CLINICAL STUDY PROTOCOL

PROTOCOL INFORMATION

STUDY TITLE:	*Open-label, Single-arm, Phase 2 Study of Initial Treatment with Elotuzumab, Carfilzomib (Kyprolis), Lenalidomide (Revlimid) and Low dose Dexamethasone (E-KRd) in Newly Diagnosed, Multiple Myeloma Requiring Systemic Chemotherapy.*
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TYPE OF RESEARCH:	Interventional, clinical multi-center
INTERVENTION:	Drug Company Supplied: Bristol Myers Squibb (Elotuzumab) Amgen (Carfilzomib)

PROTOCOL NUMBER: IRB16-1138

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Ver 1, November 9th , 2016 (initial IRB submission)
Ver 2, November 11th, 2016 (additional FDA changes)
Ver 3, January 26th, 2018
Ver 4, April 13th, 2018
Ver 5, October 22nd, 2018
Ver 6, February 15, 2019
Ver 7, Septemebr 24, 2019
Ver 8, March 26, 2020

This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

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.

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SYNOPSIS

Study Title	*Open-label, Single-arm, Phase 2 Study of Initial Treatment with Elotuzumab, Carfilzomib (Kyprolis), Lenalidomide (Revlimid) and Low dose Dexamethasone (E-KRd) in Newly Diagnosed, Multiple Myeloma Requiring Systemic Chemotherapy.*
Objectives	**Primary Objective** • The primary efficacy endpoint will be the rate of sCR and/or the rate of negative MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) at the end of 8 cycles among non-transplant candidates and transplant candidates who agreed to defer transplant. **Secondary Objectives** • To evaluate the safety and tolerability of elotuzumab in combination with KRd, when administered to subjects with newly diagnosed multiple myeloma. • To determine the rate of MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) and by multi-color flow cytometry (MFC) at the end of Cycle 4, 8,and 12 for all subjects, and end of C18 (for subjects who are MRD+ at the end of C8 but MRD- at the end of C12 only), 24 months after C1D1, and yearly after that. • To estimate time to event, including duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS). **Exploratory Objectives** ∗ GEP, proteomics, and gene sequencing to evaluate the correlation between treatment outcome and pre-treatment subject profile. ∗ Immunologic correlative studies including FcγRIIIa V genotype.
Sample Size	**40 - 55**
Study Design	This study will be a multi-center, open-label, Phase 2 study. Those **newly diagnosed with MM requiring systemic chemotherapy will be eligible for enrollment.** **Dose Schedule and Dose Levels in 28-day cycles** Subjects will be tested for Minimal Residual Disease (MRD) by Next Generation Sequencing (NGS) and flow cytometry after cycles 8 and 12. A treatment decision will be made after cycle 12 based on these results. There are three possible outcomes based on the IFM trial (Avet-Loiseau et al., 2015): 1) if the subject is MRD-negative by NGS after cycle 8 and 12, the subject will be go on E-Rd maintenance until disease progression. 2) If the subject is MRD-positive after cycle 8 but MRD-negative after cycle 12, 6 more cycles of E-KRd will be given and at the end of 18

cycles, the subject will go on E-Rd maintenance until disease progression. 3) Finally, if the subject is MRD-positive at both instances, 12 additional cycles of E-KRd will be given and at the end of 24 cycles total, the subject will go on E-Rd maintenance until disease progression. For subjects for whom NGS evaluation is not successful because of inadequate calibration specimen or not-evaluable follow-up specimen, the results of MRD testing by flow will be used for treatment decisions.

