THE LANCET
Oncology

Supplementary appendix

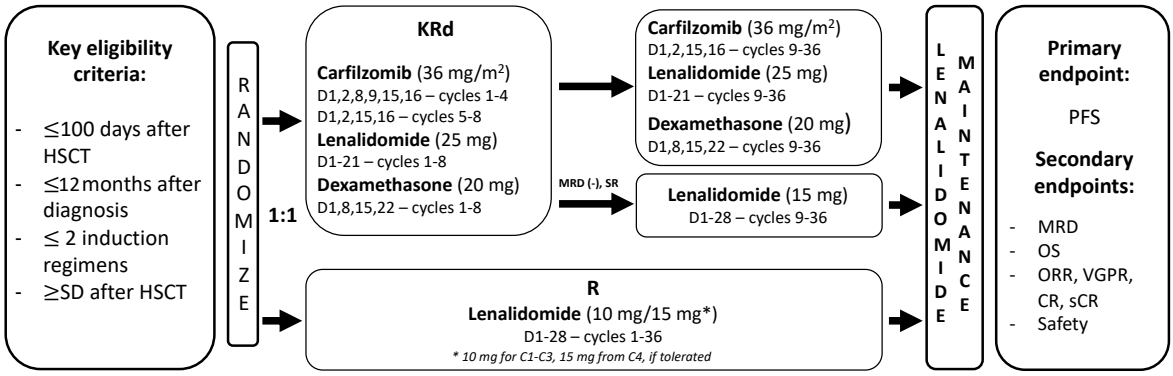
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dytfeld D, Wróbel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023; published online Jan 12. https://doi.org/10.1016/S1470-2045(22)00738-0.

Supplementary appendix

Table of Contents

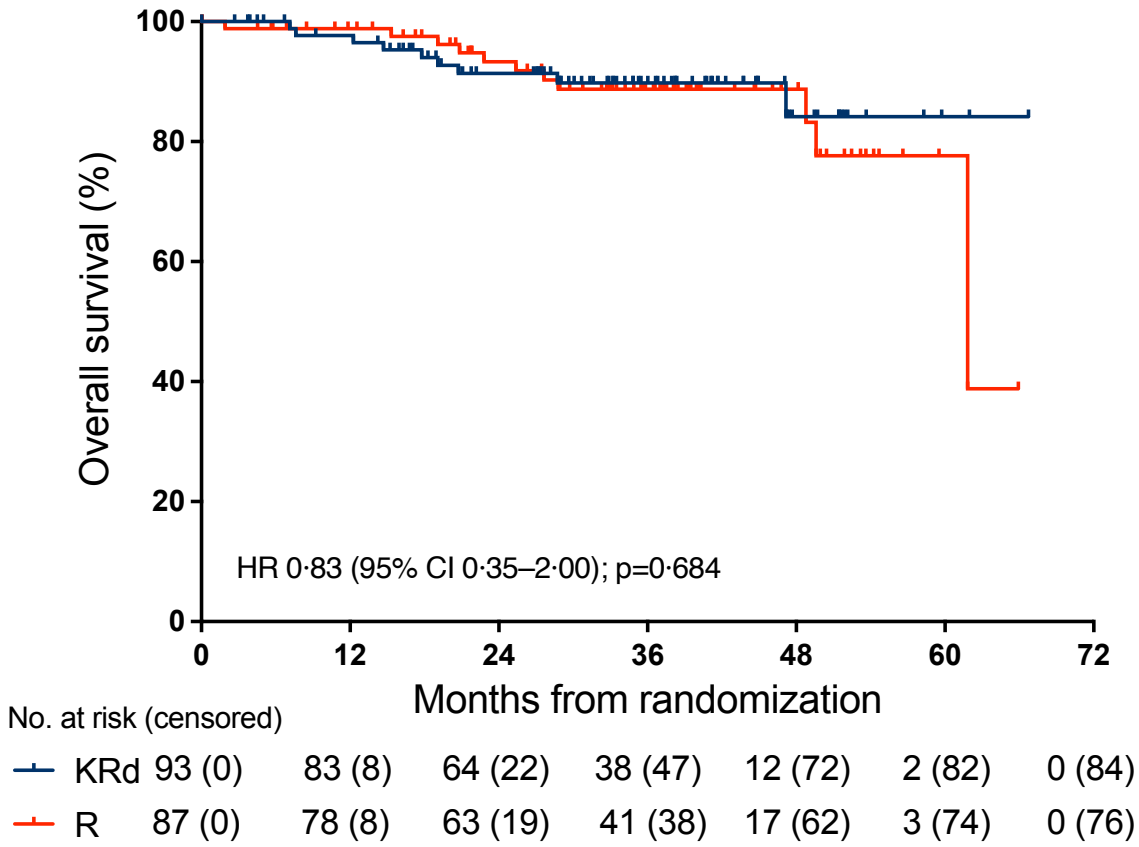
Supplementary figure S1: Study design



1. Stratification factors included a) post-transplant response (≥VGPR vs <VGPR), standard-risk vs high-risk cytogenetics (defined per protocol as presence or absence of any of del(13), t(4;14), t(14;16), del(17p), and/or hypodiploidy), site location (Poland vs USA)
2. KRd pts with standard risk cytogenetics having reached IMWG MRD negativity (Kumar et al, Lancet Oncol 2016; 17:e328-46) after C6 converted to single-agent lenalidomide after C8

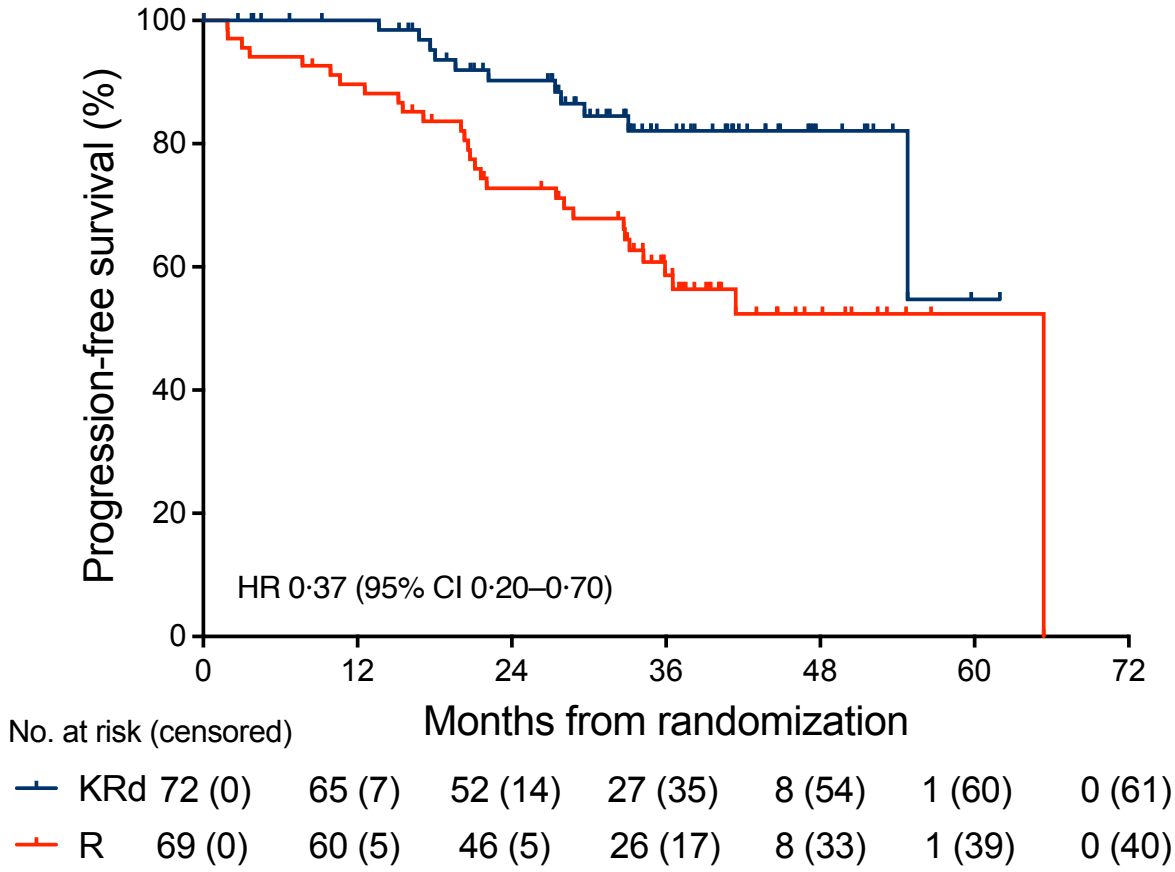
ASCT=autologous stem cell transplantation. CR=complete response. KRd=carfilzomib, lenalidomide, and dexamethasone. MRD=minimal residual disease. ORR=overall response rate. PFS=progression-free survival. R= lenalidomide. sCR=stringent complete response. SD=stable disease. SR=standard risk cytogenetics. VGPR=very good partial response.

Supplementary figure S2: Kaplan–Meier estimates of overall survival



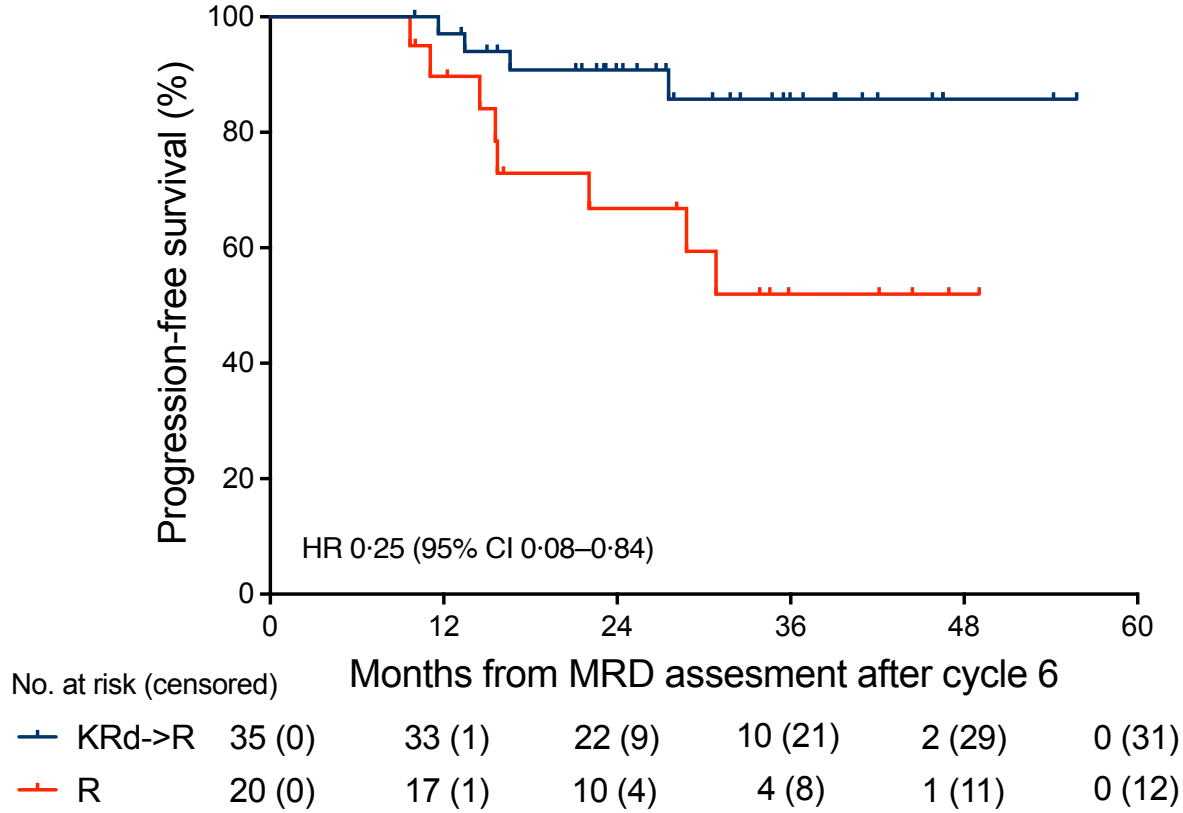
HR=hazard ratio. KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide

Supplementary figure S3: Kaplan-Meier estimates of progression-free survival in patients with standard-risk disease



HR=hazard ratio. KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

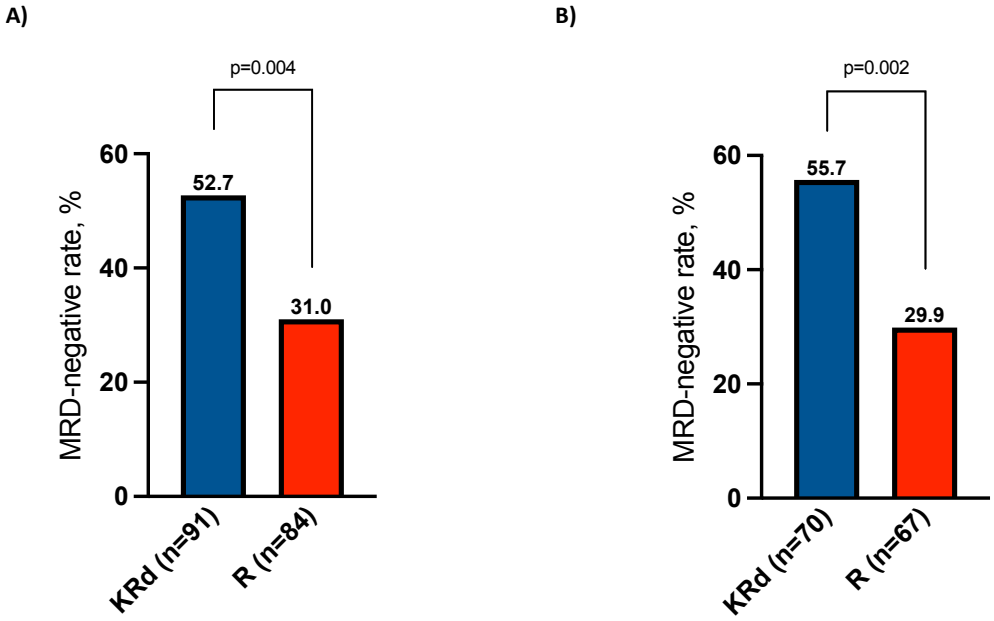
Supplementary figure S4: Kaplan-Meier estimates of progression-free survival in landmark analysis of patients with standard-risk disease and IMWG minimal residual disease negativity after cycle six.



After cycle eight, 35 patients in the KRd group who met criteria for de-escalation were converted to single-agent lenalidomide and are included in this analysis.

HR=hazard ratio. IMWG=International Myeloma Working Group. KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

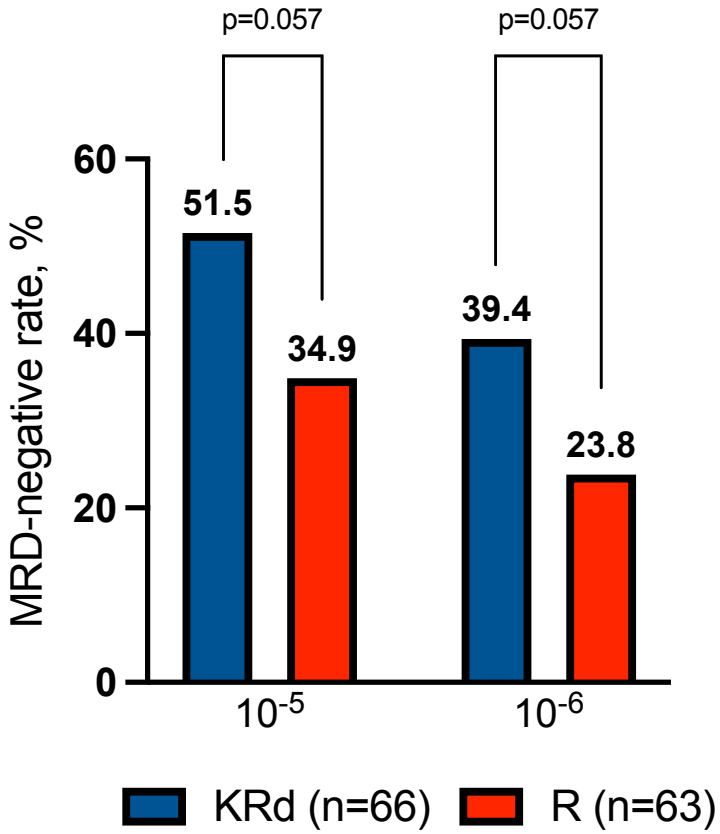
Supplementary figure S5: IMWG MRD-negativity rates



A) MRD-negativity rate in all evaluable patients
B) MRD-negativity rate in evaluable patients with standard risk cytogentics

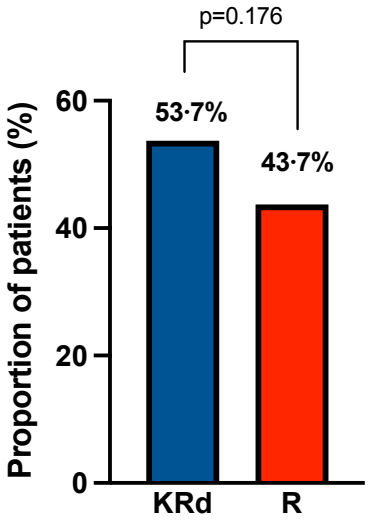
IMWG=International Myeloma Working Group. KRd=carfilzomib, lenalidomide, and dexamethasone. MRD=minimal residual disease. R=lenalidomide.

Supplementary figure S6: Sensitivity thresholds for MRD-negativity rates assessed by NGS



KRd=carfilzomib, lenalidomide, and dexamethasone. MRD=minimal residual disease. NGS=next generation sequencing. R=lenalidomide.

Supplementary figure S7: Proportion of patients with improvement in response (baseline vs best response) assessed per IMWG criteria



IMWG=International Myeloma Working Group. KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

Supplementary table S1: Study enrolment sites

Site name	Country	Primary Investigator	Number of enrolled patients
Szpital Kliniczny im. Heliodora Święcickiego w Poznaniu, Oddział Hematologii i Transplantacji Szpiku	Poland	Dominik Dytfeld	69
Uniwersytecki Szpital Kliniczny im. Jana Mikulicza Radeckiego we Wrocławiu, Klinika Hematologii, Nowotworów Krwi i Transplantacji Szpiku	Poland	Tomasz Wróbel	23
Instytut Hematologii i Transfuzjologii w Warszawie	Poland	Krzysztof Jamroziak	20
Wielospecjalistyczne Wojewódzkie Centrum Onkologii i Traumatologii w Łodzi, Klinika Hematologii	Poland	Tadeusz Robak	18
University of Chicago	USA	Andrzej Jakubowiak	18
Szpital Uniwersytecki nr 2 im. Jana Biziela w Bydgoszczy, Klinika Hematologii	Poland	Jarosław Czyż	8
Samodzielny Publiczny Szpital Kliniczny nr 1 w Lublinie	Poland	Olga Czabak	7
Narodowy Instytut Onkologii - Państwowy Instytut Badawczy im Marii Skłodowskiej-Curie w Warszawie, Klinika Nowotworów Układu Chłonnego	Poland	Jan Walewski	6
Uniwersyteckie Centrum Kliniczne w Gdańsku, Klinika Hematologii i Transplantologii	Poland	Agata Tyczyńska	6
Wielospecjalistyczny Szpital Wojewódzki w Gorzowie Wielkopolskim, Oddział Hematologii i Chorób Rozrostowych Układu Krwiotwórczego z Pododdziałem Dziennej Chemioterapii	Poland	Katarzyna Brzeźniakiewicz-Janus	2
Memorial Sloan-Kettering Cancer Center	USA	Oscar B Lahoud	2
Wayne State University Karmanos Cancer Institute	USA	Jeffrey A Zonder	1

Supplementary table S2: Dose reductions

		KRd (n=93)		R (n=87)
		KRd continued (n=52)	Conversion from KRd to R alone after cycle eight (n=41)	
Patients with drug dose reduced at data cutoff compared to the beginning of treatment	Carfilzomib	8 (15%)	4 (10%)	·
	Lenalidomide	9 (17%)	7 (17%)	35 (40%)
	Dexamethasone	10 (19%)	6 (15%)	·

KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

Supplementary table S3: Subgroup analysis of MRD-negativity rates

	Carfilzomib, lenalidomide, and dexamethasone (n=91)	Lenalidomide (n=84)	*p value*
Age, years			
<60	34/55 (61·8%)	15/44 (34·1%)	*0·006*
≥60	14/36 (38·9%)	11/40 (27·5%)	*0·291*
Sex			
Female	24/48 (50·0%)	13/34 (38·2%)	*0·292*
Male	24/43 (55·8%)	13/50 (26·0%)	*0·003*
ECOG performance status			
0	23/44 (52·3%)	8/30 (26·7%)	*0·028*
1	25/47 (53·2%)	18/54 (33·3%)	*0·044*
ISS stage			
I-II	45/77 (58·4%)	21/67 (31·3%)	*0·001*
III	3/14 (21·4%)	5/17 (29·4%)	*0·613*
Response after ASCT			
≥VGPR	46/81 (56·8%)	24/77 (31·2%)	*0·001*
<VGPR	2/10 (20·0%)	2/7 (28·6%)	*0·682*
Cytogenetic profile			
Standard risk	39/70 (55·7%)	20/67 (29·9%)	*0·002*
High risk*	9/21 (42·9%)	6/17 (35·3%)	*0·635*
Number of induction regimens			
One	43/84 (51·2%)	25/79 (31·7%)	*0·011*
Two	5/7 (71·4%)	1/5 (20·0%)	*0·079*

ASCT=autologous stem cell transplantation. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. VGPR=very good partial response.

