmacytoma evaluation is required at screening only and may be completed as physical exam or imaging if indicated and at the treating investigator's discretion. After screening, plasmacyotoma evaluation is required only for patients who have no other measurable disease and/or at investigator's discretion.
32. Two bone marrow samples for central Minimal Residual Disease (MRD) analysis by flow at the University of Chicago and by NGS at Adaptive Biotechnologies will be collected from all subjects: 1) screening (sample is required for calibration of MRD by gene sequencing In the event that a superfluous bone marrow aspirate –BMA- sample from screening was not available, slides of BMA smear or clot from a time prior to enrollment can be used), 2) end of cycle 4, 3) post-transplant, 4) end of cycle 8, 5) end of cycle 18 (EOT), 6) 1, 2, 3, and 5 years after EOT for all subjects; 7) any time that a bone marrow is performed as SOC to assess CR response. For any bone marrow collected after Cycle 4, Cycle 8 or Cycle 18, the visit may be done on Day 22-28 of that cycle.
33. A CT-PET will be performed to confirm MRD-negative disease per Standard of Care, at every time-point when MRD is checked. A bone marrow done as SOC a year after the EOT BM will be tested for MRD and a CT-PET done to confirm MRD-negative disease.

APPENDIX B. MULTIPLE MYELOMA STAGING

A. Durie-Salmon Staging

Stage I

All of the following must be present:

- Hemoglobin > 10.5 g/dL or hematocrit >32%
- Serum calcium level normal (≤ 12mg/dL)
- Low serum myeloma protein production rates as evidenced by all of the following:
  - IgG peak < 5g/dL
  - IgA peak < 3g/dL
  - Bence Jones protein < 4g/24 h
- No bone lesions

Stage II

All patients who do not meet criteria for Stage I or III are considered Stage II.

Stage III

One of the following abnormalities must be present:

- Hemoglobin < 8.5 g/dL, hematocrit < 25%
- Serum calcium >12 mg/dL
- Very high serum or urine myeloma protein production rates as evidenced by one or more of the following:
  - IgG peak > 7g/dL
  - IgA peak > 5g/dL
  - Bence Jones protein > 12g/24 h
  - > 3 lytic bone lesion on bone survey (bone scan not acceptable)

Sub-classification

a: Serum creatinine < 2.0 mg/dL

b: Serum creatinine >2.0 mg/dL

B. International Myeloma Working Group International Staging System (ISS)

1. Stage I: B2M < 3.5 plus serum albumin ≥3.5 (med S 62m)
2. Stage II: B2M < 3.5 but serum alb. < 3.5 OR B2M 3.5 - < 5.5 (med S 44m)
3. Stage III: B2M ≥ 5.5 (med S 29m)
4. Subclassify stages 1+2 according to cr< or ≥ 2 and stage 3 according to low platelets (< 130k) or high LDH

IMWG criteria for symptomatic myeloma:

All three criteria must be met:

1. Clonal bone marrow plasma cells and/or documented clonal plasmacytoma

2. Presence of serum and/or urinary monoclonal protein

3. Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

-Hypercalcemia: serumcalcium ≥ 11.5 mg/dl or

-Renal insufficiency: serum creatinine >2 mg/dl or

-Anemia: hemoglobin at least 2 g/dl below the lower limit of normal or a hemoglobin <10 g/dl or

-Bone lesions: lytic lesions, osteopenia or pathologic fractures

APPENDIX C. ECOG PERFORMANCE SCALE

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

APPENDIX D. NCI CTCAE VERSION 4.0

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

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

APPENDIX E. RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Table E1: IMWG Criteria

Response	*IMWG criteria*[1,2]
sCR Stringent Complete Response	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR Complete Response	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR Very Good Partial Response	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR Partial Response	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease

Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4]and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h)and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All relapse categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at anytime before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD:

- clarified that bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels.
- clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Table E2:Additional response criteria for specific disease states[1,2,3,4]

Minor response in patients with relapsed and refractory myeloma adapted from the EMBT criteria3	≥ 25% but < 49% reduction of serum M protein and reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required

	No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Near Complete Response nCR	The absence of myeloma protein on electrophoresis, with positive immunofixation, stable bone disease, and a normal serum calcium concentration
Immunophenotypic CR	Stringent CR plus Absence of phenotypic abarrent PC (clonal) in bone marrow with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with ≥4 colors)
Molecular CR	Stringent CR plus negative ASO-PCR (sensitivity 10^{-5})