Elotuzumab

Cycle 1-2 Days 1, 8, 15, 22	Cycle 3+ Days 1 and 15
10 mg/kg IV infusion weekly starting Cycle 1 day 1	10 mg/kg IV infusion every 2 weeks starting Cycle 3 day 1

* On days when elotuzumab and carfilzomib coincide, carfilzomib will be infused first followed by elotuzumab infusion

Carfilzomib

Cycle 1*	Cycle 2-8	Cycle 9+
IV infusion Day 1: 20 mg/m^2 Day 8 & 15: 56 mg/m^2	IV infusion 70 mg/m^2: Days 1, 8, and 15	IV infusion Last tolerated dose on Days 1 and 15

*Dose escalation may need to be modified based on toxicities in the prior week. Please see dose modifications section.

Lenalidomide

Cycle 1-8	Cycle 9+
PO at 25 mg per dose on Days 1-21	PO at last tolerated dose for days 1-21

Dexamethasone

Cycle 1-2

Tx Days 1, 8, 15	Tx Days 2, 9, 16	Tx Day 22
20 mg IV no more than 3 hrs prior to elotuzumab infusion	20 mg PO the day after elotuzumab infusion	40mg IV (C1 only) or PO, no more than 3 hrs prior to elotuzumab infusion

Cycle 3-4

Tx Days 1, 8, 15, 22
40mg PO weekly. On days when dexamethasone and elotuzumab coincide, dexamethasone should be taken no more than 3 hours prior to elotuzumab infusion

Cycle 5+

Tx Days 1, 8, 15, 22
20mg PO weekly. On days when dexamethasone and elotuzumab coincide, dexamethasone should be taken no more than 3 hours prior to elotuzumab infusion

Duration of Treatment	Cycles 1 through 4 are considered E-KRd induction cycles, cycle 5-8 E-KRd consolidation, and cycles 9+ E-KRd maintenance cycles. After Cycle 4, subjects who are deemed candidates for ASCT will proceed to stem cell harvest as per institutional guidelines. However, the study design recommends a "delayed" transplant for ASCT candidates as in completed frontline KRd study with delayed transplant for transplant candidates (Jakubowiak et al., 2012b). After completion of stem cell harvest, subjects will resume protocol treatment. Subjects who will proceed to transplant will be discontinued from the trial. Intention to go on ASCT will be required at the time of enrollment with 15 subjects planned in this category per study design. Subjects who were assigned to the 'non-ASCT' or 'deferred ASCT' category, who proceed to ASCT for reasons other than disease progression or toxicity, will be replaced (up to 5 subjects). Subjects who will continue E-KRd protocol treatment until the end of study or toxicity, will then proceed to maintenance treatment with E-Rd, i.e. with elotuzumab (every 4 weeks), lenalidomide (days 1-21), and low dose dexamethasone (weekly) at last tolerated doses in 28-day cycles until subject reaches PD.
Inclusion / Exclusion Criteria	**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. Newly diagnosed, previously untreated myeloma requiring systemic chemotherapy a. Prior treatment of hypercalcemia or spinal cord compression or active and/or aggressively progressing myeloma with corticosteroids and/or lenalidomide and/or bortezomib/PI-based regimens does not disqualify the subject. The corticosteroid treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period or not more than 1 cycle of lenalidomide and/or PI-based therapy. A higher total dose of corticosteroid is allowed for the management of cord compression at the discretion of the PI, as long as the subject does not exhibit any steroid related toxicities at the initiation of study treatment. 2. Both transplant and non-transplant candidates are eligible. 3. Diagnosis of symptomatic multiple myeloma as per current IMWG uniform criteria prior to initial treatment 4. Monoclonal plasma cells in the BM 10% or presence of a biopsy-proven plasmacytoma 5. Measurable disease, prior to initial treatment as indicated by one or more of the following: a. Serum M-protein ≥ 1 g/dL b. Urine M-protein ≥ 200 mg/24 hours

c. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative immunoglobulin levels are acceptable (≥ 1 g/dL)
d. Involved serum free light chains ≥ 10 mg/dL provided that free light chain ratio is abnormal