* Presence of any of del13, t(4:14), t(14:16), del17p, or hypodiploidy.

Supplementary table S4: Adverse events in the safety population

	KRd (n=92)			R (n=86)		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Haematological						
Neutropenia	4 (4%)	36 (39%)	8 (9%)	3 (3%)	50 (58%)	2 (2%)
Thrombocytopenia	11 (12%)	8 (9%)	4 (4%)	8 (9%)	5 (6%)	1 (1%)
Lymphopenia	11 (12%)	5 (5%)	0	6 (7%)	2 (2%)	0
Anaemia	11 (12%)	3 (3%)	1 (1%)	1 (1%)	0	0
Non-haematological						
Diarrhoea	27 (29%)	1 (1%)	0	17 (20%)	2 (2%)	0
Nausea/vomiting	12 (13%)	0	0	3 (4%)	0	0
Abdominal pain	5 (5%)	0	0	8 (9%)	0	0
Dyspepsia	5 (5%)	0	0	1 (1%)	0	0
Dental caries	2 (2%)	1 (1%)	0	0	0	0
Toothache	1 (1%)	0	0	1 (1%)	1 (1%)	0
Anal haemorrhage	0	0	0	0	1 (1%)	0
Pancreatitis	0	0	0	0	1 (1%)	0
Fever	16 (17%)	0	0	2 (2%)	0	0
Flu-like symptoms	11 (12%)	1 (1%)	0	5 (6%)	1 (1%)	0
Fatigue	10 (11%)	0	0	4 (5%)	0	0
Pain	13 (14%)	0	0	11 (13%)	0	0
Febrile neutropenia	0	3 (3%)	1 (1%)	0	5 (6%)	0
Eye disorders	10 (11%)	1 (1%)	0	5 (6%)	1 (1%)	0
Cataract	1 (1%)	1 (1%)	0	0	1 (1%)	0
Myocardial infarction	0	0	0	0	1 (1%)	0
Upper respiratory tract infection	51 (56%)	5 (5%)	0	36 (42%)	3 (4%)	0
Lower respiratory tract infection	8 (9%)	6 (7%)	1 (1%)	4 (5%)	1 (1%)	0
Urinary tract infection	7 (8%)	0	0	3 (3%)	0	0
Skin infection	5 (5%)	1 (1%)	0	9 (10%)	1 (1%)	0
COVID-19	4 (4%)	0	0	1 (1%)	1 (1%)	0
Tooth infection	3 (3%)	0	0	1 (1%)	1 (1%)	0
Enterocolitis infection	1 (1%)	1 (1%)	0	0	0	0
Papulopustular rash	1 (1%)	0	0	4 (5%)	1 (1%)	0
Influenza A	0	1 (1%)	0	0	0	0
Limb oedema	6 (7%)	0	0	2 (2%)	0	0
Allergic reaction	5 (5%)	0	0	1 (1%)	1 (1%)	0
Alanine aminotransferase increased	11 (12%)	3 (3%)	0	9 (10%)	0	0
Aspartate aminotransferase increased	9 (10%)	3 (3%)	0	4 (5%)	0	0
Creatinine increased	5 (5%)	0	0	3 (3%)	1 (1%)	0
Blood bilirubin increased	9 (10%)	1 (1%)	0	1 (1%)	0	0
Decreased gamma globulin concentration	0	1 (1%)	0	0	0	0
Hypokalaemia	7 (8%)	1 (1%)	0	4 (5%)	1 (1%)	0
Hyperglycaemia	5 (5%)	2 (2%)	0	3 (3%)	0	0
Hypocalcaemia	3 (3%)	1 (1%)	0	0	0	0

Hypomagnesemia	1 (1%)	1 (1%)	0	0	0	0
Hypophosphatemia	0	0	0	2 (2%)	1 (1%)	0
Electrocardiogram QT interval prolonged	0	1 (1%)	0	0	0	0
Peripheral sensory neuropathy	8 (9%)	0	0	10 (12%)	1 (1%)	0
Myalgia	7 (8%)	1 (1%)	0	3 (3%)	0	0
Headache	8 (9%)	1 (1%)	0	3 (4%)	0	0
Dizziness	5 (5%)	0	0	3 (4%)	0	0
Paraesthesia	5 (5%)	0	0	4 (5%)	0	0
Syncope	0	1 (1%)	0	0	1 (1%)	0
Transient ischemic attack	0	1 (1%)	0	0	0	0
Spasticity	0	0	0	1 (1%)	1 (1%)	0
Stroke	0	0	0	0	1 (1%)	0
Insomnia	7 (8%)	0	0	2 (2%)	0	0
Renal and urinary disorders	7 (8%)	0	0	4 (5%)	0	0
Psychosis	0	0	0	0	1 (1%)	0
Allergic rhinitis	8 (9%)	0	0	4 (5%)	0	0
Cough	7 (8%)	0	0	4 (5%)	0	0
Dyspnoea	5 (5%)	0	0	1 (1%)	0	0
Maculopapular rash	3 (3%)	1 (1%)	0	6 (7%)	1 (1%)	0
Sore throat	1 (1%)	0	0	5 (6%)	0	0
Respiratory failure	0	0	0	0	0	1 (1%)
Hypertension	7 (8%)	1 (1%)	0	1 (1%)	1 (1%)	0
Hypotension	2 (2%)	1 (1%)	0	1 (1%)	0	0
Thromboembolic event	1 (1%)	1 (1%)	0	1 (1%)	2 (2%)	0
Second primary malignancies	1 (1%)	0	0	2 (2%)	0	0

KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

Supplementary table S5: Serious adverse events in the safety population

	No. of patients	
SAE term	**KRd**	**R**
Abdominal aorta aneurysm	1	0
Acute cholecystitis	0	2
Acute kidney injury	1	0
Anemia	1	0
Appendicitis	1	0
Arrhythmia	1	0
Back pain	1	0
C. Difficile infection	1	0
Cardiac pain	0	1
Cellulitis	1	0
COVID-19	0	1
Dizziness	1	0
Dyspnea	0	1
Haemolysis	1	0
Haemorrhage	0	1
Heart failure	0	1
Influenza	5	0
Lower respiratory tract infection	11	3
Meningioma	1	0
Myelodysplastic syndrome	1	0
Metatarsal benign lesion	1	0
Myocardial infarction	0	2
Nausea/vomiting	1	0
Neutropenic fever	0	2
Psychosis	0	1
Pulmonary embolism	0	1
Respiratory failure	0	1
Rib fracture	1	0
Secondary acute myeloid leukemia	0	1
Septic shock	1	0
Stroke	0	1
Syncope	1	0
Thrombocytopenia	2	0
TIA	2	0
Upper respiratory tract infection	0	3
Urinary tract infection	3	0
Venous thrombosis	1	0
Vertebroplasty	0	1

Supplementary table S6: Causes of death

No.	Arm	Cause of death	Drug-related?
1	R	Disease progression	No
2	KRd	Disease progression	No
3	KRd	Disease progression	No
4	KRd	Disease progression	No
5	KRd	Lower respiratory tract infection	Yes
6	R	COVID-19	No
7	KRd	Disease progression	No
8	R	Septic shock	No
9	R	Disease progression	No
10	KRd	Influenza	No
11	KRd	Disease progression	No
12	R	Disease progression	No
13	KRd	Disease progression	No
14	R	Disease progression	No
15	R	Heart failure	No
16	R	Disease progression	No
17	R	Disease progression	No
18	KRd	Septic shock	No
19	R	Disease progression	No
20	R	Disease progression	No

KRd=carfilzomib, lenalidomide, and dexamethasone. R=lenalidomide.

Clinical Study Protocol

PROTOCOL INFORMATION

STUDY TITLE:	Phase 3 Randomized trial of carfilzomib, lenalidomide, dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma
SPONSOR IN THE EU:	Polish Myeloma Consortium
POLISH LEAD PRINCIPAL INVESTIGATOR:	Dominik Dytfeld, MD, PhD Szamarzewskiego 84 (Poland) +48 61 854-9571 (Direct) +48 61 854-9356 (Fax) dytfeld@me.com
SPONSOR IN THE US AND OVERALL STUDY SPONSOR:	The University of Chicago
US AND OVERALL LEAD PRINCIPAL INVESTIGATOR:	Andrzej Jakubowiak, MD, PhD The University of Chicago Medicine 5841 S. Maryland Avenue Chicago, IL 60637 773-834-1592 (Direct) 773-702-0963 (Fax)
STATISTICIAN:	Kent Griffith Center for Cancer Biostatistics M2180 SPH II Ann Arbor MI 48109-2029 734-615-0601 kentg@umich.edu
TYPE OF RESEARCH:	Interventional, clinical multi-center and randomized
INTERVENTION:	Drug Company Supplied: Carfilzomib (Kyprolis®) (Amgen) Lenalidomide (Revlimid®) (Celgene)
POLISH MYELOMA CONSORTIUM STUDY NUMBER:	PMC006
PROTOCOL CODE NUMBER:	CRd vs R
IRB NUMBER:	IRB15-1286
EudraCT NUMBER:	2015-002380-42
PROTOCOL VERSION:	2.0
PROTOCOL VERSION DATE:	April, 30th 2018

SPONSOR SIGNATORY PAGE

Sponsor Signatory:	**Signature:**	**Date:**
Dominik Dytfeld, MD, PhD, Polish Myeloma Consortium		12/5/18

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.

Phase 3 Randomized trial of carfilzomib, lenalidomide, dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma

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.

Site Investigator Signature Date

Print Site Investigator Name and Title Date

Contents

Summary of changes

Page	Section	Description of Text
15, 33, 74	Synopsis Secondary Objectives: 2. OBJECTIVES 2.2. Secondary Objectives 10. STATISTICAL CONSIDERATIONS 10.1.2. Secondary Objectives	• To determine the rate of MRD-negative disease at 6 and 12 months after randomization • To compare the efficacy (rate of PR, VGPR, CR, and sCR) of KRd vs. Lenalidomide alone after randomization • **To evaluate the safety and tolerability of KRd compared to lenalidomide alone**
16, 17, 36, 37	Synopsis Inclusion / Exclusion Criteria 5. PATIENT SELECTION 5.1. Inclusion Criteria 5.2. Exclusion Criteria	Inclusion Criteria: 1) Patients who completed single autologous stem cell transplant after completion of at most 2 induction regimens (excluding dexamethasone alone) and are in at least stable disease **prior to randomization** in the first 100 days after stem cell transplantation. 2) Patient must be within 12 months of initiation of induction therapy and must have had not more than 2 prior induction regimens 3) Bone marrow specimen will be required at study entry; available DNA sample **from pre-induction BM will** be used for calibration step for MRD evaluation by gene sequencing. 4) Males and females ;?:18 years of age 5) ECOG performance status of 0-1 6) Adequate hepatic function, with bilirubin :s;l.5 x ULN and aspirate aminotransferase (AST) and alanine aminotransferase (ALT) :s; 3 xULN 7) ANC ;?:1.0 x 109/L, hemoglobin ;?:8 g/dL, platelet count ;?:75 x 109/L. 8) Calculated creatinine clearance (by Cockroft-Gault) ;?:50 mljmin or serum creatinine below 2 g/ dL 9) Females of childbearing potential (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 before lenalidomide is prescribed for Cycle 1 (prescriptions must be filled within 7 days). 10) 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.

		11) 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. 12) All study participants must be consented to and registered into the mandatory RevlimidREMS® program and be willing and able to comply with the requirements of RevlimidREMS®. 13) Voluntary written informed consent Exclusion Criteria: 1) Patients who have had more than 12 months of prior therapy. Patients outside of this window may be considered for inclusion. Please contact the Sponsor's representative in Poland or the Lead Primary Investigator as appropriate on a case-by-case basis 2) Patients who progressed after initial therapy. **a) Subjects whose therapy changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression.** **b) No more than two regimens for induction will be allowed, excluding dexamethasone alone.** 3) Potential subjects with evidence of progressive disease as per IMWG criteria 4) Patients who have already started or received post-transplant maintenance or consolidation regimen 5) Patients not able to tolerate lenalidomide or carfilzomib or dexamethasone 6) POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 7) Plasma cell leukemia 8) Waldenstrom's macroglobulinemia or IgM myeloma 9) Peripheral neuropathy;:: Grade 2 at screening 10) Diarrhea > Grade 1 in the absence of antidiarrheals 11) CNS involvement 12) Pregnant or lactating females 13) Radiotherapy within 14 days before randomization. Seven days may be considered if to single area 14) Major surgery within 3 weeks prior to first dose 15) Myocardial infarction within 3 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 16) Prior or concurrent deep vein thrombosis or pulmonary embolism 17) Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening 18) Uncontrolled hypertension or diabetes 19) Acute infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose

		20) Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis 8 virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis 8 virus vaccine are eligible. 21) Non-hematologic malignancy or non-myeloma 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 22) Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
34	4. INVESTIGATIONAL PLAN 4.2. Study Procedure	Subjects enrolled into the KRd arm will initially receive lenalidomide at 15 mg per dose (see below if previously unable to tolerate 15 mg) on days 1-21, carfilzomib at 20 mg/m2 on days 1,2, escalated to 27 mg/m2 on days 8, 9, and then to 36 mg/m2 on days 15 and 16 in the first cycle and 36 mg/m2 in the subsequent cycles, and dexamethasone 20 mg on days 1, 8, 15, 22. Dose oflenalidomide will be escalated up to 25 mg per dose in cycle 2 and subsequent cycles after establishing tolerability of initial doses. Dose modifications will be mandated based on aggressive schedule of dose modification for toxicities as per specific guidelines. Otherwise, patients will continue at their best tolerated dose oflenalidomide on days 1-21 and their best tolerated dose of carfilzomib on days 1, 2,8,9, 15,16 in cycles 1-4 and days 1, 2, 15,16 in cycles 5-8 (in patients with MRD-disease at the end of cycle 6 and no risk factors) or cycles 5-36 (in patients with MRD+ disease and no risk factors or high risk patients at the end of cycle 6) as described in section 1.6. Lenalidomide will begin at a dose of 10 mg PO daily (2 capsules per day). After three months, the dose will be increased,provided ANC 1,000/µL, platelet count 75,000/µL, and all nonhematologic toxicity is :5 grade 1, to 15 mg PO daily (3 capsules per day). **Randomization will occur between Day +70 and +120 post-transplantation. Initiation of maintenance therapy with study drug will begin between day +80 and +130. Prior to randomization, subjects must undergo disease re-staging, must have adequate organ function (ANC 2:1000µL, platelet count 2:75,000µL, creatinine clearance 2: 30mL/min, bilirubin ::.2mg/dL, AST ::.3 x ULN, and Alk. Phos.s 3 x ULN), and must have no evidence of progressive disease.** All subjects will have monthly clinic visits for disease assessments. Treatment will continue on protocol for up to 36 months or if carfilzomib and lenalidomide are permanently discontinued. If dexamethasone is discontinued due to toxicity, carfilzomib and lenalidomide may be continued if tolerated without dexamethasone. Toxicity will be graded

		using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. Patients who complete 8 cycles (who are MRD-Neg and have no risk factors - checked at the end of cycle 6) or 36 cycles will then continue single agent lenalidomide in both arms, at best tolerated dose (up to 15mg) for 28 days in both arms in 28-day cycles. This regimen will continue until there is progression of the disease or the toxicities require discontinuation of the drug.
41, 114-118	6. TREATMENT PLAN 6.1. Study Procedures 6.1.1. Screening Procedures APPENDIX 7: SCHEDULE OF EVENTS	May be within **42** days of planned treatment start (does not need to be repeated if within **42** days). Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri, whole body MRI, or whole body CT.
75	10. STATISTICAL CONSIDERATIONS 10.2. Sample Size Justification & Analysis Plan 10.2.1. Primary Objective Sample Size Justification	The sample size for this trial is based on consideration of PFS after 5 years of treatment. At least sixty-five percent of patients are anticipated to be progression-free at 4 years after receiving KRd compared to 43% with lenalidomide alone, based on the studies of Attal et al. and McCarthy et al. (Attal et al., 2012; McCarthy et al., 2012), and unpublished updated results from KRd trial, (paper in preparation). Using a two-sample, two-sided test of proportions with at most 5% type I error and at least 85% power, 90 patients per study arm are required, for a total study size of 180 patients. To operationalize a time-to-event framework, and after careful consideration of our ability to accrue patients to this study across the likely institutional participants, we estimate that we can accrue 120 patients per year. Patients will be randomized in a 1:1 fashion between the KRd and R study arms, until 90 patients per arm (180 patients in total) are accrued to study, representing 1.5 years of study duration. We expect that loss-to-follow-up in the study population will be extremely low or zero given the careful clinical monitoring that will be expected and mandated by the protocol's language. The study will continue to follow patients at least until the last accrued patient has been followed for **4-6** years following randomization, for a minimum study duration of **6.5** years. The primary analysis of our hypothesis will occur at that time and will be conducted using the log-rank test comparing the product-limit estimate for PFS between study arms. A sample size of 90/arm (N=180) will achieve 85% power with two-sided alpha=0.05 based on two-sided test of proportions. The hypothesized difference in proportions at 4 years, 0.65 vs. 0.43, corresponds to HR=l.96 (assuming exponential distributions), and the study will achieve 88% power with alpha=0.05 for the log-rank test.

<table>
<tr><td>41,

114-118</td><td>6. TREATMENT PLAN
6.1. Study Procedures
6.1. Screening Procedures

APPENDIX 7: SCHEDULE OF EVENTS</td><td>The screening period is a maximum 42 days in length. The screening period starts only after the patient has signed the Informed Consent Form. Refer to the study calendar (Appendix 7)</td></tr>
<tr><td>41</td><td>6. TREATMENT PLAN
6.1. Study Procedures
6.1. Screening Procedures</td><td>Quantify percent myeloma cell involvement, obtain bone marrow aspirate for MRD analysis by flow and NGS and obtain bone marrow aspirate for conventional cytogenetics and fluorescent in situ hybridization. This is required at screening. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening. Calibration sample for MRD is required.</td></tr>
<tr><td>47</td><td>6. TREATMENT PLAN
6.3. Study Drug Administration
6.3.1. Experimental Arm
6.3.1.3. Drug Administration</td><td>Dexamethasone will be administered between 30 minutes and 4 hours preceding the carfilzomib (on days that they coincide), as follows:
• Cycles 1 - 4: 20 mg PO or IV per dose Days 1, 8, 15, 22
• Cycles 5+: 20 mg or best tolerated dose PO or IV per dose Days 1, 8, 15, 22

IV infusion of Dexamethasone only based on the PI decision and with approval from Lead Principal Investi ator.</td></tr>
<tr><td>57</td><td>6. TREATMENT PLAN
6.5. Dose-Modification Guidelines
6.5.2. Response Evaluation</td><td>The first response assessment should be completed at Cycle 2 day 1 and the M-spike value will be compared to baseline (pre-induction treatment) M-spike to determine response. If M-spike is not available, the respective pre-treatment immunoglobulin level and for light-chain-disease-only subjects, involved free light chain level or 24-hr total protein level, will be used to assess response.</td></tr>
<tr><td>60</td><td>7. SAMPLES FOR MRD EVALUATION</td><td>
<table>
<tr><th>MRD sample</th><th>Correlative Sample</th><th>Time Points</th></tr>
<tr><td>Bone Marrow Aspirate (MRD samples) and FFPE/BMA slides (ID/calibration sample from pre-treatment)</td><td>Bone Marrow Aspirate</td><td>Screening/ Pre-treatment (calibration sample for MRD only), screening, at end of 6, 12, 18, 24, and 36 months cycles, EOT, yearly after EOT, and at the time of complete response (if applicable) Progression/Relapse</td></tr>
<tr><td></td><td>Peripheral Blood</td><td>Screening, at end of 6, 12, 18, 24, and 36 cycles, EOT, yearly after EOT, and at the time of complete response (if applicable)</td></tr>
<tr><td></td><td>Plasma, Serum</td><td>Screening, at 6, 12, 18, 24, and 36 months, EOT, yearly after EOT, and at the time of complete response (if applicable) Progression/Relapse</td></tr>
<tr><td></td><td>Buccal Swab</td><td>Screening only</td></tr>
</table>
</td></tr>
</table>