1. Durie et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73
2. S. Vincent Rajkumar, Jean-Luc Harousseau, Brian Durie, Kenneth C. Anderson, Meletios Dimopoulos, Robert Kyle, Joan Blade, Paul Richardson, Robert Orlowski, David Siegel, Sundar Jagannath, Thierry Facon, Hervé Avet-Loiseau, Sagar Lonial, Antonio Palumbo, Jeffrey Zonder, Heinz Ludwig, David Vesole, Orhan Sezer, Nikhil C. Munshi, and Jesus San Miguel. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1 . Blood First Edition Paper, prepublished online February 3, 2011;DOI 10.1182/blood-2010-10-299487
3. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Srkalovic G, Alsina M, Alexanian R, Siegel D, Orlowski RZ, Kuter D, Limentani SA, Lee S, Hideshima T, Esseltine DL, Kauffman M, Adams J, Schenkein DP, Anderson KC. A Phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609, June 2, 2003.
4. Richardson et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Eng J Med. 352:2487-98, 2005

APPENDIX F. RISKS OF FETAL EXPOSURE, PREGNANCY TESTING

GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of Revlimid REMS®.

Females of childbearing potential (FCBP) must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study:

- for at least 28 days before starting lenalidomide;
- while participating in the study
- for at least 28 days after discontinuation from the study.

The 2 reliable methods of contraception must include 1 highly effective method—intrauterine device, hormonal (birth control pills, injections, or implants), tubal ligation, or partner's vasectomy—and 1 additional effective barrier method—latex condom, diaphragm, or cervical cap. FCBP must be referred to a qualified provider of contraceptive methods if needed.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Before starting lenalidomide:

Female subjects

- FCBP must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to initiating lenalidomide. The first pregnancy test must be performed within 10-14 days before, and the second pregnancy test must be performed within 24 hours beforeprescribing lenalidomide (prescriptions must be filled within 7 days).
- The subject may not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative.

Male subjects

- Must agree to use a latex condom during sexual contact with FCBP while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

During study participation and for 28 days following discontinuation from the study

All subjects

- If pregnancy or a positive pregnancy test occurs in a study subject or in the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Female subjects

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and 14 and 28 days after discontinuation from the study.
- In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use 2 reliable methods of birth control at each visit.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.

Male subjects

- Must agree to use a latex condom during sexual contact with FCBP while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

APPENDIX G: COCKROFT-GAULT ESTIMATION OF CRCL

Cockroft-Gault estimation of creatinine clearance (CrCl):
(Cockroft 1976; Luke 1990)

$$\text{CrCl (mL/min) for males:} \quad \frac{(140\text{-age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

$$\text{CrCl (mL/min) for males:} \quad \frac{(140\text{-age}) \times (\text{weight, kg}) \times 0.85}{72 \times (\text{serum creatinine, mg/dL})}$$

*Measured creatinine clearance on 24 hour urine collection can be used and is acceptable. If measured CrCl is different than calculated, measured CrCl should be used for eligibility assessment and/or dose modifications.

APPENDIX H: FACT/GOG-NEUROTOXICITY QUESTIONNAIRE, VERSION 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J ClinOncol* 1993;11(3):570-79.

APPENDIX I: IMWG CRITERIA FOR THE DIAGNOSIS OF MYELOMA

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow >/=10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (>/=1)[c] ▪ [C] Calcium elevation in the blood (serum calcium >10.5 mg/l or upper limit of normal [R] Renal insufficiency (serum creatinine >2mg per 100 ml) [A] Anemia (hemoglobin <10 g per 100 ml or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]
Monoclonal gammopathy of undetermined significance (MGUS)	• Serum monoclonal protein low[e] • Monoclonal bone marrow plasma cells <10% • No evidence of end-organ damage attributable to the clonal plasma cell disorder:

	○ Normal serum calcium, hemoglobin level and serum creatinine ○ No bone lesions on full skeletal X-ray survey and/or other imaging if performed ○ No clinical or laboratory features of amyloidosis or light chain deposition disease
Smoldering or indolent myeloma[f]	• Monoclonal protein present in the serum 3 g per 100 ml or higher or • Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy • No evidence of end-organ damage attributable to the clonal plasma cell disorder: ○ Normal serum calcium, haemoglobin level and serum creatinine ○ No bone lesions on full skeletal X-ray survey and/or other imaging if performed ○ No clinical or laboratory features of amyloidosis or light chain deposition disease
Solitary plasmacytoma of bone	• Biopsy-proven plasmacytoma of bone in a single site only. X-rays and

	magnetic resonance imaging and/or • FDG PET imaging (if performed) must be negative outside the primary site. • The primary lesion may be associated with a low serum and/or urine M-component • The bone marrow contains no monoclonal plasma cells • No other myeloma-related organ dysfunction

Adapted with permission from Kyle and Rajkumar, Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma..*Leukemia* 2009; 23: 3–9.

[a]These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[b]If no monoclonal protein is detected (non-secretory disease), then >/= 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[c]A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

[d]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then >/= 30% plasma cells are required in the bone marrow.

[e]Low is defined as serum M protein <3.0 g per 100 ml.

[f]These criteria identify Stage IA myeloma by Durie/Salmon stage.