6. Screening laboratory values must meet the following criteria and should be obtained within 21 days prior to enrollment
   - WBC ≥ 2000/μL
   - Platelets ≥ 75 x10^3/μL
   - ANC >1000/μL
   - Hemoglobin > 8.0 g/dL
   - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 50 mL/min
     a) Use the Cockcroft-Gault formula below):
        - *Female* CrCl = (140 - age in years) x weight in kg x 0.85
          - 72 x serum creatinine in mg/dL
        - *Male* CrCl = (140 - age in years) x weight in kg x 1.00
          - 72 x serum creatinine in mg/dL
     b) Alternatively to Cockcroft-Gault formula of CrCl, 24hr urine CrCl can be used
   - AST/ALT ≤ 3 x ULN
   - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) or ≤ 2 x ULN if lenalidomide is being prescribed.
7. Males and females ≥ 18 years of age
8. ECOG performance status of 0-1
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

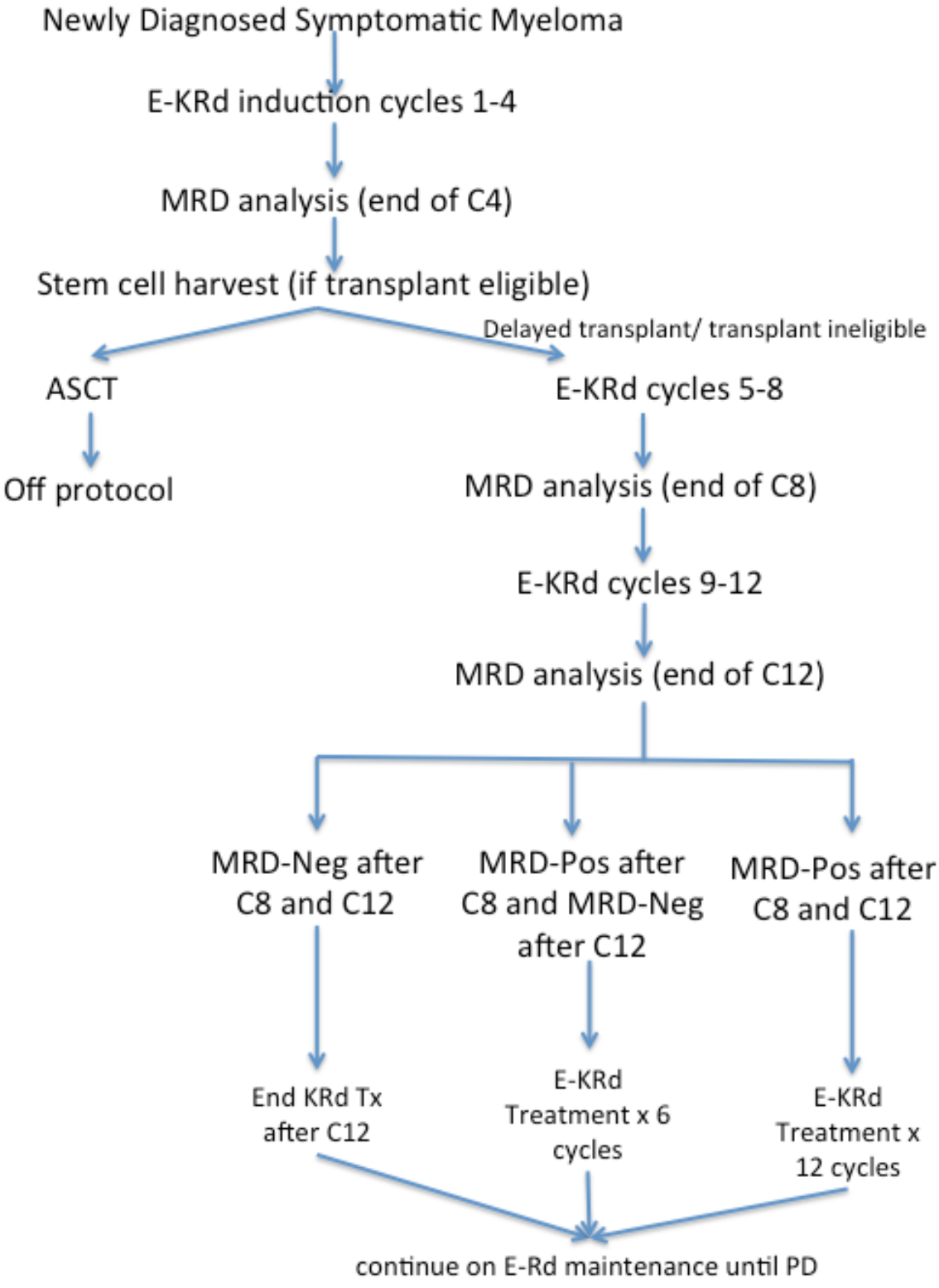
Exclusion Criteria:

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

1. Non-secretory or hyposecretory multiple myeloma, prior to initial treatment defined as <1.0 g/dL M-protein in serum, <200 mg/24 hr urine M-protein, and no measurable disease as per IMWG by Freelite.
2. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
3. Geriatric assessment score of ≥2 as defined by Palumbo et al.
4. Known or suspected Amyloidosis
5. Plasma cell leukemia
6. Within 4 weeks since any plasmapheresis
7. Within 3 weeks of any corticosteroids except per inclusion criteria #1.a.
8. Waldenström's macroglobulinemia or IgM myeloma
9. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ($t_{1/2}$) prior to first dose, whichever time is greater
10. Subjects not able to tolerate elotuzumab, lenalidomide, carfilzomib, or dexamethasone
11. Peripheral neuropathy ≥ Grade 2 at screening
12. Prior CVA with persistent neurological deficit
13. Diarrhea > Grade 1 in the absence of antidiarrheals
14. CNS involvement
15. Corrected calcium ≥ 11.5 mg/dL within 2 weeks of randomization
16. Pregnant or lactating females
17. Radiotherapy within 14 days before randomization. Seven days may be considered if to single area
18. Major surgery within 3 weeks prior to first dose
19. Subject has clinically significant cardiac disease, including:

	• myocardial infarction within 1 year before Cycle 1 Day 1, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV • uncontrolled cardiac arrhythmia (NCI CTCAE Version 4 Grade 2:2) or clinically significant ECG abnormalities • screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec 20. Uncontrolled HTN 14 days prior to enrollment 21. Prior or concurrent deep vein thrombosis or pulmonary embolism 22. Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening 23. Uncontrolled hypertension (defined as average systolic blood pressure ≥140 or average diastolic blood pressure ≥90, with blood pressure measured ≥3 times in the two weeks prior to enrollment) or diabetes 24. Acute infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose 25. Active infection 26. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Subjects who are seropositive because of hepatitis B virus vaccine are eligible. 27. 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 28. 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), only used if SPEP and IFIX are felt to be unreliable. In this case, the same magnitude of decrease of involved heavy chain immunoglobulin as defined in IMWG response criteria for M-spike will be used for assigning specific response level. Bone marrow biopsy is required to confirm response at time of suspected nCR or better (if nCR determination is not possible, then VGPR will be used to trigger a bone marrow biopsy. A Bone Marrow Biopsy to confirm nCR or VGPR will not be required if the subject is within 2

	months of a landmark BMBX timepoint), or if PD in marrow is suspected. MRD by gene sequencing and flow cytometry Plasmacytoma evaluation should be completed if clinically indicated
Safety Variables & Analysis	The safety and tolerability of elotuzumab, 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 55 subjects will be enrolled in a single-stage Phase II design. Time to progression or death will be calculated from the date of first treatment on protocol until the date of disease progression or death from any cause. Subjects at the time of analysis not having either endpoint will be censored as of the last negative exam (tumor assessment). Adherence to protocol and ability to follow subjects in follow-up is expected to be excellent; however, if any subject revokes consent for further follow-up not due to disease progression, they will be censored as of the last negative exam. Likewise, subjects in follow-up that are lost or that refuse or revoke further study participation will be censored as of the last negative exam.