114-118	APPENDIX 7: SCHEDULE OF EVENTS	Day 8 Visit for cycles 5-36 were added in table with schedule of events. The following visits are conducted on cycles 5-36: - Visit on day 1 - Visit on day 2 - **Visit on day 8** - Visit on day 15 - Visit on day 16 - Visit on day 22
114-118	APPENDIX 7: SCHEDULE OF EVENTS	1. Informed consent may be obtained within 30 days of start of treatment **any timepoint prior to screening procedures begin** but and must be obtained prior to any research-related activity.
114-118	APPENDIX 7: SCHEDULE OF EVENTS	14. Disease assessment including bone marrow biopsy (as indicated), SPEP, UPEP, SFLC to be done at any point during treatment when response is suspected. The first response assessment should be completed on Cycle 2 Day 1. **Response will be assessed comparing day 1 of each cycle values to the respective baseline (pre-induction treatment) values for each subject.**
114-118	APPENDIX 7: SCHEDULE OF EVENTS	16. Bone marrow aspirate and biopsy - quantify % myeloma cell involvement; bone marrow sample for cytogenetics and fluorescent **in** situ hybridization (FISH). Repeat bone marrow biopsy/aspirate if CR is suspected and as appropriate to confirm achievement of sCR, CR, or nCR. Bone marrow biopsy/aspirate performed outside of the **42-day** window may be considered for inclusion. Please contact the Lead Primary Investigator at the coordinating site on a case-by-case basis. Cytogenetics and FISH are required at screening only. If cytogenetics/FISH are completed at a time point other than screening, the results should be captured in eCRF.
114-118	APPENDIX 7: SCHEDULE OF EVENTS	17. Bone marrow samples for Minimal Residual Disease (MRD) will be collected from all subjects. **FFPE or BMA slides from subject's pre-induction treatment/high load disease are required for calibration of MRD by gene sequencing, and fresh bone marrow aspirates from the following time-points will be collected:** 1) screening, 2) end of cycle 6, 12, 18, 24, and 36 3) EOT **(when other than Cycle 8),** 4) yearly (±30 days) for up to 6 years from randomization thereafter (LTFU), and 5) any time that bone marrow is performed as SOC to assess CR response. If CR is achieved between cycles 6 and 12, the evaluation for confirmation of CR (and MRD) must be done at cycle 12 ±2 months. If CR is recorded in the middle of a year, it is OK to postpone the BM biopsy until the next scheduled aspiration after discussion with the Lead Principal Investigator. US sites: all samples **(except calibration slides and end of C6, which will go to Adaptive directly)** will be shipped to the University of Chicago. Polish Sites: all samples will be shipped to Poznan University of Medical Science.
114-118	APPENDIX 7: SCHEDULE OF EVENTS	**30. A CT-PET will be performed to confirm MRD-negative disease per Standard of Care at study site, at every time-point when MRD is checked.**
68-70	8.4. Expedited Reporting by the Lead	**The Amgen protocol number (20159903) and the institutional protocol number should be included on SAE reports to Amgen.** **Am2en Dru2 Safety and Pharmacovi2ilance Contact Information in the EU:**

	Principal Investigator Amgen and Celgene	**Phone: +48 509 680 978** **E-mail: eu-pl-safety@amgen.com**

<table>
<tr><td>Study Title</td><td>Phase 3 Randomized trial of carfilzomib, lenalidomide, dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma</td></tr>
<tr><td>Objectives</td><td>Primary Objective
To compare PFS between KRd and lenalidomide arm
Secondary Objectives
To determine the rate of MRD-negative disease at 6 and 12 months after randomization
To compare the efficacy (rate of PR, VGPR, CR, and sCR) of KRd vs. Lenalidomide alone after randomization
To evaluate the safety and tolerability od KRd compared to lenalidomide alone
Exploratory Objectives
Determination of markers of response based on pre-treatment characteristics</td></tr>
<tr><td>Sample Size</td><td>180 (120-140 in Poland and 40-60 in the US)</td></tr>
<tr><td>Study Design</td><td>This is a phase 3, open-label study in which subject who completed autologous stem cell transplant for symptomatic myeloma who are considered for lenalidomide maintenance will be eligible

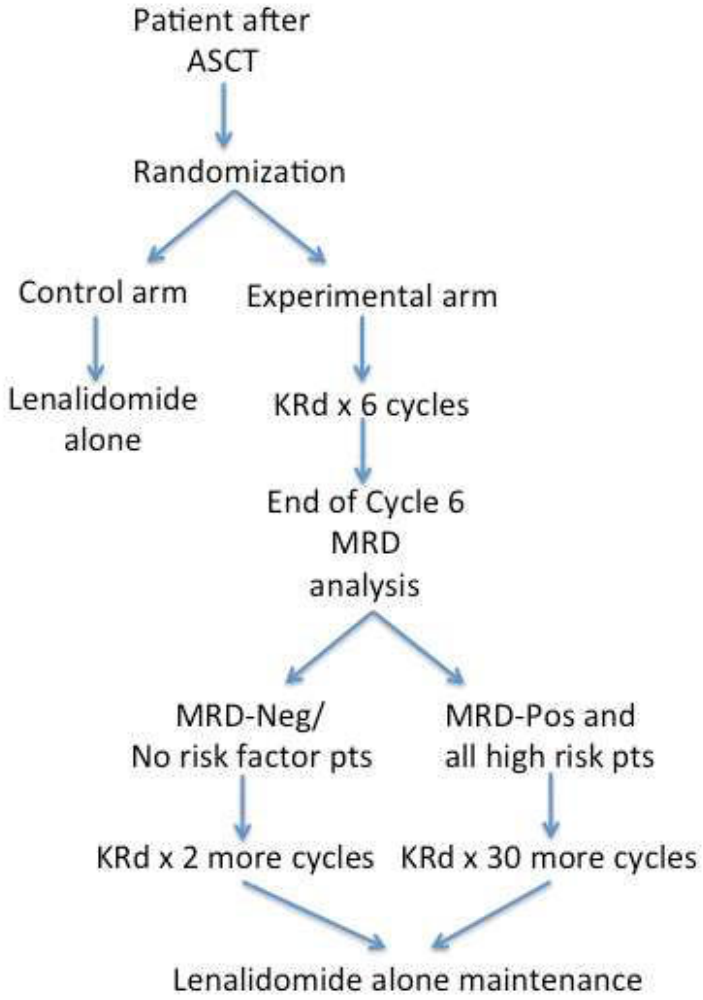
Dose Schedule and Dose Levels
<table>
<tr><td></td><td>Control</td><td colspan="3">Experimental</td></tr>
<tr><td></td><td>Lenalidomide</td><td>Lenalidomide</td><td>Carfilzomib</td><td>Dexamethasone</td></tr>
<tr><td>Cycle 1-4</td><td>Initially 10 mg per dose, can be escalated to 15 mg per dose after 3 cycles if tolerated</td><td>First cycle: 15 mg days 1-21
Cycle 2+: 25 mg per dose if tolerated</td><td>Cycle 1: 20 mg/m^2 days 1 and 2
36 mg/m^2 days 8, 9, 15, and 16
Cycles 2-4: 36 mg/m^2</td><td>Initially 20mg per dose
(see dose modifications in section 7.5)</td></tr>
<tr><td>Treatment Days</td><td>1-28</td><td>1-21</td><td>1, 2, 8, 9, 15, 16</td><td>1, 8, 15, 22</td></tr>
<tr><td>Cycle 5+</td><td>Best tolerated dose</td><td>Best tolerated dose</td><td>Best tolerated dose</td><td>20mg or best tolerated dose</td></tr>
<tr><td>Treatment Days</td><td>1-28</td><td>1-21</td><td>1, 2, 15, 16</td><td>1, 8, 15, 22</td></tr>
<tr><td>Maintenance _ cycle 8+</td><td>1- 28</td><td>1-28</td><td>N/A</td><td>N/A</td></tr>
</table></td></tr>
</table>

	(for pts with MRD-Negative disease and no high risk factors – checked at the end of cycle 6)				

Duration of Treatment	Treatment will continue on protocol for up to 36 months or if carfilzomib and lenalidomide are permanently discontinued. If dexamethasone is discontinued due to toxicity, carfilzomib and lenalidomide may be continued if tolerated without dexamethasone. Patients who complete 8 cycles of KRd (who have MRD-negative disease and no high risk factors – checked at the end of cycle 6) and patients who complete 36 cycles will continue single agent lenalidomide (in both arms) at best tolerated dose (max of 15mg) for 28 days in 28-day cycles. This treatment will continue until disease progresses or toxicity levels require drug discontinuation.
Inclusion / Exclusion Criteria	**Inclusions:** 1. Patients who completed single autologous stem cell transplant after completion of at most 2 induction regimens (excluding dexamethasone alone) and are in at least stable disease prior to randomization in the first 100 days after stem cell transplantation. 2. Patients must be within 12 months of initiation of induction therapy and must have had not more than 2 prior induction regimens. 3. Bone marrow specimen will be required at study entry; available DNA sample from pre-induction BM will be used for calibration step for MRD evaluation by gene sequencing. 4. Males and females ≥ 18 years of age 5. ECOG performance status of 0-1 6. Adequate hepatic function, with bilirubin ≤ 1.5 x ULN and aspirate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN 7. ANC ≥ 1.0 x 10^9/L, hemoglobin ≥ 8 g/dL, platelet count ≥ 75 x 10^9/L. 8. Calculated creatinine clearance (by Cockcroft-Gault) ≥ 50 ml/min or serum creatinine below 2 mg/dL 9. Females of childbearing potential (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 before lenalidomide is prescribed for Cycle 1 (prescriptions must be filled within 7 days). 10. 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.

	11. 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. 12. All study participants in the US must be consented to and registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of Revlimid REMS®. 13. Voluntary written informed consent **Exclusions:** Patients meeting any of the following exclusion criteria are not eligible to enroll in this study. 1. Patients who have had more than 12 months of prior therapy 2. Patients who progressed after initial therapy. a) Subjects whose therapy changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression. b) No more than two regimens for induction will be allowed, excluding dexamethasone alone. 3. Potential subjects with evidence of progressive disease as per IMWG criteria 4. Patients who have already started or received post-transplant maintenance or consolidation regimen 5. Patients not able to tolerate lenalidomide or carfilzomib or dexamethasone 6. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 7. Plasma cell leukemia 8. Waldenström's macroglobulinemia or IgM myeloma 9. Peripheral neuropathy ≥ Grade 2 at screening 10. Diarrhea > Grade 1 in the absence of antidiarrheals 11. CNS involvement 12. Pregnant or lactating females 13. Radiotherapy within 14 days before randomization. Seven days may be considered if to single area 14. Major surgery within 3 weeks prior to first dose 15. 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 16. Prior or concurrent deep vein thrombosis or pulmonary embolism 17. Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening 18. Uncontrolled hypertension or diabetes 19. Acute infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose 20. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or

	hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible. 21. Non-hematologic malignancy or non-myeloma 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 22. 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
Response	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains Serum quantitative immunoglobulins (Igs) Bone marrow biopsy is required to confirm response at time of suspected CR or better. MRD by gene sequencing and flow cytometry Plasmacytoma evaluation should be completed if clinically indicated
Safety Variables & Analysis	The safety and tolerability of lenalidomide and carfilzomib will be evaluated by means of drug related AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) V 4.0 will be used for grading of AEs. Treating Investigators will provide their assessment of causality as 1) unrelated, 2) unlikely related 3) possibly related, or 4) probably or 5) definitely related for all AEs.
Statistical Analysis	A total of 180 patients will be enrolled in a single-stage Phase III design. Time to progression or death will be calculated from the date of first treatment on protocol follow-up treatment group assignment. Subjects at the time of analysis not having either endpoint will be censored. Adherence to protocol and ability to follow patient in follow-up is expected to be excellent; however, if any patient revokes consent for the study not due to disease progression, they will be censored on their last clinical visit follow-up date. Likewise, patients in follow-up that are lost or that refuse or revoke study participation will be censored on their last clinical visit follow-up date.



LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

□C	degrees Centigrade
□F	degrees Fahrenheit
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time (also PTT)
ASaT	All Subjects as Treated
ASCT	Autologous Stem Cell Transplant
AST	Aspartate aminotransferase
ASO-PCR	Allele-Specific Oligonucleotide Polymerase Chain Reaction
Bid	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count

CFR	Code of Federal Regulations

CHF	Congestive heart failure
CK	Creatinine kinase
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case report form(s)
CRM1	Chromosome region maintenance protein 1
CRO	Clinical research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
CV	Curriculum vitae
CYP450	Cytochrome P450
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DVT	Deep venous thrombosis
EC	Ethical Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FAS	Full Analysis Set
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FLC	Free light chain
FPI	First Patient In
FU	Follow-up
G-CSF	Granulocyte colony stimulating factor
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony stimulating factor
GSH	Glutathione
H	Hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	ICF
HL	
IA	
IB	

Hu	ciency virus
man	Hodgkin's Lymphoma
imm	Interim analysis
uno	Investigator Brochure
defi	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Igs	Immunoglobulins
IMWG	International Myeloma Working Group
IMiD®	Immunomodulatory
IND	Investigational New Drug (Application)
INR	International Normalized Ratio

IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram(s)
KRAS	Kirsten Rat sarcoma
KRd (CRd)	Kyprolis (Carfilzomib), Revlimid, Dexamethasone
LDH	Lactate dehydrogenase
MFC	Multiparameter Flow Cytometry
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	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
nCR	Near Complete Response
NCT	National Center for Tumor Diseases
NHL	Non-Hodgkin's lymphoma
NYHA	New York heart association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PBSCT	Peripheral Blood Stem Cell Transplant
PCCC	Personal Cancer Care Consortium (of the University of Chicago)
PD	Progressive disease
PDn	Pharmacodynamics
PFS	Progression-free survival
PI	Proteasome Inhibitor
PIS	Patient Information Sheet
PK	Pharmacokinetics
PO	Per os (oral)
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
Pt	Patient
PTT	Partial thromboplastin time
QDx5	Daily dosing for five days
QIU	Qualified Investigator Undertaking Form
RA	Regulatory Authority
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

SAP	Statistical Analysis Plan
sCR	Stringent complete response
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results

SFLCs	Serum Free Light Chains
SINE	Selective Inhibitor of Nuclear Export
SOC	System Organ Class
SPEP	Serum protein electrophoresis
SPM	Second Primary Malignancies
STD_{10}	Severely toxic dose in 10% of animals
SUSAR	Suspected unexpected serious adverse reaction
TK	Toxicokinetics
TLS	Tumor lysis syndrome
TSH	Thyroid Stimulating Hormone
TSP	Tumor Suppressor Protein
TTP	Time to tumor progression
UCM	University of Chicago Medicine
UPEP	Urine Protein Electrophoresis
URPLWMiPB	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
VGPR	Very Good Partial Response

1. INTRODUCTION

1.1. Overview of Multiple Myeloma

Multiple myeloma is a clonal neoplastic proliferation of plasma cells affecting 19,900 US patients each year (Ries LAG, 2007). 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 front-line treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide (Revlimid®) and their combinations with and without corticosteroids. In addition, two agents Pomalidomide (Pomalyst®) and Carfilzomib (Kyprolis®) have been recently approved in the treatment of relapsed disease. 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 (Kumar et al., 2008).

1.2. Proteasome Background

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

1.3. Carfilzomib Background

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib (Arastu-Kapur S, Nov 2008; Demo et al., 2007).

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 (Kirk CJ, Nov 2008). 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 (Kirk CJ, Nov 2008). 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 (Bross et al., 2004; FDA, 2003). DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to related to C_{max} 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 (Demo et al., 2007; Kuhn et al., 2007; Ries LAG, 2007). 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 (Demo et al., 2007; Kuhn et al., 2007).

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 (Demo et al., 2007).

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, was completed (Alsina M, 2007). 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 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 partial response (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 tumor lysis syndrome (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 (Alsina M, 2007). Four MM patients achieved a 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, [illegible] weekly dosing, 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 were conducted 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 17% 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 3.5 months with a DOR of 7.2 months (mean follow up of 7.6 months) (Jagannath S, 2009).

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 (Siegel et al., 2012). Patients received 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. This dosing regimen was overall well tolerated. The most common side effects reported were fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Thirty-three

patients (12.4%) experienced peripheral neuropathy, primarily grades 1 or 2 and were similar to the A0 portion of the study. 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 The overall response rate was 23.7% with median duration of response of 7.8 months. Median overall survival was 15.6 months

In PX-171-004, a first cohort of patients received 20 mg/m^2. The subset of patients (N=54) that had not seen bortezomib had an overall response rate (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) (Siegel D, Nov 2009; Wang L, 2009). The median time to progression (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/m^2 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.

Indications and Usage: Carfilzomib (Kyprolis®) was approved by the FDA as single agent for refractory and relapsed myeloma and in combination with lenalidomide and dexamethasone for the treatment of myeloma patients who have received 1-3 lines of prior therapy. More details can be found in the Package Insert.

1.4. 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 (Dredge et al., 2005). 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 (Dredge et al., 2005). Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity (Corral et al., 1999).

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 (Schafer et al., 2003). 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 (Davies et al., 2001).

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 Investigator Brochure and the IND Safety Letters.

1.5. Combination 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 vs. high-dose dexamethasone alone in relapsed multiple myeloma patients with up to 3 prior therapies (Dimopoulos et al., 2007; Weber et al., 2007).

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 MTD and activity of the bortezomib, lenalidomide, and dexamethasone combination in subjects with heavily pre-treated relapsed and/or refractory multiple myeloma (Anderson KC, 2008). 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 (Richardson P, Dec 6, 2008). 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 dexamethasone dose reduction. G3 polyneuropathy was reported in one patient (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 significant 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 (Rajkumar et al., 2005). 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) (Rajkumar P, 2007). 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 (Richardson P, 2007; Richardson et al., 2010). 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 stem cell transplant (SCT). Further investigations with combination therapy with these agents in newly diagnosed disease are warranted.

1.5.1. Experience with Carfilzomib in Combination with Lenalidomide and Dexamethasone

PX-171-006 is a Phase 1b study in patients with relapsed multiple myeloma in which carfilzomib was administered in combination with lenalidomide (Revlimid®) and dexamethasone (CRd, renamed to KRd) "Low-dose" dexamethasone 40 mg/day was given on Days 1, 8, 15, and 22 in all cases. Carfilzomib was administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide was administered PO on Days 1 through 21. The MTD was not reached in this study and the maximum doses used per protocol were: carfilzomib ($27mg/m^2$), lenalidomide 25mg and low dose dexamethasone were being used (Niesvizky, April 15, 2013). Eight patients were treated in the phase I portion of the trial and 44 patients were accrued to the expansion cohort. After a median follow-up of 24.4 months, the ORR was 76.9% with a median DOR 22.1 months and median progression free survival (PFS) of 15.4 months. The ORR was 69.2% in bortezomib-refractory patients and 69.6% in lenalidomide-refractory patients. The regimen was overall well tolerated with a median of 9.5 cycles administered. Generally KRd was well tolerated with manageable adverse events (AEs). The most common grade 3/4 AEs being hematologic in nature and included Grade 3/4 AEs included lymphopenia (48.1%), neutropenia (32.7%), thrombocytopenia (19.2%), and anemia (19.2%). Nonhematologic AEs were generally grade 1/2 in severity. Dose reductions of carfilzomib due to AEs were required in 7.7% of patients with a discontinuation rate of 19% and not associated with a specific type of AE. In addition, the rate of peripheral neuropathy was similar to that reported for single agent carfilzomib and did not increase with the addition of lenalidomide (Wang, Oct 31, 2013). Phase III study (PX-171-009; ASPIRE trial) comparing KRd and Rd (Revlimid/Dexamethasone) showed significant improvement in the KRd arm across all categories, including an improvement of primary end-point of PFS (26.3 vs 17.6 months) with no to significant added toxicity (Stewart et al., 2015). More recently ENDEAVOR (carfilzomib/dexamethasone vs bortezomib dexamethasone) trial reported significant superiority of carfilzomib arm in relapsed and refractory myeloma (Dimopoulos, 2015).

Together, these results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone 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, even up to 27mg/m^2, suggesting that carfilzomib will combine well with other anti-cancer agents.

1.5.2. **Dose Rationale**

1.5.2.1. Carfilzomib Dose Rationale

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. 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 have demonstrated that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

In addition, 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 pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

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

In the phase 1 dose escalation study (PX-171-007) of single agent carfilzomib in solid tumors patients started in the initial Phase 2 portion of the study at 36 mg/m^2 (bolus administration over 2-10 minutes). A review of the tolerability of 36 mg/m^2 carfilzomib in these patients indicates that this regimen was very well tolerated and an overall adverse event profile similar to that seen with the 27 mg/m^2 carfilzomib experience with bolus dosing. Three patients completed >12 cycles of therapy at 36 mg/m^2 with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability 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 doses of 20/36 (20 mg/m^2 given on Days 1 and 2 of cycle 1 only; followed by 36 mg/m2 for all subsequent doses), 20/45, 20/56 mg/m^2 and so forth are being investigated. Doses of 20/56 mg/m^2 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/m^2) indicated that it is reasonably well tolerated, with minimal infusion reactions. In some cases at 20/56mg/m^2, dexamethasone was increased from 4mg/dose to 8mg with

the 56mg/m2 doses in order to reduce fevers and hypotension. Patients with advanced, refractory MM being treated at 36mg/m^2 and 45mg/m^2 have shown very good tolerability (>6 months in some cases) with documented minimal and partial responses in these heavily pretreated 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/m^2 carfilzomib are now administering the drug as a 30-minute infusion.