Newly Diagnosed Symptomatic Myeloma
E-KRd induction cycles 1-4
MRD analysis (end of C4)
Stem cell harvest (if transplant eligible)
Delayed transplant/ transplant ineligible
ASCT
E-KRd cycles 5-8
Off protocol
MRD analysis (end of C8)
E-KRd cycles 9-12
MRD analysis (end of C12)
MRD-Neg after C8 and C12
MRD-Pos after C8 and MRD-Neg after C12
MRD-Pos after C8 and C12
End KRd Tx after C12
E-KRd Treatment x 6 cycles
E-KRd Treatment x 12 cycles
continue on E-Rd maintenance until PD

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 Subject 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	Human immunodeficiency virus
HL	Hodgkin's Lymphoma
IA	Interim analysis
IB	Investigator Brochure
ICF	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	Subject Information Sheet
PK	Pharmacokinetics
PO	Per os (oral)
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
Pt	Subject
PTT	Partial thromboplastin time
QDx5	Daily dosing for five days
QI	Qualified Investigator Undertaking Form
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
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 subjects 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, Carfilzomib (Kyprolis®), Pomalidomide (Pomalyst®), daratumumab (Darzalex®), elotuzumab (Empliciti®), and ixazomib (Ninlaro®) have been approved in the treatment of relapsed disease. Younger subjects 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 subjects 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, Kyprolis®) 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).

Indications and Usage: Carfilzomib (Kyprolis®) is a proteasome inhibitor indicated for the treatment of subjects with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. More details can be found on the package insert and in the Investigator Brochure.

Adverse Events: Most commonly reported adverse reactions (incidence ≥ 30%) are fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.Complete and updated adverse events are available in the Investigator Brochure and the IND Safety Letters.

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 subjects resistant to melphalan, doxorubicin and dexamethasone (Davies et al., 2001).

Indications and Usage: REVLIMID is a thalidomide analogue indicated for the treatment of subjects with:

- **Multiple myeloma (MM), in combination with dexamethasone**
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib

Adverse Events: Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, peripheral edema, insomnia, muscle cramp/spasms, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor (6.1).

Complete and updated adverse events are available in the package insert.

1.4.1. **Dose Rationale**

1.4.1.1. 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 70 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 subjects being treated for >10 cycles without cumulative toxicities.

Carfilzomib is currently approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of subjects with relapsed multiple myeloma who have received one to three prior lines of therapy. The recommended dose is 20mg/m^2 on cycle 1 day 1 and can be escalated to 27mg/m^2 on day 8 of cycle 1 on twice weekly schedule, i.e. on days 1, 2, 8, 9, 15, 16 in 28-day cycles. At this time, the MTD had not been defined but the dose of 36 mg/m^2 on the same schedule was established as tolerated in newly diagnosed myeloma (Jakubowiak et al., 2012b; Jakubowiak, 2016; Korde et al., 2015).

In the past year, an alternative schedule of carfilzomib with weekly infusion on days 1, 8, 15 in 28-days cycles was evaluated in several studies. A number of already published as well as ongoing

evaluations reported the MTD of carfilzomib at 70mg/m^2 given once weekly in combinations (Berenson et al., 2016). Additionally, this weekly dose of carfilzomib was formally evaluated versus original twice-weekly schedule in the randomized ARROW trial, which completed enrollment with results still pending. Finally, the KRd+Daratumumab arm of the ongoing Janssen MMY1001 trial completed enrollment using weekly dosing of carfilzomib with 70mg/m^2 per dose in combination with lenalidomide, dexamethasone, and daratumumab.