In addition to the above observations, a phase I study of carfilzomib in 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.[12] 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.

1.6. **Study Rationale**

Previous studies have indicated that patients may benefit from prolonged treatment regardless of their response (Benboubker et al., 2014). More recent studies demonstrated that deep responses (CR, nCR, sCR, VGPR), increased control of multiple myeloma, and possibly a functional cure in some patients, might be achieved if extended treatment is delivered to patients with newly diagnosed disease. In patients who undergo autologous stem cell transplantation, post-transplant maintenance treatment represents a form of extended treatment. Interestingly, recent studies demonstrated that the benefit of maintenance is observed not only in patients with measurable residual disease but also in patients who achieved deep disease reduction (CR, nCR, sCR, VGPR), as also shown in non-transplant setting (Attal et al., 2012).

As more sensitive methods for the assessment of minimal residual disease have been developed, including allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), multiparameter flow cytometry (MFC), and more recently gene sequencing, MRD negativity is evolving as the new goal of therapy and possibly a new surrogate marker for progression free survival and overall survival (OS). For example, in a multivariate analysis of 295 newly diagnosed MM patients, MRD negativity at 100 days post-transplant was the most important, independent prognostic factor for PFS and OS (Paiva et al., 2008). However, the optimal method of measurement of MRD is not established. Furthermore, it remains unclear whether patients with post-transplant MRD-negativity benefit or not from additional extended treatment such as maintenance. One of goals of our study will be to address this question.

There is now vast data demonstrating that post-transplant maintenance improves outcomes. Most recently, two studies have shown that post-transplant maintenance with single-agent Lenalidomide improves PFS and in one of these two studies OS (Attal et al., 2012; McCarthy et al., 2012). Based on these results, post-transplant maintenance with Lenalidomide has now been incorporated into the MM treatment algorithm in the United States. Improved outcomes in the maintenance phase have been also shown with single agent thalidomide and bortezomib (Sonneveld et al., 2012; Spencer et al., 2009; Stewart et al., 2013).

Furthermore, there is also emerging evidence that two- or three-drug regimens are active in post-transplant setting. For example, bortezomib, thalidomide, dexamethasone (VTd) when given every 3 months, was reported to prolong PFS when compared to thalidomide alone, with surprisingly significant benefit for standard risk but not poor risk patients (Rosinol et al., 2012). In addition, there is also mounting evidence that post-transplant consolidation, given in addition to or prior to

maintenance, deepens the response and likely contributes to improved PFS, particularly with 3-drug regimens including a proteasome inhibitor (PI) and a immunomodulatory drug (IMiD) (McCarthy and Hahn, 2013).

Extended treatment with bortezomib, lenalidomide, dexamethasone (RVd) and carfilzomib, lenalidomide, dexamethasone (KRd) resulted in deeper responses over time and likely contributed to the excellent results with CR+nCR rate of 57% and 67%, respectively (phase 2) and an estimated 18-month and 24-month PFS of 92% and 75%, respectively. In a recently presented follow-up of our KRd study, the rate of MRD negativity improved by about 20% between 8 and 16 months of KRd maintenance (Jakubowiak, 2013). Furthermore, it was demonstrated that extended, 2-year treatment with three drug combinations (KRd and RVd), which included low-dose dexamethasone is well tolerated, with limited and mostly mild toxicity, including toxicity related to dexamethasone (Jakubowiak, 2013).

Taken together, these studies suggest that combinations of a PI and an IMiD with or without low dose of steroids may be superior compared to single agents in the consolidation/maintenance phase and result in improved depth of response and prolonged PFS and OS.

Currently in the United States, lenalidomide maintenance is most commonly used in the post-transplant setting and considered the standard of care. The benefit of lenalidomide maintenance was seen in all groups of patients, including patients in CR, representing approximately 30% of patients initiating lenalidomide maintenance after transplant (McCarthy et al., 2012). Still, a majority of patients (~70%) are in less than CR, which increases the probability of earlier relapse and the risk of shorter survival.

The combination of carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (KRd) has been shown to be high efficacious in newly diagnosed MM without transplant (Jakubowiak et al., 2012). In addition, an extended treatment with KRd resulted in deepening of the response with an estimated median time to achieving stringent complete response (sCR) in ~11-14 months range, and further conversion of less than sCR responses in an additional ~20% of patients after 12 cycles of KRd based on recent updates (unpublished). Moreover, these deepening responses have been associated with an excellent PFS (estimated 3-year PFS 79% and OS 92%) after median ~3 years of follow-up. Recently updated evaluations show statistically significant correlation between sCR and PFS and OS, prompting a need for development of strategies to improve rates of sCR. To evaluate whether we can further improve on these results, we are currently conducting a KRd trial with autotransplant with extended KRd treatment after 4 initial KRd cycles. Preliminary results are very encouraging and show (1) that post-transplant KRd consolidation increases the sCR response rate from 29% post-transplant to 65% at the end of 4-cycles of post-transplant consolidation and (2) that post-transplant KRd treatment is well tolerated, with no apparent or unexpected toxicities other than already published for KRd without transplant (Zimmerman, 2014). In addition, more extended treatment after the completion of 4 cycles of KRd consolidation for an additional 10 cycles (total of 14 cycles of KRd post-transplant) using KRd maintenance schedule is well tolerated and results in further improvement of the responses and rates of sCR (unpublished).

Based on these observations, we hypothesize that extended post-transplant KRd treatment followed by lenalidomide maintenance, will result in a superior outcome compared to extended post-transplant treatment (maintenance) with single agent lenalidomide. We would like to investigate this in the proposed study, as is has not been established and a strong argument can be made with post-transplant maintenance with single agent ultimately providing similar outcomes compared to multi-drug post-transplant treatment.

We propose to evaluate this hypothesis in patients who are otherwise considered for single agent lenalidomide maintenance post-transplant, using a randomized study design. The primary end-point

is PFS, using very well established estimates for PFS from 2 prior randomized trials using lenalidomide maintenance.

Among secondary objectives, we propose to evaluate the status of MRD disease at established landmark time-points in both arms, and to use MRD status to determine the duration of KRd treatment. We anticipate that KRd treatment will result in a statistically improved rate of MRD-negative disease compared to the MRD rate observed in patients who continue single agent lenalidomide. Since there is vast evidence that the rate of sCR and in particular the rate of MRD-negative disease translates into longer PFS, the study is powered to test this hypothesis, but also to generate information to provide the rationale for future studies with MRD as an early measureable surrogate end-point for PFS.

Based on analysis of updated results of our original KRd trial (manuscript in preparation) and the results of the ongoing KRd + transplant trial (IST-CAR-578) (Zimmerman, 2015) as well as the results of the ASPIRE trial (Stewart et al., 2015) and observations by Nooka et al. (Nooka et al., 2014), we propose to use different durations of KRd treatment using two modifying criteria: (1) MRD status and (2) risk factors per International Myeloma Working Group (IMWG) criteria. Patients without risk factors and having MRD-negative disease at the completion of 6 cycles of KRd will receive a shorter, a total 8 cycles, duration of KRd treatment followed by lenalidomide maintenance. Based on the result of IST-CAR-578, we anticipate that more than 50% of patients will stop KRd treatment after 8 cycles. The remaining patients, i.e. patients without risk factors and MRD + disease at the completion of 6 cycles and all high risk patients regardless of MRD status, will received extended KRd treatment for a total of up to 36 cycles.

To make safety the highest priority, the protocol will (1) incorporate scheduled dose reductions of dexamethasone and will (2) provide aggressive required dose modifications with the emergence of any treatment related toxicities greater than G1. In addition, the data safety and monitoring committee will be required to mandate study design changes if any increase in toxicities in the KRd arm is significantly above the R arm and/or above those reported for lenalidomide single agent are observed.

An extended treatment with lenalidomide in post-transplant setting may raise concerns for increased risk of second primary malignancies (SPM). While the risk of SPM has been reported with lenalidomide maintenance, in a recent large meta-analysis by Palumbo et al, the risk of SPM was greatest in patients in the context of recent melphalan, particularly in patients who received oral melphalan in addition to lenalidomide. Moreover, in the post-transplant setting, mostly initial exposure to lenalidomide accounted for SMPs, and there is no evidence to date that an extended treatment with lenalidomide beyond an initial period of 1 year increases this rate (Palumbo et al., 2014). In addition, the overall cumulative risk of death due to myeloma was much greater compared to risk of death from SPM, suggesting a positive benefit/risk profile in patients receiving lenalidomide (Palumbo et al., 2014), further supporting the proposed duration of treatment on this protocol.

1.7. **Study Population and Sample Size**

A total of 180 (120-140 in Poland and 40-60 in the US) patients who completed single autologous stem cell transplant after completion of at most 2 induction regimens (excluding dexamethasone alone) and are in at least stable disease in the first 100 days after stem cell transplantation will be included in this trial.

1.8. **Assessment for Response**

Response will be determined according to the IMWG response criteria for multiple myeloma (2006). Disease assessment for response will include Serum Protein Electrophoresis (SPEP), Urine Protein

Electrophoresis (UPEP), Serum Free Light Chains (SFLC) and Immunoglobulins (Igs). Bone marrow procedures should be completed at the time of suspected complete response. Additionally, for subjects who have a plasmacytoma or disease measured by imaging at baseline, plasmacytoma evaluations and radiographic imaging should be completed as per standard of care and in accordance with IMWG response criteria for multiple myeloma. Patients who achieve SD, PR, or CR will continue therapy until disease progression. Patients with disease progression will discontinue the treatment regimen and be removed from protocol.

2. OBJECTIVES

2.1. Primary Objective

- To compare PFS between KRd and Lenalidomide arm after randomization

2.2. Secondary Objectives

- To determine the rate of MRD-negative disease at 6, 12, 18, 24, and 36 months after randomization
- To compare the efficacy (rate of PR, VGPR, CR, and sCR) of KRd vs. Lenalidomide alone after randomization
- To evaluate the safety and tolerability of KRd compared to lenalidomide alone

2.3. Exploratory Objectives

- Determination of markers of response based on pre-treatment characteristics

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The comparison of PFS rates between patients treated with KRd vs. R alone after SCT will be achieved by measuring the time to progressive disease or death as defined by IMWG criteria.

3.2. Secondary Endpoints

- Determine the correlation between the MRD status at 6, 12, 18, 24, and 36 months and median PFS in both arms
- Determine rates of improvement of the depth of response by at least one category according to IMWG response criteria. (For example, an improvement from very good partial response (VGPR) to near complete response (nCR) or better than nCR including conversion from CR to MRD negative disease [overall response]) at 6 and 12 months
- Compare overall survival between arms
- Determine the duration of MRD-negative disease
- Safety and tolerability of experimental arm vs. control

3.3. Tertiary/Exploratory Endpoints

Conduct Proteomic studies to establish markers of response and duration of response to treatment strategy using KRd or R as consolidation after autoPBSCT.

4. INVESTIGATIONAL PLAN

4.1. Overview of Study Design and Dosing Regimen

This is a Phase 3, randomized, open-label, multicenter study comparing two treatment regimens (Kyprolis, Revlimid, dexamethasone –KRd or CRd–vs. Revlimid – R) for subjects with multiple myeloma after at most two induction regimens who are at least in stable disease in the first 100 days after stem cell transplantation. Eligible subjects will be randomized in a 1:1 ratio to receive either the R or KRd. Randomization will be stratified for level of response from initial treatment at study entry (< VGPR vs ≥ VGPR), presence or absence of at least one poor prognostic risk factor (Yes/No to at least one cytogenetic risk factor including del-13, t(4;14), t(14;16), del17p, hypodiploidy), and by treatment country (USA and Poland).

Subjects will receive the treatment determined by randomization until disease progression or unacceptable toxicity (whichever occurs first). The primary endpoint of this Phase 3 study is progression-free survival.

4.2. Study Procedures

Subjects enrolled into the KRd arm will initially receive lenalidomide at 15 mg per dose (see below if previously unable to tolerate 15 mg) on days 1-21, carfilzomib at 20 mg/m^2 on days 1,2, escalated to 27 mg/m^2 on days 8, 9, and then to 36 mg/m^2 on days 15 and 16 in the first cycle and 36 mg/m^2 in the subsequent cycles, and dexamethasone 20 mg on days 1, 8, 15, 22. Dose of lenalidomide will be escalated up to 25 mg per dose in cycle 2 and subsequent cycles after establishing tolerability of initial doses. Dose modifications will be mandated based on aggressive schedule of dose modification for toxicities as per specific guidelines. Otherwise, patients will continue at their best tolerated dose of lenalidomide on days 1-21 and their best tolerated dose of carfilzomib on days 1, 2, 8, 9, 15, 16 in cycles 1-4 and days 1, 2, 15,16 in cycles 5-8 (in patients with MRD- disease at the end of cycle 6 and no risk factors) or cycles 5-36 (in patients with MRD+ disease and no risk factors or high risk patients at the end of cycle 6) as described in section 1.6. Lenalidomide will begin at a dose of 10 mg PO daily (2 capsules per day). After three months, the dose will be increased, provided ANC ≥ 1,000/μL, platelet count ≥ 75,000/μL, and all nonhematologic toxicity is ≤ grade 1, to 15 mg PO daily (3 capsules per day).

Randomization will occur between Day +70 and +120 post-transplantation. Initiation of maintenance therapy with study drug will begin between day +80 and +130. Prior to randomization, subjects must undergo disease re-staging, must have adequate organ function (ANC ≥1000μL, platelet count ≥75,000μL, creatinine clearance ≥ 30mL/min, bilirubin ≤2mg/dL, AST ≤3 x ULN, and Alk. Phos.≤ 3 x ULN), and must have no evidence of progressive disease.

All subjects will have monthly clinic visits for disease assessments. Treatment will continue on protocol for up to 36 months or if carfilzomib and lenalidomide are permanently discontinued. If dexamethasone is discontinued due to toxicity, carfilzomib and lenalidomide may be continued if tolerated without dexamethasone. Toxicity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. Patients who complete 8 cycles (who are MRD-Neg and have no risk factors checked at the end of cycle 6) or 36 cycles will then continue single agent lenalidomide in both arms, at best tolerated dose (up to 15mg) for 28 days in

both arms in 28-day cycles. This regimen will continue until there is progression of the disease or the toxicities require discontinuation of the drug

Minimal residual disease analysis will be performed at the end of cycle 6 to determine the course of treatment (either move to lenalidomide alone or continue with KRd after the completion of cycle 8, see section 1.6). MRD analysis will be performed using the most recent Spanish protocol by multiparameter flow cytometry (10-color) will be assessed in all bone marrow samples at the beginning of the study, after cycles 6, 12, 24, and 36, and at any time a bone marrow biopsy is completed to assess response for suspected CR. From the time CR is established, MRD analysis should continue at 12-month intervals from randomization up to 5 years in patients with ongoing sCR. All flow cytometry analysis from US sites will be performed at the University of Chicago and in Poland at the Medical University in Poznan, based on a consensus for the most recent technical guidelines and flow cytometry (current EuroFlow technique) parameters as outlined by Orfeo et al. (MRD IMWG meeting New York, NY 2014). The same samples will be evaluated by Sequenta using LymphoSIGHT® platform after isolation of DNA at the University of Chicago site. For this purpose (and to establish a baseline), sites will be required to provide unstained pre-treatment slides to assess MRD status by sequenta.

Treatment responses will be assessed by serum free light chains (SFLC), quantitative immunoglobulin levels (Igs), and serum and urine monoclonal protein starting at Cycle 2 Day 1 and at the beginning of each subsequent cycle. Subjects with stable disease or better will continue treatment until disease progression or the development of unacceptable toxicities. All patients will then undergo a final visit (end of treatment visit).

4.2.1. **Number of Centers**

A total of 6 centers in Poland and up to 6 centers in the US will participate.

4.2.2. **Definition of Treatment Cycle and Duration**

Each treatment cycle is 28 days. The study is planned to start in Q1 2016 with respect to first patient in (FPI). With an expected accrual rate of 2-4 patients per month across 12 centers, and a total number of 180 patients planned, the anticipated enrolment period is 4 - 8 months. Hence the last patient in will be included not prior to Q4 2016. The length of treatment period will be up to 36 months. Patients will be followed for survival for 2 years after their end of treatment visit or until death, whichever occurs first.

4.2.3. **Treatment Phase**

Treatment will be continued until progression of disease according to IMWG criteria, unacceptable toxicities occur in individual subjects or consent is withdrawn.

4.2.4. **End of Treatment Visit**

Patients that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, 28 days after the last dose of study medication.

4.2.5. **Long Term Follow Up**

Patients will be followed up every 3 months for progression and survival after the end of treatment. Patients will be followed for survival for 2 years after their end of treatment visit or until death, whichever occurs first. The follow up will be done over the phone.

5. PATIENT SELECTION

5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study. No enrollment waivers will be granted.

1. Patients who completed single autologous stem cell transplant after completion of at most 2 induction regimens (excluding dexamethasone alone) and are in at least stable disease prior to randomization in the first 100 days after stem cell transplantation.
2. Patients must be within 12 months of initiation of induction therapy and must have had not more than 2 prior induction regimens.
3. Bone marrow specimen will be required at study entry; available DNA sample from pre-induction BM will be used for calibration step for MRD evaluation by gene sequencing.
4. Males and females ≥ 18 years of age
5. ECOG performance status of 0-1
6. Adequate hepatic function, with bilirubin ≤ 1.5 x ULN and aspirate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 xULN
7. ANC ≥ 1.0 x 10^9/L, hemoglobin ≥ 8 g/dL, platelet count ≥ 75 x 10^9/L.
8. Calculated creatinine clearance (by Cockroft-Gault) ≥ 50 mL/min or serum creatinine below 2 g/dL
9. 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 before lenalidomide is prescribed for Cycle 1 (prescriptions must be filled within 7 days).
10. 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.
11. 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.
12. All study participants in the US must be consented to and registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of Revlimid REMS®.
13. Voluntary written informed consent

5.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study. No enrollment waivers will be granted.

1. Patients who have had more than 12 months of prior therapy
2. Patients who progressed after initial therapy.

   a) Subjects whose therapy changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression.

b) No more than two regimens for induction will be allowed, excluding dexamethasone alone.

3. Potential subjects with evidence of progressive disease as per IMWG criteria
4. Patients who have already started or received post-transplant maintenance or consolidation regimen
5. Patients not able to tolerate lenalidomide or carfilzomib or dexamethasone
6. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
7. Plasma cell leukemia
8. Waldenström's macroglobulinemia or IgM myeloma
9. Peripheral neuropathy ≥ Grade 2 at screening
10. Diarrhea > Grade 1 in the absence of antidiarrheals
11. CNS involvement
12. Pregnant or lactating females
13. Radiotherapy within 14 days before randomization. Seven days may be considered if to single area
14. Major surgery within 3 weeks prior to first dose.
15. 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
16. Prior or concurrent pulmonary embolism
17. Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening
18. Uncontrolled hypertension or diabetes
19. Acute infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose
20. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.
21. Non-hematologic malignancy or non-myeloma 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
22. Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

5.3 SUBJECT ENROLLMENT AND REGISTRATION

5.3.1 Registration Process

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 5.

Registration will happen separately between the US and Polish sites. Although subject approval for enrollment will be done separately in the two countries, all patients who have signed consent, regardless of if they are enrolled are not, will be entered into the University of Chicago Clinical Trials Management database, eVelos, within 24 hours of signing consent. Subjects will be assigned a unique subject number that will remain consistent for the duration of the study. Sites should make all enrollment requests at least 72 hours before the anticipated start date of Cycle 1 Day 1. Screening and on-treatment assessments are expected to be entered into eVelos within two weeks of study required visits.

5.3.2 Registration in the US

The US Lead PI or designee will be responsible for approving the eligibility of all patients in US sites. Specifically, once all required screening assessments have been performed, the information will have to be reviewed by the US Lead Principal Investigator or designee. When the subject's study eligibility has been confirmed by the US Lead Principal Investigator or designee, they or an authorised site staff, will finalize data entry into eVelos. At this enrollment stage, subjects will be randomly assigned to the appropriate treatment arm. Treatment may not start until the approved enrollment form, including the designated treatment arm, is sent back to the site.

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study: (773) 702-7716 and/or PhaseIICRA@medicine.bsd.uchicago.edu. Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & full copy of the signed informed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.

- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.

- The date the patient 's eligibility is confirmed by the CRA will be considered the patient's "Enrolled/On Study Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the Lead Site CRA on this date. Subjects that sign consent and do not go "On Study" will be recorded in the database as "Not Enrolled" with the date they signed consent and the reason they were not enrolled (e.g., Ineligible, Screen Failure or Withdrawn Consent).

5.3.3 Registration in Poland

In Poland, the Polish Lead Principal Investigator or their designee will be responsible for reviewing and confirming the eligibility of all Polish patients as well as entering them into eVelos. As soon as the patient signs consent, this date and status ("Patient Signed Consent") must be entered into eVelos within 24 hours and once all required screening assessments have been performed, the information will have to be reviewed by the Polish Lead Principal Investigator or their designee. When the patient's eligibility has been confirmed by thePolish Lead Principal Investigator , they or an authorised site staff member, will update the subject's status as "Enrolled/On Study" in eVelos. At this stage, subjects will be randomly assigned to the appropriate treatment arm. Treatment may not start until the approved enrollment form, including the designated treatment arm, is sent back to the site. As soon as the subject starts Cycle 1 Day 1, their status in eVelos must be updated to "On Tx" with the date the treatment was started.

Please see the Study Procedures Manual for further details.

5.4 Randomization

The same randomization procedure will be followed for all subjects in the US and Poland. This procedure will be done using REDCap, a web-based system. The process, however, will be conducted within each country, separately. Specifically, the randomization of Polish subjects will be handled by the Polish Lead Principal Investigator and his team, while randomization for US subjects will be handled by the US Lead PI and his team. Subjects will be randomized in a 1:1 fashion between the KRd and R study treatment arms. Randomization will be stratified by the level of response from prior initial treatments at study entry (<VGPR vs ≥ VGPR), the presence or absence of at least one poor prognostic risk factor - del-13, t(4;14), t(14;16), del17p, and/or hypodiploidy), and the location of the site (USA and Poland).

6. TREATMENT PLAN

Please refer to the Study Calendar (Appendix 7) for an overview.

After screening, eligibility determination and enrollment, subjects in the experimental arm will receive carfilzomib, Lenalidomide, and dexamethasone, while control arm subjects will receive Lenalidomide alone, in 28-day cycles until progression, unacceptable toxicity or subject withdraws consent.

A subject is considered to be off-treatment following a 30-day safety follow-up period after the last treatment. Long-term follow-up for survival will be 2 years from the End of Treatment visit.

6.1. Study Procedures

6.1.1. Screening Procedures

The screening period is 42 days in length. The screening period starts only after the patient has signed the Informed Consent Form. Refer to the study calendar (Appendix 7)

Signed written informed consent	Obtained prior to any study specific assessments
Demographics and medical history	• Age, gender, ethnic background • Details on myeloma diagnosis • Details on prior cancer therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities • Previous and concurrent relevant diseases • Current symptoms and/ or residual toxicities from prior therapies
Pregnancy test (if applicable)	FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting study treatment. The first pregnancy test must be performed within 10-14 days prior to the start of study treatment and the second pregnancy test must be performed 24 hours before lenalidomide is prescribed.
Physical examination and vital signs	• Body height and weight • BSA • ECOG Performance Status (Appendix 2) • Blood pressure, pulse, temperature • Physical examination
Cardiac evaluation	12-lead ECG
Echocardiogram	Required
Urinalysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein.
Hematology (CBC)	Hemoglobin, hematocrit, white blood cell (WBC) count, WBC differential, red blood cell count, platelets. WBC differential may be automated or manual as per institutional standards.
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, urate, LDH, CRP
Coagulation	Prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).

β2 microglobulin	Required
Myeloma Disease Assessment – laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains (SFLC) • Serum quantitative immunoglobulins (Igs) All of the above assessments are required at screening regardless of the disease classification.
Bone Marrow Biopsy	Quantify percent myeloma cell involvement, obtain bone marrow aspirate for MRD analysis by flow and NGS and obtain bone marrow aspirate for conventional cytogenetics and fluorescent *in situ* hybridization. This is required at screening. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening. Calibration sample for MRD is required
Skeletal Survey	May be within 42 days of planned treatment start (does not need to be repeated if within 42 days). Includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri, whole body MRI, or whole body CT.
Neurotoxicity Assessment	Includes Neurotoxicity Questionnaire (Appendix 5)
Adverse Events and Concomitant medication	Only SAEs considered related to study procedure need to be reported. Concomitant medication currently used

6.1.2. **Treatment Phase Procedures**

The following assessments should be performed on Day 1 of each cycle before administering drug unless otherwise noted. Please refer to Appendix 4 for details of response evaluation to be completed at any time throughout the trial when a CR or better is suspected.

Complete Physical examination and vital signs on Day 1 Symptom-directed Physical Exam Day 8, 15 Vital signs on each treatment day with Carfilzomib	• Body weight • BSA • ECOG Performance Status • Blood pressure, pulse, temperature • Pulse oximetry to investigator discretion
Hematology (Experimental Arm: Day 1, 8, 15 before carfilzomib administration;	Hemoglobin, hematocrit, white blood cell (WBC) count, WBC differential, red blood cell count, platelets. WBC differential may be automated or manual as per institutional standards.

Control Arm: Day 1 of each cycle or as indicated by treating physician)	
Complete clinical chemistry (Experimental Arm: Day 1, 8, 15 before carfilzomib administration; Control Arm: Day 1 of each cycle or as indicated by treating physician)	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.
Limited clinical chemistry (Experimental Arm: days 2, 9, 16 if clinically indicated)	Sodium, chloride, bicarbonate, BUN, creatinine, glucose, uric acid
Pregnancy Test	FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 28 days of study participation and then every 28 days while on 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.
Myeloma Disease Assessment - laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs) Only those assessments used to follow the myeloma disease are required past screening. All assessments are required for confirmation of response.
Neurotoxicity Assessment	Including Neurotoxicity Questionnaire (Appendix 5)
Adverse events	Assessed on an ongoing basis
Concomitant Medications	Pre-treatment concomitant medications (refer to section 7.2.2). All other con-meds assessed on an ongoing basis
Study Treatment	Section 7 and Appendix 7

6.1.3. **End of Treatment Procedures and Long-Term Follow-Up**

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 7 days) after the last application of study drug. Following the end of tre atment, subjects will be followed for survival for 2 years.

At the EOT visit, the patients will undergo the following assessments:

Pregnancy test (if applicable)	FCBP pregnancy testing required at treatment discontinuation and at 28-days following treatment discontinuation. If menstrual cycles are irregular,

	additional testing 14-days following treatment discontinuation is required
Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination • Pulse oximetry to investigator discretion
Hematology	Hemoglobin, hematocrit, white blood cell (WBC) count, WBC differential, red blood cell count, platelets. WBC differential may be automated or manual as per institutional standards.
Clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, uric acid, total protein, albumin, calcium, phosphorus, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.
Myeloma Disease Assessment– laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs)
Adverse events and concomitant medication	Record through 30-days after last treatment. All SAEs considered related to treatment must be followed until resolution.

6.2. **Pretreatment Preparation**

6.2.1. **Hydration**

At least 48 hours before Cycle 1 Day 1, oral hydration should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. In subjects considered at risk for TLS, oral hydration should be continued in Cycle 2 and beyond as required by the subject's medical condition and at the Treating Investigator's discretion.

IV hydration will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (e.g.,≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

6.2.2. **Concomitant Medications**

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medication(s) must be reported in the case report form

(CRF) from time of signing the informed consent form through 30 days following the last dose of study drugs. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings.

The following are **required** concomitant medications to 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) 81 or 325 mg PO QD or low molecular weight heparin at prophylactic doses for the duration of treatment. (Subjects with known high thrombotic risk, e.g., prior thrombosis, DVT, etc, should receive full anticoagulation at the Treating Investigator's discretion.) **Patients with platelets < 30,000/mm^3 or risk of platelets dropping to Grade 3 thrombocytopenia or with active bleeding should have all anticoagulation treatment held.**

The following are **recommended** medications to be started on Cycle 1 Day 1 or up to 24 hours prior to Cycle 1 Day 1:

- Lansoprazole (Prevacid) 15 mg PO QD, or other PO proton-pump inhibitor or H1 blocker to prevent peptic disease for the duration of treatment. Note that this is a recommended (optional) treatment.
- Mycostatin or Nystatin to prevent oral thrush. Note that this is a recommended (optional) treatment.
- Allopurinol (or other approved uric acid-lowering agent) in subjects at high risk for tumor lysis syndrome due to high tumor burden may be prescribed at the Treating investigator's discretion. Allopurinol should be prescribed according to the package insert.

6.2.2.1. Contraception

Females of childbearing potential (FCBP) must:

- Avoid pregnancy for at least 4 weeks before beginning lenalidomide
- Have 2 negative pregnancy tests prior to starting treatment, the first test within 10 to 14 days and the second test 24 hours before prescribing lenalidomide.
- Pregnancy tests weekly for the first month of treatment
- Pregnancy tests monthly during treatment after the first month or semimonthly for women of childbearing potential with irregular menstruation
- Agree to abstain from heterosexual sexual intercourse or to use 2 methods of effective contraception beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and for 3 months following the last dose of drug (more frequent pregnancy tests may be conducted if required per local regulations)

An FCBP is defined as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., no menses at any time in the preceding 24 consecutive months). Amenorrhea following cancer therapy does not rule out childbearing potential.

Male subjects and their partners must use 1 highly effective method of birth control plus 1 additional effective method of birth control (contraception) at the SAME TIME during treatment and for 3

months following the last dose of drug, even if they have undergone a successful vasectomy. Male subjects must not donate sperm while taking lenalidomide and for 28 days after stopping lenalidomide.

Highly effective methods of contraception include:

- Intrauterine device (IUD)
- Hormonal therapy (birth control pills, injections, implants)
- Tubal ligation
- Vasectomy

Additional effective methods include:

- Latex condom
- Diaphragm
- Cervical Cap

6.2.3. **Prohibited 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 $\geq$ 4mg/day or prednisone > 20 mg/day are not permitted. Other investigational agents are not to be used during the study.

6.2.4. **Use of Blood Products**

Subjects may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Lead Principal Investigator.

Appropriate anti-coagulation is allowed during the study (eg: LMW heparin, direct factor Xa inhibitors, etc). Warfarin is allowed during the study provided that patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with bisphosphonates, erythropoietin, darbepoetin, G-CSF or GM-CSF, pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

6.2.5. **Radiation Treatment**

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drugs should be held for 3-5 days before the start of palliative radiation therapy and 3-5 days after palliative radiation therapy.

6.3. Study Drug Administration

6.3.1. Experimental Arm

6.3.1.1. Carfilzomib Administration

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. The dose will be calculated using the subject's actual BSA at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Dose adjustments do not need to be made for weight gains/losses of ≤ 10%. Subjects with a Body Surface Area (BSA) of greater than 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level), 59.4 mg of carfilzomib (at the 27 mg/m^2 dose level), or 79.2 (at the 36 mg/m^2 dose level).

Carfilzomib will be given as an IV infusion over 30 minutes on Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will be pre-hydrated with 250mL normal saline or other appropriate IV fluid formulation on cycle 1 Day 1. Other hydration procedures will be optional and per the discretion of the treating physician. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1. Subjects should be monitored periodically during this period for evidence of fluid overload. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Refer to Table 7-1 for guidance regarding dose reduction in subjects with compromised renal function.

Doses of carfilzomib may be rescheduled up to 2 days if the scheduled day falls upon a holiday or with approval from the Lead Principal Investigator . If day 2 of Carfilzomib dosing is delayed (i.e., Day 2, 9, 16) 4 mg of dexamethasone premedication is required to be used prior to second treatment. Missed doses will not be replaced during a cycle. Carfilzomib will be escalated from $20mg/m^2$ (Cycle 1 Days 1 and 2) to $36mg/m^2$ (Cycle 1 Days 8, 9, 15, 16 - see below) as long as the subject does not present with cytokine release symptoms (fever, rash, dyspnea, etc) after Cycle 1 Day 2. If the subject does have concerning symptoms, they will be treated at $27mg/m^2$ on days 8 and 9 before being escalated to $36mg/m^2$.

- Cycle 1: 20 mg/m^2 Days 1, 2; 36 mg/m^2 Days 8, 9, 15, 16
- Cycle 2-4: 36 mg/m^2 if tolerated Days 1, 2, 8, 9, 15, 16
- Cycles 5-8 (patients that are MRD- and have no risk factors at the end of cycle 6) and Cycle 5 - 36 (for MRD+ patients and high risk patients at the end of cycle 6): best tolerated dose Days 1, 2, 15, 16

6.3.1.2. Lenalidomide Administration

US: 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 and 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 Lenalidomide will be counted and documented by each site. Unused Lenalidomide will be returned to Celgene by the site using instructions provided by Celgene.

Poland: Lenalidomide will be provided by Celgene and must be prescribed in compliance with Revlimid® PPP program of Celgene Corporation. 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. Sponsor will be responsible for destruction of unused Revlimid®

Subjects randomized to the experimental arm will receive lenalidomide as follows in 28-day cycles:

- Cycle 1: 15 mg days 1-21
- Cycles 2-4: 25 mg days 1-21 if tolerated, otherwise continue at lower dose
- Cycles 5 and beyond: best tolerated dose days 1-21

Lenalidomide should be taken each evening at approximately the same time. 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. Subjects should be instructed to never take Lenalidomide past Day 21 of each cycle.

6.3.1.3. Dexamethasone Administration

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

• Cycles 1 – 4: 20 mg PO or IV per dose Days 1, 8, 15, 22

• Cycles 5+: 20 mg or best tolerated dose PO or IV per dose Days 1, 8, 15, 22

IV infusion of Dexamethasone only based on the PI decision and with approval from Lead Principal Investigator.

Split weekly dosing (e.g. 10mg on Day 1 and 10mg on Day 2, etc.) is permitted with approval from Lead Principal Investigator.

Dexamethasone given on days without carfilzomib (on Days 22 and 23 of Cycles 1-8) may be self-administered by the subject on an outpatient basis.

If day 2 of Carfilzomib dosing is delayed (i.e., Day 2, 9, 16) 4 mg of dexamethasone premedication is required to be used prior to second treatment. Missed doses will not be replaced during a cycle.

Missed doses of dexamethasone will not be made up.

6.3.2. **Control Arm**

6.3.2.1. Lenalidomide administration

US: 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 Lenalidomide will be counted and documented by each site. Unused Lenalidomide will be returned to Celgene by the site using instructions provided by Celgene.

Poland: Lenalidomide will be provided by Celgene and must be prescribed in compliance with Revlimid® PPP program of Celgene Corporation. 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. Sponsor will be responsible for destruction of unused Revlimid®.

Subjects randomized to the control arm will receive lenalidomide as follows:

- Cycles 1-4: Days 1-28. Lenalidomide will begin at a dose of 10 mg PO daily (2 capsules per day). After three months, the dose will be increased, provided ANC $\geq$ 1,000/μL, platelet count $\geq$ 75,000/μL, and all nonhematologic toxicity is $\leq$ grade 1, to 15 mg PO daily (3 capsules per day).
- Cycles 5 and beyond: best tolerated dose days 1-28

Lenalidomide should be taken each evening at approximately the same time. 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.

6.3.3. **Maintenance treatment (both arms)**

Patients that complete 8 cycles of KRd (who were MRD-negative and had no risk factors after cycle 6) and all patients that complete 36 cycles in both arms, will continue a regimen of lenalidomide alone at best tolerated dose, up to 15mg, daily for 28 days in 28 day cycles.

6.3.4. **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.

6.4. **Instructions for Initiation of a New Cycle**

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 $\geq 30 \times 10^9$/L
- Any other study drug-related adverse event must have resolved to grade 1 or baseline (see Appendix 2)
- Serum uric acid and creatinine concentrations 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 carfilzomib or lenalidomide 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.

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 Lead Principal Investigator and the Co-Investigator at the treating institution.

Dexamethasone may be discontinued without the subject discontinuing study treatment.

6.5. **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, Secondary Site, or Treating Investigator, warrants discontinuation.

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 ba seline value or to ≤ Grade 1 within 21 days; otherwise study drug will be permanently discontinued. Any deviations from this plan must be approved by the Lead Principal Investigator

All clinically-significant non-hematologic toxicities must be resolved to Grade 1 or baseline.

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

Experimental Arm:

Table 7-1 Carfilzomib Dose Adjustments

Nominal carfilzomib dose	**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 7-2 Lenalidomide Dose Adjustments

Nominal Lenalidomide Dose	**Dose -1**	**Dose -2**	**Dose -3**	**Dose -4**	**Dose -5**
25 mg Days 1-21	20 mg	15 mg	10 mg	5 mg	5 mg every other day
15 mg Days 1-21 (if dose not escalated after cycle 1)	10 mg	5 mg	5 mg every other day	Discontinue	N/A

Table 7-3 Dexamethasone Dose Adjustments

Nominal Dexamethasone Dose	**Dose -1**	**Dose -2**	**Dose -3**
20 mg	12 mg	8 mg	4 mg

*Split dosing of dexamethasone on days 1,2, 8,9, 15,16, 22,23 may be implemented to control toxicities that do not require a dose reduction. Split dosing requires the approval of the Lead Principal Investigator before implementing.

Control Arm

Table 7-4 Lenalidomide Dose Adjustments

Nominal Lenalidomide Dose	Dose -1	Dose -2	Dose -3	Dose -4
15 mg Days 1-28	10 mg	5 mg	5 mg Days 1-21	5 mg every other day Days 1-21
10 mg Days 1-28	5 mg	5 mg Days 1-21	5 mg every other day Days 1-21	Discontinue

NOTE: Dose modifications of lenalidomide maintenance in subjects on both arms (lenalidomide only and KRd after the completion of 8 or 36 cycles), should follow guidelines from control arm (lenalidomide only).

6.5.1. Toxicity Management Guidelines

Treatment guidelines for specific hematologic toxicities are outlined in Section 7.5.1.1 and nonhematologic toxicities in Section 7.5.1.2. In addition to dose reductions, administration of carfilzomib and/or lenalidomide may be held temporarily in the event of a treatment-related toxicity at the Treating Investigator's discretion.

6.5.1.1. Hematologic Toxicity

Table 7-5 Dose Modification Guidelines for Hematologic Toxicities

When Platelets:	Lenalidomide	Carfilzomib	
Fall to < 30 x 10^9/L	• Hold dose, follow CBC weekly • Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L • Then resume at 1 dose decrement	If platelets 10-30 x10^9/L without evidence of bleeding	• Hold • With resolution restart at previous dose
		If evidence of bleeding or platelets < 10 x10^9/L	• Hold • With resolution restart at previous dose
For each subsequent drop to < 30 x 10^9/L	• Hold dose, follow CBC weekly • Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L • Then resume at additional dose decrement	If platelets 10-30 x 10^9/L without evidence of bleeding	• Hold • With resolution restart at previous dose
		If evidence of bleeding or platelets < 10 x10^9/L	• Hold • With resolution restart at 1 dose decrement
Grade 4 thrombocytopenia without evidence of bleeding, carfilzomib dosing may occur at the discretion of the Treating Investigator. However, subjects should receive supportive measures in accordance with institutional guidelines.			

Table 7-6 Dose Modification Guidelines for Hematologic Toxicities

When ANC:	Lenalidomide	Carfilzomib

Fall to < 0.75 x 10^9/L	• Hold dose, administer myeloid growth factor • Follow CBC weekly • Resume at full dose when ANC ≥ 0.75 x 10^9/L	If ANC 0.5-0.75 x 109/L	• Continue at full dose
		If ANC < 0.5 x109/L	• Hold • Resume at 1 dose decrement when ANC returns to ≥ 0.5 x10^9/L
For each subsequent drop to < 0.75 x 10^9/L	• Hold dose, administer myeloid growth factor • Follow CBC weekly • Resume at 1 dose decrement when ANC ≥ 0.75 x 10^9/L	If ANC 0.5-0.75 x 10^9/L	• Continue at full dose
		If ANC < 0.5 x10^9/L	• Hold • Resume at 1 dose decrement when ANC returns to ≥ 0.5 x10^9/L

6.5.1.2. Non-hematologic Toxicity

Table 7-7 Dose Modifications for Non-hematologic 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 7-7 Dose Modifications for Non-hematologic 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

Table 7-7 Dose Modifications for Non-hematologic Toxicity

Recommended Action		
	Lenalidomide	**Carfilzomib**
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 LOH	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.
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>S0 mL/min	Full dose	Full dose
CrCl <SO 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

Table 7-7 Dose Modifications for Non-hematologic Toxicity

Recommended Action		
	Lenalidomide	**Carfilzomib**
CrCl< 30 mL/min	Reduce lenalidomide to 15 mg every 48 h	Hold carfilzomib until CrCl> 30 mL/min; restart at 1 dose decrement
CrCI< 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 7-7 Dose Modifications for Non-hematologic 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
Pericardia) 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
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

Table 7-7 Dose Modifications for Non-hematologic Toxicity

Recommended Action		
	Lenalidomide	**Carfilzomib**
Pulmonary Toxicities: Interstitial Lung Disease (inc. pneumonitis), Acute Respiratory Failure, and Adult Respiratory Distress Syndrome (ARDS)	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
Gastrointestinal Perforation	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1 Resume at one level dose reduction
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
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 7-8 Dose Modification 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 H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.

Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H2 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.

6.5.2. **Response Evaluation**

The first response assessment should be completed at Cycle 2 day 1 and the M-spike value will be compared to baseline (pre-induction treatment) M-spike to determine response. If M-spike is not available, the respective pre-treatment immunoglobulin level and for light-chain-disease-only subjects, involved free light chain level or 24-hr total protein level, will be used to assess response. If at any time throughout the treatment a complete response or better is suspected, a complete disease assessment should be performed to confirm response according to IMWG criteria:

Myeloma Disease Assessment – laboratory

M-protein determination:

- Serum Protein Electrophoresis (SPEP) and immunofixation
- Urine Protein Electrophoresis (UPEP) and immunofixation
- Serum Free Light Chains
- Serum quantitative immunoglobulins (Igs)

Bone Marrow Biopsy	Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for conventional cytogenetics and fluorescent *in situ* hybridization. For subjects who give consent for correlative samples, an additional aspirate sample should be collected at screening, at time of complete response (if applicable), at the end of cycles, 6, 12, 24, and 36, and time of progression.
Radiographic Imaging	As per standard of care

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

6.6. Treatment Discontinuation

Subjects will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/ removed if necessary in order to protect their health (see reasons for withdrawal below).

Patients will be removed from further treatment for the following reasons:

- Disease Progression
- Non-compliance with study procedures
- Subject no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Treatment-related toxicity requiring treatment discontinuation
- Incidence or severity of AEs that indicates a potential health hazard to the subject
- For the fourth occurrence of the same Grade ≥ 3 non-hematological toxicity
- A delay in treatment > 21 days unless approved by the Lead Principal Investigator or the as well that due to Congestive Heart Failure unresolved for > 28 days the treatment shall be discontinued (see table 7-7)
- Treating Investigator discretion
- Requirement for alternative therapy
- Suspected or positive pregnancy
- Termination of the study by the sponsor

The Lead Principal Investigator should be contacted regarding any impending discontinuation of a study subject. 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 for further follow-up. The reason for withdrawal from study must be documented in the case report form.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT should be performed, if possible. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The Treating Investigator should contact the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, with an explanation of why the patient is withdrawing from the study.

6.6.1. **Duration of Follow Up**

Long-term follow up will include an assessment for disease progression in subjects who did not progress during treatment. This should occur every 3 months (+/- 30 days) for 2 years from safety follow-up visit (28 days post-last study treatment).

6.7. **Safety Considerations & Supportive Care**

Supportive measures for optimal medical care shall be provided during participation in this clinical trial. Supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers), glucocorticoids, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. As needed and per individual study site institutional guidelines, prophylactic therapies, including antivirals, antifungals, and antibiotics, may be administered to ameliorate risks associated with non-malignant disorders or of immune system compromise.

6.7.1. **First Dose Effect (Carfilzomib)**

A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.

All subjects should be well hydrated (Section 7.2.1). Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment.

Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.

6.7.2. **Tumor Lysis Syndrome**

TLS, which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with carfilzomib. All subjects should follow the hydration guidelines outlined in Section 7.2.1. If subjects are considered to be at risk for TLS, hydration should be continued into Cycle 2 if clinically indicated.

MM subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III), rapidly increasing M-protein or light chains, or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

During Cycles 1 and 2, serum electrolytes and chemistries are closely monitored as outlined in Section 7.1.2. 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.

If TLS occurs, 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 TLS must be reported to the Lead Principal Investigator (who will, in turn be responsible for distributing this information to all sites) and to Amgen as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

6.7.3. **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 during treatment with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Refer to Table 7-7 for guidance regarding dose reduction in subjects with compromised renal function.

7. SAMPLES FOR MRD EVALUATION

Bone marrow samples for this evaluation are required and as per the standard of care and will be collected prior to initiation of treatment (screening), at the completion of 6 cycles of KRd, at 12, 24, and 36 months and then yearly or at the time of complete response (if applicable) if more than 2-3 months from scheduled evaluation, and/or progression/relapse

MRD sample	Correlative Sample	Time Points
Bone Marrow Aspirate (MRD samples) and FFPE/BMA slides (ID/calibration sample from pre-treatment)	Bone Marrow Aspirate	Screening/Pre-treatment (calibration sample for MRD only), screening, at end of 6, 12, 18, 24, and 36 months cycles, EOT, yearly after EOT, and at the time of complete response (if applicable) Progression/Relapse
	Peripheral Blood	Screening, at end of 6, 12, 18, 24, and 36 cycles, EOT, yearly after EOT, and at the time of complete response (if applicable)
	Plasma, Serum	Screening, at 6, 12, 18, 24, and 36 months, EOT, yearly after EOT, and at the time of complete response (if applicable) Progression/Relapse
	Buccal Swab	Screening only

All bone marrow procedures (including those performed at screening, response and/or progression/relapse) are considered standard of care and a subject may give consent to have extra research samples collected at these visits.

Please refer to the Laboratory Manual for detailed 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 in the US:

1. An inventory sheet 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 contact lab technician to alert him/her of an incoming shipment by email:

   myeloma-lab@bsd.uchicago.edu
4. Please ship Monday, Tuesday, Wednesday or Thursday, as shipments cannot be received on weekends and/or on holidays.

Andrzej J Jakubowiak, MD, PhD
Attention: Myeloma Laboratory
900 E 57th St
KCBD 7240 LB17
Chicago, IL 60637
Business Phone (773) 702-1345 or 773-834-1592
Business Fax 773-248-330-6027

Shipping Instructions in Poland:

1. An inventory sheet 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 contact lab technician to alert him/her of an incoming shipment by email:
4. For shipping instructions, please refer to the Polish laboratory manual

Note: Please follow your institution's policy regarding destruction of patient samples upon withdrawal of informed consent.

8. ADVERSE EVENTS

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

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

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

Whenever possible, the 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 3). 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:

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.

8.1. Causality

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

Definite (5) – The AE *is clearly related* to the study treatment.

Probable (4) – The AE *is likely related* to the study treatment.

Possible (3) – The AE *may be related* to the study treatment.

Unlikely (2) – The AE *is doubtfully related* to the study treatment.

Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

All AEs will be considered for dose-limiting toxicity evaluation unless the event can clearly be determined to be unrelated to the drug.

8.2. Adverse Event Reporting Procedures

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

All Adverse Events **must** be reported in routine study data submissions to the lead PI, who will review and will be responsible for alerting all participating sites about the AE as required. **AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below**

must <u>also</u> be reported in routine study data submissions in eVelos. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome as shown on the eCRF in eVelos . All AEs must be followed to resolution or stabilization regardless of relationship to study drug.

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

AEs must be reported from the date of the first dose of treatment through 30 days post-last dose of study treatment or initiation of a new anti-cancer therapy, whichever occurs first. 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 that 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. SAEs continuing at 30 days post-last dose should be followed until resolution or stabilization.

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. Only grade 1 & 2 abnormal laboratory values continued clinically significant, related to study treatment, and/or requiring concomitant medication will be recorded. 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 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 Lead Principal Investigator and that they are listed on the delegation log.

8.3. Serious Adverse Events

Information about all serious adverse events (SAE) will be collected independently in Poland and the US (6 sites in Poland and 6 sites in the US).

The Lead Principal Investigator in Poland will collect and review the information from all Polish sites and only those SAEs deemed "Serious Unexpected Suspected" (SUSARs, see below for definition) will be reported to the Lead Principal Investigator at University of Chicago via the Polish Myeloma Consortium (PMC) using the completed MedWatch 3500 form for appropriate reporting in the US and distribution to US sites. The Lead Principal Investigator in Poland will follow local regulations for distribution of SAEs/SUSARs to Polish sites, Ethics Committee and to the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. All SUSARs must also be reported to EudraVigilance Clinical Trials Module.

All SAEs from US sites will be collected by the UC CRA and reviewed by the Lead Principal Investigator at University of Chicago. Only those determined to be SUSARs by the Lead Principal Investigator will be distributed to all US participating sites (using the completed MedWatch 3500 form) and also to the PMC to allow for distribution in Polish sites according to European regulations. To ensure patient safety, each serious adverse event occurring in the US must be reported to the

Lead Principal Investigator and he or a designee will in turn, report to the University of Chicago Comprehensive Cancer Center via entry on the SAE eCRF in eVelos within 24 hours of learning of its occurrence. In the event that direct entry into eVelos is not available, a paper SAE form is provided for this study and may be used and sent via fax or email.

The Lead Principal Investigator is responsible for notifying the ethics committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations.

The Site Investigator is also responsible for notifying the local ECs in accordance with local regulations. Additionally, the Lead Principal Investigator is responsible for reporting SAEs to Amgen and Celgene as described in section 8.4.

8.3.1. **Serious Adverse Event Definition**

An SAE is one that meets the following criteria:

- Results in 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 or any other medicinal product effects, which the doctor by his state of knowledge deemed serious
- 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 Principal Investigator as an SAE.

ALL Serious Adverse Events occurring in the US MUST be reported to the US Lead Principal Investigator and to the University of Chicago Comprehensive Cancer Center (UC CCC), and those occurring in Poland to the Polish Lead Principal Investigator (via entry on the SAE eCRF in eVelos or paper submission via fax or email). This is whether or not they are considered related to the study agent. Refer to Section 8.3.3 for reporting guidelines.

8.3.2. **Serious and Unexpected Suspected Adverse Reaction (SUSAR)**

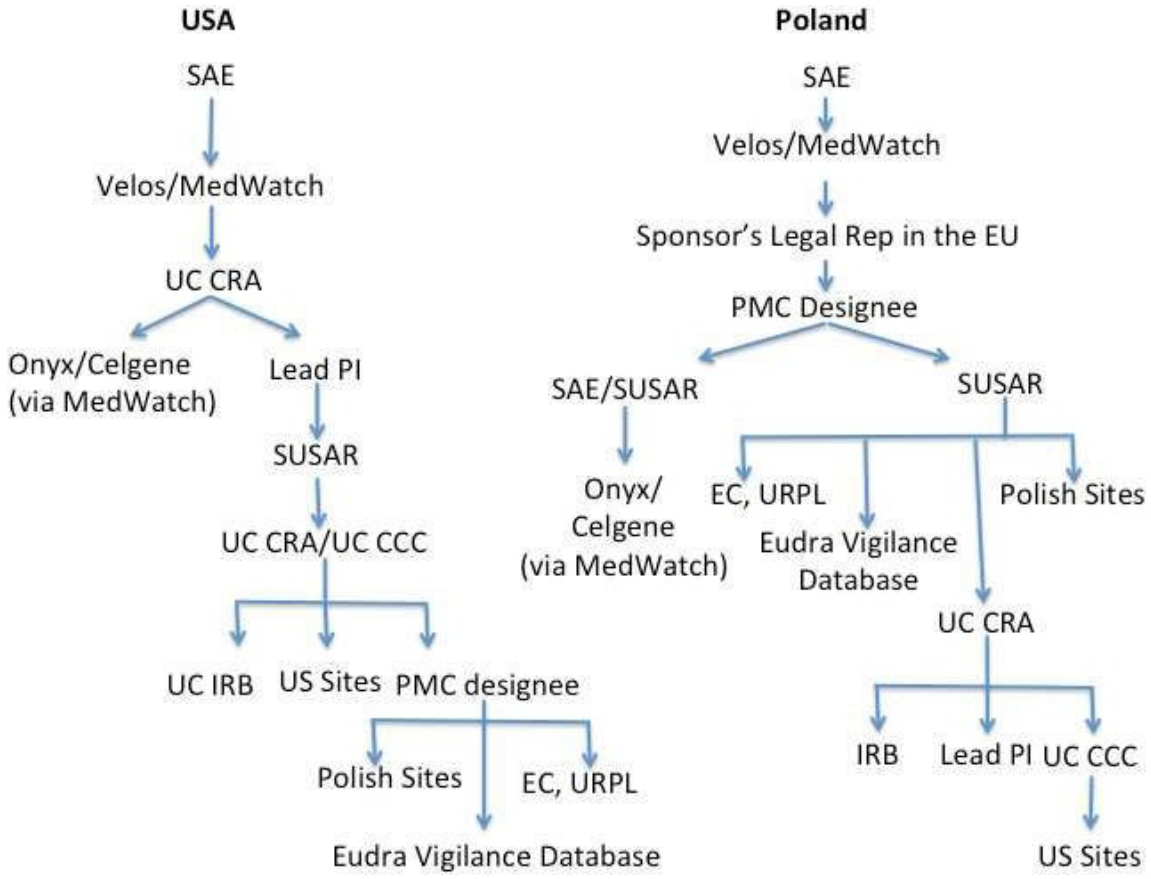
A serious adverse event is considered to be a suspected adverse reaction if there is evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens Johnson Syndrome), one or more occurrence of an event 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, or FDA or EU-approved package insert. This includes adverse events listed

in the protocol or consent 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 agent.

The lead institution (University of Chicago) is responsible for notifying all participating investigators, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports that are determined by the Lead Principal Investigator to be Unexpected.

8.3.3. **Serious Adverse Event Reporting and Documentation Requirements**



8.3.3.1. Serious Adverse Event Reporting <u>to</u> the Coordinating Center in the US

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined above) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC).

SAEs in the US will be reviewed by the Lead Principal Investigator, who will determine whether they are SUSARs. The Lead Principal Investigator or designee will report all SUSARs to the UC CRA and UC CCC, who will report simultaneously to the UC IRB, other US sites, and the PMC designee according to regulations (see below).

Similarly, SAEs in Polish sites have to be reported to the Polish Lead Principal Investigator, or designee. He will in turn, review the information, and determine whether it is a SUSAR. The Polish Lead Principal Investigator or designee will report SUSARs to the PMC, which will be responsible for reporting all Polish SUSARs to the UC CRA. The UC CRA is responsible for reporting all SUSARs for Polish patients appropriately to the US Lead Principal Investigator, the UC CCC, and the UC IRB (see below).

The responsible Research Nurse or other designated individual at the treating site in the US should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the UC CCC CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

8.3.3.2. Serious and Unexpected Adverse Event reporting by the Coordinating Center in the US

The designated UC CCC Regulatory Manager will notify all participating sites and the Polish Myeloma Consortium of all SUSARs that occur on this clinical trial and which are reported to the UC Institutional Review Board (IRB). The PMC designee is then responsible for distributing this information to Polish sites. A copy of the completed Form 3500 (MedWatch) will be distributed to all participating sites.

8.3.3.3. Serious Adverse Event Reporting to the Polish Myeloma Consortium in the EU

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined above) occurring on Polish patients have to be reported to the Polish Lead Principal Investigator, or designee. He will in turn, review the information, and

determine whether it is a SUSAR. The Polish Lead Principal Investigator or designee will report all SAEs and SUSARs to the PMC according to local regulations.

The responsible Investigator or other designated individual at the treating site should report the SAE to the Polish Lead Principal Investigator or designee within 24 hours of being made aware of the event regardless of whether all information regarding the event is available. Reports should be made using the 'Serious Event Report' Form. Please scan and send fax to the following:

Fax: +48 61 854 93 56

All serious adverse events should also be reported to the EC and URPL, if requested, and recorded according to their policies and procedures.

8.3.3.4. Serious and Unexpected Adverse Event reporting by the Polish Myeloma Consortium in the EU

The designee of the PMC will notify the University of Chicago CRA as well as all participating Polish sites, EC, and responsible authorities (URPL and EudraVigilance database– Clinical Trials Module) of all SUSARs that occur on Polish Patients on this clinical trial. The designee of the PMC is responsible for reporting all SUSARs within appropriate timeframes to the EudraVigilance, URPL and ECs according to the EudraLex Volume 10 Clinical trials guidelines Fatal and life-threatening SUSARs shall be reported within 7 calendar days with follow-up within the next 8 calendar days. All other SUSARs shall be reported within 15 calendar days. As stated above, the University of Chicago will be responsible for notifying the U of C IRB and other US sites of SUSARs occurring to Polish patients.

8.4. Expedited Reporting by the Lead Principal Investigator Amgen and Celgene

The University of Chicago CRA will inform Onyx and Celgene (US) in writing by email or facsimile of any SAE occurring to US patients within 24 hours of being aware of the event using a completed MedWatch3500 Form.

Similarly, the PMC designee will inform Amgen and Celgene (EU) in writing by email or facsimile using a completed MedWatch3500 Form, of any SAE occurring to Polish patients within 24 hours of being aware of the event.

The date of awareness should be noted on the report. 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). A final report to document resolution of the SAE is required.

SAE Reporting by the Lead Principal Investigator to Amgen

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

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Amgen in English.

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

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

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

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

Reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the Lead Principal Investigator submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. The Lead Principal Investigator will support reconciliation of all ICSRs at the end of the study at a minimum.

The Onyx protocol number **(IST-CAR-720)** and the institutional protocol number should be included on SAE reports to Onyx.

Onyx Drug Safety and Pharmacovigilance Contact Information in the US:

- Fax: Toll-free US 888-814-8653
- +1 805-480-9205 (toll, global)
- Drug Safety Reporting by secure e-mail can be established upon request.

The Amgen protocol number **(20159903)** and the institutional protocol number should be included on SAE reports to Amgen.

Amgen Drug Safety and Pharmacovigilance Contact Information in the EU:

Phone: +48 509 680 978

E-mail: eu-pl-safety@amgen.com

SAE Reporting by Lead Principal Investigator **to Celgene**
The Celgene protocol number (RV-CL-MM-PI-005610) and institutional numbers should be included on SAE reports to Celgene. A copy of the fax transmission or email confirmation of the SAE report (or on the fax cover letter) sent to Celgene should be attached to the SAE and retained with the patient records

Celgene Drug Safety and Pharmacovigilance Contact Information in the US

Phone: (908) 673-9115

E-mail: drugsafety@celgene.com

Celgene Drug Safety and Pharmacovigilance Contact Information in the EU

Local Drug Safety Office Poland

Phone: +48 22 550 37 05/09

Mobile: +48 665 536 776 or +48 695 277 667

e-mail: drugsafetypoland@celgene.com

fax: +48 22 842 12 52

8.4.1. **Pregnancy Reporting**

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—Lenalidomide, dexamethasone, and carfilzomib—are to be discontinued immediately. 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 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 Amgen and Celgene using expedited reporting procedures listed in Section 8.4 and 8.4.1.

Pregnancy Reporting by Lead Principal Investigator to Celgene

For Lenalidomide pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on Lenalidomide, or within 28 days of the subject's last dose of Lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately and the subject instructed to return any

unused portion of the Lenalidomide to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the IIT Sponsor who will inform Celgene immediately using the Pregnancy Reporting Form provided by Celgene or an approved equivalent form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the Lenalidomide should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male subject, the investigator should ask if the female partner is willing to share information with Celgene Drug Safety and allow the pregnancy related event to be followed up to completion.

The Sponsor will inform Celgene immediately, using the Pregnancy Reporting Form provided by Celgene or an approved equivalent form, of any information related to pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in partner of Patients while the Patients are still treated with Lenalidomide or within 28 days of the Patients' last dose of Lenalidomide.

Pregnancy Reporting by Lead Principal Investigator to Amgen

Report Pregnancy and potential infant exposure including Lactation, within ten (10) calendar days of the Lead Principal Investigator awareness. Provide to Amgen the SAE reports associated with pregnancy.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy.

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.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Carfilzomib

9.1.1. Description

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

9.1.2. 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®).

9.1.3. Storage

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

9.1.4. Accountability

Amgen and the Site 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.

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.

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

9.2. Lenalidomide

9.2.1. 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 C13H13N3O3, 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.

9.2.2. **Supply**

US

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.

Poland

Celgene shall provide Lenalidomide free of charge in the quantity and presentation required to complete the Study in accordance with the Protocol. Lenalidomide will be prescribed in accordance with the Revlimid® PPP program of Celgene Corporation. Lenalidomide is for PO (oral) administration only.

9.2.3. **Storage Conditions**

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

9.2.4. **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.

9.2.5. **Prescribing Information**

US

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.

Poland

Lenalidomide will be provided in accordance with the Revlimid® PPP program of Celgene Corporation. Per standard Revlimid® PPP 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® PPP 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. Sponsor will be responsible for destruction of unused Revlimid® .

9.2.6. Special Handling Instructions

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

9.3. Dexamethasone

Dexamethasone may be given IV or PO

9.3.1. 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.

9.3.2. Formulation

Dexamethasone is a commercially available PO drug, supplied as 0,5 and 1 mg tablets.

9.3.3. Storage conditions

Store dexamethasone at controlled room temperature 20 to 25°C (68 to 77°F)

9.3.4. Accountability

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

10. STATISTICAL CONSIDERATIONS

10.1. Objectives

10.1.1. Primary Objective

- To compare PFS between KRd and lenalidomide arm after randomization

10.1.2. Secondary Objectives

- To determine the rate of MRD-negative disease at 6 and 12 months after randomization
- To compare the efficacy (rate of PR, VGPR, CR, and sCR) of KRd vs. Lenalidomide alone after randomization
- To evaluate the safety and tolerability of KRd compared to lenalidomide alone

10.1.3. Exploratory Objectives

- Establishment of markers of response and duration of response to treatment strategy using KRd or R as consolidation after autoPBSCT based on proteomic studies

10.2. Sample Size Justification & Analysis Plan

A total of 180 patients will be enrolled in a 1:1 ratio (80-100 per arm) stratified according to level of response from initial treatment at study entry (<VGPR vs ≥ VGPR), presence or absence of at least one poor prognostic risk factor (Yes/No to at least one cytogenetic risk factor including del-13, t(4;14), t(14;16), del17p, hypodiploidy), and by treatment site (University of Chicago and Poland).

10.2.1. **Primary Objective Sample Size Justification**

The primary objective of this study is to compare PFS between the two arms. Time to progression or death will be calculated from the date of first treatment on protocol follow-up treatment group assignment. Subjects at the time of analysis not having either endpoint will be censored. Adherence to protocol and ability to follow patient in follow-up is expected to be excellent; however, if any patient revokes consents for the study not to disease progression, they will be censored on their last clinical visit follow-up date. Likewise, patients in follow-up that are lost or that refuse or revoke study participation will be censored on their last clinical visit follow-up date.

The sample size for this trial is based on consideration of PFS after 5 years of treatment. At least sixty-five percent of patients are anticipated to be progression-free at 4 years after receiving KRd compared to 43% with lenalidomide alone, based on the studies of Attal et al. and McCarthy et al. (Attal et al., 2012; McCarthy et al., 2012), and unpublished updated results from KRd trial, (paper in preparation). Using a two-sample, two-sided test of proportions with at most 5% type I error and at least 85% power, 90 patients per study arm are required, for a total study size of 180 patients. To operationalize a time-to-event framework, and after careful consideration of our ability to accrue patients to this study across the likely institutional participants, we estimate that we can accrue 120 patients per year. Patients will be randomized in a 1:1 fashion between the KRd and R study arms, until 90 patients per arm (180 patients in total) are accrued to study, representing 1.5 years of study duration. We expect that loss-to-follow-up in the study population will be extremely low or zero given the careful clinical monitoring that will be expected and mandated by the protocol's language. The study will continue to follow patients at least until the last accrued patient has been followed for 4-6 years following randomization, for a minimum study duration of 6.5 years. The primary analysis of our hypothesis will occur at that time and will be conducted using the log-rank test comparing the product-limit estimate for PFS between study arms. A sample size of 90/arm (N=180) will achieve 85% power with two-sided alpha=0.05 based on two-sided test of proportions. The hypothesized difference in proportions at 4 years, 0.65 vs. 0.43, corresponds to HR=1.96 (assuming exponential distributions), and the study will achieve 88% power with alpha=0.05 for the log-rank test

10.2.2. **Secondary Objective Sample Size Justification**

The rate of MRD-negative disease will be reported at screening, 6, 12, 18, 24, and 36 months and then yearly after randomization for both groups. Additionally, sites will be required to provide unstained pre-treatment slides to assess MRD by sequenta. Comparison between groups may be made using a standard chi- square or Fisher's exact test. At the conclusion of the trial, with all subjects evaluated for PFS assessment at 4-years, the rate of MRD-negative status will be compared within treatment groups. This analysis may be conduct by contingency tables, or by adjusted logistic regression models, which may adjust for other important confounders. Improvement of response during therapy measured at 6 and 12 months post randomization will be compared between groups. Proportions of improving patients will be reported by treatment group, and comparisons of those proportions will be conducted using the chi-square or Fisher's exact tests. Overall survival will be calculated from date of randomization until death from any cause and measured based upon the intention-to-treat paradigm, and will be compared between treatment groups using the product-limit method of Kaplan and Meier and the log-rank test statistic. The duration of MRD-negative disease will be calculated between the date of first occurrence of MRD-negative status, until such time as MRD-positive disease assessment or date of disease progression. Comparisons of duration of MRD-negative status may require the use of interval censoring methods. And final, safety of the regimens will be assessed by comparing CTCAE grade toxicity occurrence between groups. Toxicity of grade 2 and higher will be tabulated for each system organ class (SOC) and common individual toxicities

occurring with SOCs reported. The maximum graded toxicity overall and within SOC will be reported per patient with the results summarized by treatment group.

11. DATA REPORTING

Data reporting will be performed utilizing the eVelos electronic data capture system for all patients but data reporting will be done separately between the two countries, using two instances of the protocol in eVelos. The University of Chicago CRA will provide the applicable user registration information in the US and the PMC will provide the applicable user registration information in Poland.

All required data must be recorded in the eVelos database within two weeks of the completion of each cycle. AEs and SAEs are to be entered in eVelos in real time. SAEs in the US are also to be recorded on the paper Serious Adverse Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). SAEs in Poland are to be recorded on the Serious Adverse Event Form within 24 hours of the site's knowledge of the event and sent via fax to the Polish Myeloma Consortium (Fax: +48 61 854 93 56)

All case report forms must be completed by designated study personnel. Each screened patient (signed informed consent) is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, providing supporting documentation is required as per Patient Enrollment and Registration policies. 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. **Each site 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 form.

12. REGULATORY OBLIGATIONS

12.1. Responsibilities of the Polish Myeloma Consortium

As this is collaborative study in managed jointly as per agreement between UC and the PMC in different legislations and the PMC has whole responsibilities for actions in the EU, PMC shall be considered as a Sponsor with accordance to the EU legal regulations, whereas UC is a Sponsor as per US regulations.

The PMC is responsible for the following activities for all Polish Sites:

a. Patient registration/check for eligibility: Polish patients will be enrolled by each Polish site separately (after confirmation from the Polish Lead Principal Investigator or designee). Source documents will be kept at each local site due to local privacy regulations.
b. Data entry: the PMC will train site PIs on appropriate data entry on eVelos. It will be the responsibility of the site PI or designee to enter data correctly and in a timely manner.
c. Monitoring: PMC will be responsible for monitoring each Polish site according to local regulations

d. Training: the PMC will be responsible for arranging a site initiation visit (SIV) and training each Polish site (after the initial SIV teleconference with University of Chicago) on all aspects of the protocol including data entry, SAE reporting, etc.
e. SAE/SUSAR Reporting: the PMC will be responsible for reporting SAEs and SUSARs according to local regulations. Additionally, they will report SUSARs to UC via the US CRA.
f. Auditing Polish Sites, if necessary
g. Data aggregation for the DSMB. A report will be comprised of:
    i. Enrollment/ registration numbers
    ii. AEs
    iii. Response data
    iv. Other Efficacy data

12.2. 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.

In the US, the Lead PI will provide the US Site Investigator with an Informed Consent Form (ICF) developed by the Lead PI. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to this document must be submitted to the University of Chicago CCTO for approval, prior to submission to the participating site IRB. The IRB will review the Informed Consent Form for approval. A copy of the IRB approval form must be submitted to the University of Chicago CCTO 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. A copy of signed ICF will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection by the designated Lead Principal Investigator representative at any time.

The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the Investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

In Poland, the PMC will provide the polish Site Investigator with a sample Patient Information Sheet (PIS) and Informed Consent Form (ICF) developed by the PMC. Local and/or institutional requirements may require disclosure of additional information in both PIS and ICF documents. Any changes to these documents must be submitted to the PMC for approval, prior to submission to the

participating site IEC. The valid IEC will review the Patient Information Sheet and Informed Consent Form for approval. A copy of the IEC approval form must be submitted to the PMC 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. Two original copies of PIS and ICF shall be signed and dated by the subject or the subject's legally authorized representative at the time of consent. One copy of signed PIS and ICF will be given to the subject or subject's legally authorized representative. The other original signed consent must be maintained by the Site Investigator and available for inspection by a PMC representative at any time.

The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the Investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

12.3. Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, The Act of 6 September 2001 on Pharmaceutical Law in Poland and applicable local health law and authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee and The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland (URPWMiPB). Before the investigational drug is shipped to the Site Investigator, the Lead Principal Investigator or designee will provide Amgen and Celgene with a copy of the IRB or Ethics Committee and URPL approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Lead Principal Investigator and Site Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval, respectively, throughout the duration of the study, when necessary.

The Lead Principal Investigator and Site Investigator are also responsible for notifying their IRB or Ethics Committee and URPL respectively of any significant adverse events that are serious and unexpected as per their policies.

Amgen will provide the Lead Principal Investigator 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 PMC, the IRB/ECs, participating sites, and other Investigators participating in the study and URPL, when necessary.

Celgene will provide the Lead Principal Investigator with any expedited safety reports generated from any ongoing studies with lenalidomide, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of lenalidomide during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs, participating sites, and other Investigators participating in the study and URPL, when necessary.

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

Before the start of the study at a Polish site, documents described in Regulation of Ministry of Health dated 2 May 2012, named 'Rozporządzenie Ministra Zdrowia z dnia 2 maja 2012 r. w sprawie wzorów dokumentów przedkładanych w związku z badaniem klinicznym produktu leczniczego oraz w sprawie wysokości i sposobu uiszczania opłat za złożenie wniosku o rozpoczęcie badania klinicznego.' must be on file with the PMC and approval of both EC and URPL has to be obtained for each Site.

12.4. 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 the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA/URPL/EMA 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 and Polish Act on the Protection of Personal Data.

12.5. Multicenter Guidelines

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

The Study Lead PI/Coordinating Center in US and Country Coordinator in EU are responsible for distributing all official protocols, amendments, and Unexpected Event Safety Reports to all participating institutions for submission to their applicable local IRBs/EC as required.

13. ADMINISTRATION AND LEGAL OBLIGATIONS

13.1. Institutional Review Board (IRB) Approval and Consent

Unless otherwise specified, each participating institution must obtain approval from a valid IRB/EC before enrolling patients on this study. It is expected that the IRB/EC will have the proper representation and function in accordance with valid mandated regulations. The IRB/EC should approve the consent form and protocol.

In obtaining and documenting informed consent, the Treating Investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA/EU Regulations and local or state regulations. Once this essential information has been provided to the patient and the Treating Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB/EC-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

13.1.1. Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRB/ECs at least once a year for the duration of the study. The annual IRB/EC renewal approvals for participating institutions should be forwarded promptly to the University of Chicago's Regulatory Manager in the US and to the PMC in Poland. If the institution's IRB/EC requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

For Polish Sites, the Polish Lead Principal Investigator will assure an Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments. The Polish Lead Principal Investigator will provide the IEC with documents as described in Regulation of Ministry of Health dated 2 May 2012, named 'Rozporządzenie Ministra Zdrowia z dnia 2 maja 2012 r. w Dobrej Praktyki Klinicznej' concerning the GCP implementation to polish law.

Final Reports will be provided to IRBs/IECs and URPLWMiPB and the Lead Principal Investigator within 1 year since the end of long term follow up.

13.2. Required Documentation

Before the study can be initiated at any US site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the Site Investigator and any sub-investigators who will be involved in the study.
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

Before the study can be initiated at any EU site, the following documentation must be provided to the Polish Myeloma Consortium.

- A copy of the valid EC approval letter for the protocol and informed consent
- A copy of the valid RA approval letter for the protocol and informed consent
- EC membership list

- CVs and medical licensure for the Polish Lead Principal Investigator and any sub-investigators who will be involved in the study.
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the EC/RA.

13.3. Protocol Amendments and Study Termination

All protocol amendments will be implemented by the Lead PI and must receive IRB/IEC and RA, approval before implementation, except where necessary to eliminate an immediate hazard to subjects. Amendments should only be submitted to the IRB/IEC/RA after consideration of Amgen and Celgene.

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB and Polish Myeloma Consortium for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications.

Only the Study Lead PI together with Polish Myeloma Consortium can authorize any modifications, amendments, or termination of the protocol.

13.3.1. Amendments to the Protocol at US Sites

In the US, once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions and to the PMC electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **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 dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

In Poland, protocol amendments will be submitted by the PMC for approval to both the EC and RA. After approval the amendment can be implemented in Polish sites and as per Polish regulations. The PMC designee will also send the amended protocol and consent (if applicable) to the Lead Principal

Investigator and his designee will submit it for approval by the University of Chicago IRB. After IRB approval, the amendment and consent (if applicable) will be distributed to US sites for IRB approval and implementation (see above guidelines).

13.4. Study Documentation and Archive

13.4.1. 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 Lead Principal Investigator and the Polish Lead Principal Investigator will prepare and maintain adequate and accurate source documents in the two countries separately (i.e. the Lead PI and his team will be responsible for keeping adequate source documents in US sites, while the Polish Lead Principal Investigator will have this responsibilities for Polish sites). 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.

13.4.2. Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Lead PI-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the US Study Lead Principal Investigator (for US patients) or the Polish Lead Principal Investigator (for Polish patients). Study documents should be kept on file until three years after the completion and final study report of this investigational study or five years after a marketing application is approved for the drug for the indications for which it is being investigated (see 14.4.4), whichever is longer.

13.4.3. Case Report Form Completion

The data collected for this study will be entered into a secure database eCRF. The Lead PI (in the US) or the PMC (in Poland) will provide the applicable user registration information. Source documentation must be available to support the computerized patient record. 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. Each site 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 form. Upon registration, source documentation including demographics, screening labs, subject demographics, physician's notes for confirmation of concurrent conditions, and confirmation of disease status and treatment history. Additional information may be requested on a case-by case basis.

AEs are to be entered in real time. SAEs are to be entered in eCRF on the SAE reporting form within 24 hours of the site's knowledge of the event (in addition to the paper SAE form). All other data is to be entered within 5 days of source acquisition.

The University of Chicago CRA is responsible for training US affiliate sites and the PMC on eCRF completion. This will be done over a teleconference. After this, the PMC will be responsible for including this information on the site-initiation visits and training for each Polish site (see section 14.6 on Data Safety and Monitoring).

13.4.4. **Archival of Records**

According to 21 CFR 312.62I, the US Lead Principal Investigator (for US patients) and the Polish Lead Principal Investigator (for Polish patients) shall retain records required to be maintained under this part for a period of 5 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, it is suggested that the US Lead Principal Investigator (for US patients) and the Polish Lead Principal Investigator (for Polish patients) retain these records until 15 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The US Lead Principal Investigator and the Polish Lead Principal Investigator must retain protocols, amendments, IRB/IEC/URPL 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.

13.5. **Clinical Monitoring Procedures**

Clinical studies coordinated by the Lead Principal Investigator 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 monitored independently in the two countries. Specifically, University of Chicago will be responsible for monitoring all US sites, while the Polish CRO will monitor all Polish sites. Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document. The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Sites will be required to participate in monitoring as described in the Monitoring Plan (section 14.6). Sites will be alerted to schedule a monitoring visit, when required, and to request source documentation.

13.5.1. **Obligations of Study Site Investigators**

The Study Site Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations, valid local regulations and the Declaration of Helsinki. The Study Site Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and

other study staff members, adhere to the study protocol and all FDA/GCP/NCI/local regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. If monitoring visits or audits are conducted, he/she must provide access to original records to permit verification of proper entry of data.

13.5.2. **Protocol Deviations**

Protocol deviations in the US are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Protocol deviations in the EU are to be documented using the Protocol Deviation Form and sent via email to dytfeld@me.com

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 within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) in the US or the PMC in Poland if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB/valid EC of record according to their policies and procedures.

13.6. **Data Safety and Monitoring**

The US sites participating on this study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, any participating US site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

The EU sites participating on this study will be monitored by the Polish CRO in accordance with the Polish Myeloma Consortium standard operating procedures and Monitoring Plan to ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. As was stated above, the PMC will undergo a training session performed by University of Chicago CRA on CRF completion and data entry onto eVelos prior to taking on the responsibility for training Polish sites.

Prior to subject recruitment, and unless otherwise specified, any participating EU site will undergo a Site Initiation Visit to be conducted by the designee of the Polish Myeloma Consortium. The Site Investigator and his or her study staff must attend the site initiation meeting. During this visit, the site will be trained on CRF and eVelos usage for proper data entry.

Participating US 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 to ensure that the Site Investigator is aware of his/her ongoing responsibilities.

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

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI- and Polish Myeloma Consortium -approved Data and Safety Monitoring Plan. The conference will review:

- 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

13.6.1. **Data Safety and Monitoring Board**

An independent Data and Safety Monitoring Board (DSMB) composed of two medical oncologists and a biostatistician will be established to review the safety and efficacy data on average every 6 months. Reports will be generated and provided to the DSMB by the protocol statisticians. The reports will contain enrollment/ registration numbers, AEs, response data, and other efficacy data. After each meeting, the DSMB will produce a report with a recommendation for the steering committee.

13.6.2. **DSMB Member Scope of Work**

The Data and Safety Monitoring Board (DSMB) is an independent body composed of a two medical oncologists and a biostatistician. Their main responsibilities are to review data and safety monitoring reports prepared by the Coordinating Center and the Polish Myeloma Consortium at periodic intervals. They will also monitor patient accrual, submit requests for additional analyses as deemed necessary, evaluate the performance of the participating clinical sites, evaluate the performance of the Coordinating Center, and provide recommendations to the steering committee regarding protocol modifications and whether the study should continue as planned. They will review reports of adverse events to ensure patient safety as well as efficacy analyses to determine whether sufficient evidence has emerged that one treatment is superior to another, which would prompt consideration of early termination of the trial. The DSMB will participate in conference calls and/or face-to-face meetings with the US Lead Principal investigator, Polish Lead Principal Investigator , and study statisticians approximately every six months. The DSMB may also call for additional meetings and data reviews if they feel it is necessary for the safety of patients or the progress of the study. The DSMB is expected to approve meeting minutes and maintain confidentiality of all study results

13.6.3. **Steering Committee**

There will be a steering committee composed of the US Lead Principal Investigator, Polish Lead Principal Investigator , and the statisticians. This committee will meet monthly to discuss the progress of the trial in both countries. Additionally, the steering committee will make final decisions on the evolution of the trial according to its progress.

13.7. **Quality Assurance & Auditing**

Auditing of US and Polish sites will occur separately and by country. University of Chicago will be responsible for quality assurance at US sites, while the PMC will be responsible for this task at Polish sites. See below for details.

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 at the University of Chicago 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 formal 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 US 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.

Auditing procedures for participating EU sites must be specified and approved as per procedures of Polish Myeloma Consortium.

A regulatory authority (e.g. FDA, URPL) 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 US Site Investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made. If an inspection has been requested by a regulatory authority, the EU Site Investigator must immediately inform the Polish Myeloma Consortium that such a request has been made.

REFERENCES

Alsina M, T. S., Vallone M, Molineaux C, Kunkel L, and Goy A (2007). Phase 1 Single Agent Antitumor Activity of Twice Weekly Consecutive Day Dosing of the Proteasome Inhibitor Carfilzomib (PR-171) in Hematologic Malignancies. In, (Blood (ASH Annual Meeting Abstracts)), p. 110:411.

Anderson KC, J. S., Jakubowiak AJ (2008). Phase II Study of Lenalidomide (Len), Bortezomib (Bz), and Dexamethasone (Dex) in Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM). In, (J Clin Oncol), p. 26 (suppl); Abstract 8545.

Arastu-Kapur S, S. K., Parlati F, and Bennett M (Nov 2008). Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib In, (Blood (ASH Annual Meeting Abstracts)), p. 112: 2657.

Attal, M., Lauwers-Cances, V., Marit, G., Caillot, D., Moreau, P., Facon, T., Stoppa, A. M., Hulin, C., Benboubker, L., Garderet, L.*, et al.* (2012). Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med *366*, 1782-1791.

Benboubker, L., Dimopoulos, M. A., Dispenzieri, A., Catalano, J., Belch, A. R., Cavo, M., Pinto, A., Weisel, K., Ludwig, H., Bahlis, N.*, et al.* (2014). Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med *371*, 906-917.

Bross, P. F., Kane, R., Farrell, A. T., Abraham, S., Benson, K., Brower, M. E., Bradley, S., Gobburu, J. V., Goheer, A., Lee, S. L.*, et al.* (2004). Approval summary for bortezomib for injection in the treatment of multiple myeloma. Clin Cancer Res *10*, 3954-3964.

Corral, L. G., Haslett, P. A., Muller, G. W., Chen, R., Wong, L. M., Ocampo, C. J., Patterson, R. T., Stirling, D. I., and Kaplan, G. (1999). Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol *163*, 380-386.

Davies, F. E., Raje, N., Hideshima, T., Lentzsch, S., Young, G., Tai, Y. T., Lin, B., Podar, K., Gupta, D., Chauhan, D.*, et al.* (2001). Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood *98*, 210-216.

Demo, S. D., Kirk, C. J., Aujay, M. A., Buchholz, T. J., Dajee, M., Ho, M. N., Jiang, J., Laidig, G. J., Lewis, E. R., Parlati, F.*, et al.* (2007). Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res *67*, 6383-6391.

Dimopoulos, M., Spencer, A., Attal, M., Prince, H. M., Harousseau, J. L., Dmoszynska, A., San Miguel, J., Hellmann, A., Facon, T., Foa, R.*, et al.* (2007). Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med *357*, 2123-2132.

Dimopoulos, M. A., Moreau, Philippe, Palumbo, Antonio, Joshua, Douglas E., Pour, Ludek, Hajek, Roman, Facon, Thierry, Ludwig, Heinz, Oriol, Albert, Goldschmidt, Hartmut, Rosinol, Laura,

Straub, Jan, Suvorov, Aleksandr, Araujo, Carla, Pika, Tomas, Gaidano, Gianluca, Weisel, Katja, Goranova-Marinova, Vesselina, Gillenwater, Heidi H., Chng, Wee Joo (2015). Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR. In, (J Clin Oncol 33), p. (suppl; abstr 8509).

Dredge, K., Horsfall, R., Robinson, S. P., Zhang, L. H., Lu, L., Tang, Y., Shirley, M. A., Muller, G., Schafer, P., Stirling, D., *et al.* (2005). Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. Microvasc Res *69*, 56-63.

FDA (2003). Bortezomib Drug Details, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. In.

Jagannath S, V. R., Stewart K, Somlo G, Jakubowiak AJ, Trudel S, Shwartz T, Siegel D, and Kunkel L,The Multiple Myeloma Research Consortium (MMRC) (2009). Final Results of PX-171-003-A0, Part 1 of an Open-label, Single-arm, Phase II Study of Carfilzomib (CFZ) in Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM) In, (ClinOncol.), p. 27:15s (suppl. abstr 8504).

Jakubowiak, A. J., Dytfeld, D., Griffith, K. A., Lebovic, D., Vesole, D. H., Jagannath, S., Al-Zoubi, A., Anderson, T., Nordgren, B., Detweiler-Short, K., *et al.* (2012). A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood *120*, 1801-1809.

Jakubowiak, A. J., Dytfeld, Dominik , Griffith, Kent A., Jasielec, Jagoda, McDonnell, Kathryn, Lebovic, Daniel, Vesole, David H, Jagannath, Sundar, Chottiner, Elaine G., Anderson, Tara B., Detweiler-Short, Kristen, Stockerl-Goldstein, Keith , Ahmed, Asra Z., Jobkar, Terri L., Durecki, Diane E., Mietzel, Melissa A, Couriel, Daniel R., Vij, Ravi, Stefan Kaminski, Mark (2013). TREATMENT OUTCOME WITH THE COMBINATION OF CARFILZOMIB, LENALIDOMIDE, AND LOW-DOSE DEXAMETHASONE (CRD) FOR NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) AFTER EXTENDED FOLLOW-UP. In, (J Clin Oncol), pp. 31, 2013 (suppl; abstr 8543).

Kirk CJ, J. J., Muchamuel T, Dajee M, Swinarski D, Aujay M, Bennett MK, Yang J, Lewis E, Laidig G, and Molineaux CJ (Nov 2008). The Selective Proteasome Inhibitor Carfilzomib is Well Tolerated in Experimental Animals with Dose Intensive Administration. In, (Blood (ASH Annual Meeting Abstracts)), p. 112: 2765.

Kuhn, D. J., Chen, Q., Voorhees, P. M., Strader, J. S., Shenk, K. D., Sun, C. M., Demo, S. D., Bennett, M. K., van Leeuwen, F. W., Chanan-Khan, A. A., and Orlowski, R. Z. (2007). Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood *110*, 3281-3290.

Kumar, S. K., Rajkumar, S. V., Dispenzieri, A., Lacy, M. Q., Hayman, S. R., Buadi, F. K., Zeldenrust, S. R., Dingli, D., Russell, S. J., Lust, J. A., *et al.* (2008). Improved survival in multiple myeloma and the impact of novel therapies. Blood *111*, 2516-2520.

McCarthy, P. L., and Hahn, T. (2013). Strategies for induction, autologous hematopoietic stem cell transplantation, consolidation, and maintenance for transplantation-eligible multiple myeloma patients. Hematology Am Soc Hematol Educ Program *2013*, 496-503.

McCarthy, P. L., Owzar, K., Hofmeister, C. C., Hurd, D. D., Hassoun, H., Richardson, P. G., Giralt, S., Stadtmauer, E. A., Weisdorf, D. J., Vij, R.*, et al.* (2012). Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med *366*, 1770-1781.

Niesvizky, e. a. (April 15, 2013). Phase 1b Dose-Escalation Study (PX-101-006) of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone in Relapsed or Progressive MM. . In, (Clin Cancer Res), pp. 19(18): 2248-2256.

Nooka, A. K., Kaufman, J. L., Muppidi, S., Langston, A., Heffner, L. T., Gleason, C., Casbourne, D., Saxe, D., Boise, L. H., and Lonial, S. (2014). Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia *28*, 690-693.

Paiva, B., Vidriales, M. B., Cervero, J., Mateo, G., Perez, J. J., Montalban, M. A., Sureda, A., Montejano, L., Gutierrez, N. C., Garcia de Coca, A.*, et al.* (2008). Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood *112*, 4017-4023.

Palumbo, A., Bringhen, S., Kumar, S. K., Lupparelli, G., Usmani, S., Waage, A., Larocca, A., van der Holt, B., Musto, P., Offidani, M.*, et al.* (2014). Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol *15*, 333-342.

Rajkumar P, J. S., Taje N, et al. (2007). Phase III Trial of Lenalidomide Plus High-Dose Dexamethasone versus Lenalidomide Plus low-Dose Dexamethasone in Newly Diagnosed Multiple Myeloma (E4A03): A Trial Coordinated by the Eastern Cooperative Oncology Group. In, (J Clin Oncol), p. 25 (18S): Abstract LBA 8025.

Rajkumar, S. V., Hayman, S. R., Lacy, M. Q., Dispenzieri, A., Geyer, S. M., Kabat, B., Zeldenrust, S. R., Kumar, S., Greipp, P. R., Fonseca, R.*, et al.* (2005). Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood *106*, 4050-4053.

Richardson P, J. S., Jakubowiak AJ (Dec 6, 2008). Lenalidomide, Bortezomib, and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Encouraging Response Rates and Tolerability with Correlation of Outcome and Adverse Cytogenetics in a Phase II Study. In, (American Hematology Society Congress # 1742, San Francisco, CA, USA).

Richardson P, J. S., Raje N, et al. (2007). Lenalidomide, Bortezomib, and Dexamethasone (Rev/Vel/Dex) as Front-Line Therapy for patients with Multiple Myeloma (MM): Preliminary Results of a Phase 1/2 Study. In, (Blood), p. 110 (111): Abstract 187.

Richardson, P. G., Weller, E., Lonial, S., Jakubowiak, A. J., Jagannath, S., Raje, N. S., Avigan, D. E., Xie, W., Ghobrial, I. M., Schlossman, R. L., *et al.* (2010). Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood *116*, 679-686.

Ries LAG, M. D., Krapcho M, et al (eds.) (2007). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975-2004/, based on November 2006 SEER data submission, posted to the SEER website, . In.

Rosinol, L., Oriol, A., Teruel, A. I., Hernandez, D., Lopez-Jimenez, J., de la Rubia, J., Granell, M., Besalduch, J., Palomera, L., Gonzalez, Y., *et al.* (2012). Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood *120*, 1589-1596.

Schafer, P. H., Gandhi, A. K., Loveland, M. A., Chen, R. S., Man, H. W., Schnetkamp, P. P., Wolbring, G., Govinda, S., Corral, L. G., Payvandi, F., *et al.* (2003). Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. J Pharmacol Exp Ther *305*, 1222-1232.

Siegel D, W. L., Orlowski RZ, Kaufman JL, Stewart AK, Kukreti V, Alsina M, Jakubowiak AJ, Jagannath D, McDonagh KT, Belch A, Bahlis NJ, Shustik C, Le MH, Kunkel L, Bennett MK, Kauffman M, Vij R, and the Multiple Myeloma Research Consortium (MMRC) (Nov 2009). PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed of Refractory Myeloma (MM); Updated Results From the Bortezomib-Treated Cohort In, (Blood (ASH Annual Meeting Abstracts)), p. 114: 3877.

Siegel, D. S., Martin, T., Wang, M., Vij, R., Jakubowiak, A. J., Lonial, S., Trudel, S., Kukreti, V., Bahlis, N., Alsina, M., *et al.* (2012). A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood *120*, 2817-2825.

Sonneveld, P., Schmidt-Wolf, I. G., van der Holt, B., El Jarari, L., Bertsch, U., Salwender, H., Zweegman, S., Vellenga, E., Broyl, A., Blau, I. W., *et al.* (2012). Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol *30*, 2946-2955.

Spencer, A., Prince, H. M., Roberts, A. W., Prosser, I. W., Bradstock, K. F., Coyle, L., Gill, D. S., Horvath, N., Reynolds, J., and Kennedy, N. (2009). Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol *27*, 1788-1793.

Stewart, A. K., Rajkumar, S. V., Dimopoulos, M. A., Masszi, T., Spicka, I., Oriol, A., Hajek, R., Rosinol, L., Siegel, D. S., Mihaylov, G. G., *et al.* (2015). Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med *372*, 142-152.

Stewart, A. K., Trudel, S., Bahlis, N. J., White, D., Sabry, W., Belch, A., Reiman, T., Roy, J., Shustik, C., Kovacs, M. J., *et al.* (2013). A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the

National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood *121*, 1517-1523.

Wang (Oct 31, 2013). Phase 2 Dose-Explansion Study (PX-171-006) of Carfilzomib, Lenalidomide, and Low-Dose Dex in Relapsed or Progressive MM. In, (Blood), pp. Vol 122 no 118: 3122-3128.

Wang L, S. D., Kaufman JL, Stewart AK, Jakubowiak A, Alsina M, Kukreti V, Bahlis NJ, McDonagh KT, Belch A, Sebag M, Gabrail N, Le MH, Bennett MK, Kunkel L, Kauffman M, Orlowski RZ, Vij R, and The Multiple Myeloma Research Consortium (MMRC) (2009). Updated Results of Bortezomib-Naïve Patients in PX-171-004, An Ongoing Open-Label, Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Regractory Myeloma (MM) In, (Blood (ASH Annual Meeting Abstracts)), p. 114: 302.

Weber, D. M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmauer, E. A., Siegel, D., Borrello, I., Rajkumar, S. V., Chanan-Khan, A. A.*, et al.* (2007). Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med *357*, 2133-2142.

Zimmerman, T. M., Griffith, Kent A., Jasielec, Jagoda, Rosenbaum, Cara A., McDonnell, Kathryn, Waite-Marin, Jessica, Berdeja, Jesus G., Raje, Noopur S., Reece, Donna E., Vij, Ravi, Alonge, Mattina, Rosebeck, Shaun, Gurbuxani, Sandeep, Faham, Malek, Kong, Katherine A., Levy, Joan, Jakubowiak, Andrzej J. (2015). Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). In, (J Clin Oncol 33,), p. (suppl; abstr 8510).

Zimmerman, T. M., Griffith, Kent, Jasielec, Jagoda K. , Rosenbaum, Cara A. McDonnell, Kathryn, Waite-Marin, Jessica, Anastazi, John, Berdeja, Jesus G., Vij, Ravi, Jakubowiak, Andrzej J. (2014). INITIAL RESULTS FROM A PHASE 2 STUDY OF CARFILZOMIB, LENALIDOMIDE, AND LOW-DOSE DEXAMETHASONE (KRD) PLUS AUTOLOGOUS STEM CELL TRANSPLANTATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA. In, (EHA (Abstract: P347)).

APPENDIX 1: 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 (≤12 mg/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:
   a. Hypercalcemia: serum calcium ≥11.5 mg/dL or
   b. Renal insufficiency: serum creatinine >2mg/dL or
   c. 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 2: ECOG PERFORMANCE STATUS

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 3: 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_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX 4: RESPONSE CRITERIA FOR MULTIPLE MYELOMA

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.

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 5: FACT/GOG-NEUROTOXICITY QUESTIONNAIRE, V. 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 6: Revlimid Pregnancy Risk Minimization Plan for Celgene Clinical Trials

Lenalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 0) provides the following information:
    - Potential risks to the fetus associated with lenalidomide exposure
    - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
    - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
    - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
    - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 2 and Section 3 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 4) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

1.1. Risks Associated with Pregnancy

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. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

1.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

1.2. Counseling

1.2.1. Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 1.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

1.2.2. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

1.2.3. Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

1.3. Contraception

1.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not

appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 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 subjects with neutropenia.

1.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

1.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be

performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential 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 taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

1.5. Pregnancy Precautions for Lenalidomide Use

1.5.1. Before Starting Lenalidomide

1.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

1.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

1.5.2. During and After Study Participation

1.5.2.1. Female Subjects

- Females of childbearing potential 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 taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- 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 must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

1.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

1.5.3. Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

2. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____DOB: _____/_____/_____(dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

2.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     - Examples of highly effective methods:
       - Intrauterine device (IUD)
       - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot

injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
    - Tubal ligation
    - Partner's vasectomy
  - Examples of additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

2.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject has not and will never share lenalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

3. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____DOB: _____/_____/_____(dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. LENALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX 7: SCHEDULE OF EVENTS

Assessment	**Screening**	**Cycles 1-4**							**Cycles 5-36**						**End of Cycle 6, and every 12 months after CR**	**End of Cycle 12**	**End of Cycle 18**	**End of Cycle 24**	**End of Cycle 36**	**EOT**	**LTFU**
Day	**-42 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**1**	**2**	**8**	**15**	**16**	**22**							
Informed Consent[1]	X																				
Medical History/ Treatment History[2]	X																				
Skeletal Survey[3]	X																				
ECG[4]	X																				
Echocardiogram[5]	X																				
Physical Exam/ ECOG[6]	X	X							X						X					X	
Vital Signs[7]	X	X	X	X	X	X	X		X	X		X	X								
24-hour urine[8]	X	X							X						X					X	
Urinalysis[9]	X																				
Coagulation Tests[10]	X																				

Assessment	**Screening**	**Cycles 1-4**							**Cycles 5-36**						**End of Cycle 6, and every 12 months after CR**	**End of Cycle 12**	**End of Cycle 18**	**End of Cycle 24**	**End of Cycle 36**	**EOT**	**LTFU**
Day	**-42 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**1**	**2**	**8**	**15**	**16**	**22**							
C-Reactive Protein	X	X							X												
Hematology[11]	X	X		[X]		[X]			X			[X]								X	
Serum Chemistry[12]	X	X	[X]	[X]	[X]	[X]	[X]		X	[X]		[X]	[X]							X	
Pregnancy Test[13]	X	X							X											X	
Disease Assessment[14]																					
β2-microglobulin	X																				
SPEP, UPEP[15]	X	X							X						X					X	
BM Aspirate/ biopsy, cytogenetics, FISH[16]	X														X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]
BM aspirate sample for MRD analysis[17]	X														X[18]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]
CT-PET[30]	X														X	X	X	X	X	X	X
Quantitative	X	X							X						X					X	

Assessment	Screening	Cycles 1-4							Cycles 5-36						End of Cycle 6, and every 12 months after CR	End of Cycle 12	End of Cycle 18	End of Cycle 24	End of Cycle 36	EOT	LTFU
Day	**-42 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**1**	**2**	**8**	**15**	**16**	**22**							
IgGs																					
SFLC[19]	X	X							X						X					X	
Neurological Assessment[20]	X	X							X											X	
Adverse Event[21]			X																		
Control Arm																					
Lenalidomide[22,23]		Days 1-28								Days 1-28											X
Experimental Arm																					
Carfilzomib[24]		X	X	X	X	X	X		X	X		X	X								
Lenalidomide[22,25]		Days 1-21							Days 1-21												X[25]
Dexamethasone[27]		X		X		X		X	X		X	X		X							
Survival and Evaluation of Second Primary Malignancies[28,29]																					X

[X] Denotes if clinically indicated

1. Informed consent may be obtained at any timepoint prior to screening procedures begin and must be obtained prior to any research-related activity
2. Includes baseline symptoms as well as detailed history of prior cancer therapies including start/stop dates; neuropathy history and documentation of the CTCAE grade if peripheral neuropathy is present at baseline.
3. May be within 42 days of planned start. Includes: lateral radiograph of skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Skeletal surveys performed outside of the 42 day window may be considered for inclusion after discussion with the Lead Principal Investigator. Skeletal survey only needs to be repeated throughout the trial if clinically indicated.
4. 12-Lead ECG including QTc interval. ECG should be performed throughout the study only as clinically indicated
5. Echocardiogram must be completed at screening to demonstrate LVEF ≥ 40%. ECHO may be performed throughout the study if clinically indicated.
6. For Day 1 of cycle 1, screening results may be used if within 7 days of treatment start. 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 at Day 1 of each cycle (height only required at screening). In the Experimental Arm, Days 8 and 15 exams may be symptom directed.
7. Systolic and diastolic blood pressure, pulse, respiration, temperature approximately 1 hour before carfilzomib dosing
8. 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
9. Urine analysis will include appyeearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated. Urinalysis is required at screening and performed throughout treatment at any time as clinically indicated.
10. Prothrombin time, activated partial thromboplastin time, and international normalized ratio. Coagulation tests are required at screening and performed throughout treatment at any time as clinically indicated.
11. Hemoglobin, hematocrit, WBC with complete differential, RBCs, platelet count. Results must be reviewed before dosing. Note that hematology assessment on the control arm is not required and should be performed as needed.
12. Full serum chemistry panel at screening, day 1 for control arm or as indicated by the treating physician, days 1, 8, and 15 for experimental arm, and EoT for all patients: 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. Abbreviated serum chemistry panel (for experimental arm only) on days 2, 9 and 16 if clinically indicated: sodium, chloride, bicarbonate, BUN, creatinine, glucose, uric acid
13. 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 13.6). When applicable, females must have a pregnancy test at the EoT.
14. Disease assessment including bone marrow biopsy (as indicated), SPEP, UPEP, SFLC to be done at any point during treatment when response is suspected. The first response assessment should be completed on Cycle 2 Day 1. Response will be assessed comparing day 1 of each cycle values to the respective baseline (pre-induction treatment) values for each subject.
15. 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
16. Bone marrow aspirate and biopsy - quantify % myeloma cell involvement; bone marrow sample for cytogenetics and fluorescent in situ hybridization (FISH). Repeat bone marrow biopsy/aspirate if CR is suspected and as appropriate to confirm achievement of sCR, CR, or nCR. Bone marrow biopsy/aspirate performed outside of the 42-day window may be considered for inclusion. Please contact the Lead Primary Investigator at the coordinating site on a case-by-case basis. Cytogenetics and FISH are required at screening only. If cytogenetics/FISH are completed at a time point other than screening, the results should be captured in eCRF.
17. Bone marrow samples for Minimal Residual Disease (MRD) will be collected from all subjects. FFPE or BMA slides from subjects pre-induction treatment/high load disease are required for calibration of MRD by gene sequencing, and fresh bone marrow aspirates from the following time-points will be collected: 1) screening 2) end

of cycle 6, 12, 18, 24 and 36, 3) EOT (when other than Cycle 8) 4) yearly (±30 days) for up to 5 years from randomization thereafter (LTFU), and 5) any time that bone marrow is performed as SOC to assess CR response. If CR is achieved between cycles 6 and 12, the evaluation for confirmation of CR (and MRD) must be done at cycle 12 ±2 months. If CR is recorded in the middle of a year, it is OK to postpone the BM biopsy until the next scheduled aspiration after discussion with the Lead Principal Investigator. US sites: all samples (except calibration slides and end of C6, which will go to Adaptive directly) will be shipped to the University of Chicago. Polish Sites: all samples will be shipped to Poznan University of Medical Science.

18. Patients in the experimental arm that are MRD negative and have no high risk factors after cycle 6, will receive 2 more cycles of KRd (for a total for 8 cycles) and then moved to lenalidomide alone maintenance (see footnote 26).
19. SFLC repeated only to confirm CR. For subjects whose disease is being monitored by SLFC, additional post baseline assessments are required as indicated.
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. AEs will be collected from the time of first study drug treatment through 30-days after end of study treatment.
22. US: Lenalidomide must be prescribed through and in compliance with the RevlimidREMS™ 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 RevlimidREMS program. Poland: Lenalidomide will be provided by Celgene and must be prescribed in compliance with Revlimid® PPP program of Celgene Corporation. 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. Sponsor will be responsible for destruction of unused Revlimid®.
23. Control Arm: Lenalidomide on days 1-28 10 mg Cycle 1 with option to increase to 15 mg Cycle 2+. After 36 cycles, recommended single agent lenalidomide treatment at best tolerated dose Days 1-28 of 28 day cycle
24. Carfilzomib days 1,2, 8,9, 15,16 at assigned dose Cycles 1-4 followed by Days 1,2, 15,16 Cycles 5+. Cycle 1 step-up dosing is required: 20mg/m^2 Days 1, 2; 27mg/m^2 Days 8, 9; 36mg/m^2 Days 15, 16. Dosing may be rescheduled up to two days. Hydration directions from section 7.2.1 must be followed
25. Experimental Arm: Lenalidomide dosing Days 1-21. Cycle 1 Lenalidomide will be administered 15 mg with option to increase to 25 mg daily starting with Cycle 2. Lenalidomide should be taken in the evening at approximately the same time each day. After 8 cycles (for MRD- and no risk factor at cycle 6 pts) or 36 cycles are complete, single agent lenalidomide treatment at best-tolerated dose (up to 15mg) Days 1-28 of 28 day cycle is recommended.
26. Lenalidomide maintenance dosing: daily on days 1-28 in 28-day cycles at 10 – 15mg. If the MTD is higher than 15mg, the patient will be dosed with 15mg lenalidomide. This dosing will apply to patients who have finished 36 cycles of KRd (and move into lenalidomide alone maintenance), as well as patients with MRD negative disease and no risk factors at cycle 6 moving to lenalidomide maintenance after cycle 8.
27. Days 1, 8, 15 and 22 30 minutes to 4 hours prior to carfilzomib administration
28. Patients will be followed for survival and development of any new cancers, at least every 3 months for 2 years from last treatment. Reports of any death should include date of death and specific cause (disease under study or specify other cause).
29. Assessment for disease progression in subjects who did not progress during treatment. Every 3 months (+/- 30 days) for 2 years from safety follow-up visit (28 days post-last study treatment or ASCT, if applicable).
30. A CT-PET will be performed to confirm MRD-negative disease per Standard of Care at study site, at every time-point when MRD is checked.