1.5. **Elotuzumab Background**

Elotuzumab (HuLuc63/BMS-901608) is a humanized monoclonal IgG1 antibody product directed to human CS1 (CD2 subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein with homology to the CD2 family of cell surface proteins (Boles and Mathew, 2001; Tassi and Colonna, 2005). Originally, CS1 was identified as a natural killer cell (NK) marker and was shown to be expressed in a subset of circulating leukocytes (Boles et al., 2001). Blood analysis confirmed expression of CS1 on the cell surface of NK, NK-like T-cells (NKT), activated monocytes, CD8 positive T cells, and on tissue plasma cells (Hsi et al., 2008)**.** High CS1 expression was seen in plasma cells obtained from normal healthy donors and from subjects with MGUS, SMM, and active MM. More than 90% of MM bone marrow samples, irrespective of cytogenetic abnormalities, express CS1. In addition CS1 expression is maintained in MM subjects after relapse from therapy. A paired analysis of a subset of subjects with MM showed that CS1 gene expression is detectable in subjects both at diagnosis and at relapse.

In agreement with the gene chip data, flow cytometry analysis demonstrated that CD138+ plasma cells from MM bone marrow stained strongly positive for elotuzumab binding. In addition, immunohistochemistry (IHC) using anti-CS1 antibodies showed strong staining of MM cells in 9/9 plasmacytoma tissue samples and in 20/20 myeloma bone marrow cores tested (Hsi et al., 2008) The proposed mechanism of action of elotuzumab involves natural killer (NK) cell mediated antibody dependent cell-mediated cytotoxicity (ADCC). Elotuzumab monotherapy can kill MM cell lines and primary myeloma cells in vitro in the presence of peripheral blood mononuclear cells (PBMCs) or purified NK cells. In addition, elotuzumab exhibits significant in vivo monotherapy anti-tumor activity against human myeloma xenograft models grown in severe combined immunodeficient (SCID) mice (Hsi et al., 2008; Tai et al., 2008). This in vivo anti-tumor activity of elotuzumab appears to be largely dependent on the presence of active NK cells. Experiments using an in vivo mouse xenograft model suggest that maximal antitumor activity is reached at elotuzumab serum levels of 70 to 430 mcg/mL.

Indications and Usage: Elotuzumab (EMPLICITI®) is a SLAMF7-directed immunostimulatory antibody indicated in combination with lenalidomide and dexamethasone for the treatment of subjects with multiple myeloma who have received one to three prior therapies. More details can be found on the package insert and in the Investigator Brochure.

Dosage and Administration:

- With lenalidomide and dexamethasone: 10 mg/kg administered intravenously every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity.
- Pre-medicate with dexamethasone, diphenhydramine, ranitidine and acetaminophen

Adverse Reactions: Most common adverse reactions (20% or higher) are fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, pneumonia.

Complete and updated adverse events are available in the package insert.

1.5.1.1. Infusion Reactions

Elotuzumab can cause infusion reactions. Infusion reactions were reported in approximately 10% of subjects treated with elotuzumab with lenalidomide and dexamethasone in the randomized trial in multiple myeloma. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of subjects. The most common symptoms of an infusion reaction included fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions.

In the trial, 5% of subjects required interruption of the administration of elotuzumab for a median of 25 minutes due to infusion reactions, and 1% of subjects discontinued due to infusion reactions. Of the subjects who experienced an infusion reaction, 70% (23/33) had them during the first dose.

Administer premedication consisting of dexamethasone, antihistamines (H1 and H2 blockers) and acetaminophen prior to elotuzumab infusion (See section 6.5.2)

Interrupt elotuzumab infusion for Grade 2 or higher infusion reactions and institute appropriate medical management (See section 6.5.2).

1.5.1.2. Overall Risk/Benefit Assessment

Elotuzumab is a humanized monoclonal IgG1 antibody directed to human CS1, a cell surface glycoprotein. CS1 is expressed on plasma cells and a subset of circulating leukocytes. Since elotuzumab does not recognize non-human CS1, minimal animal toxicology has been performed. Non-clinical activity as monotherapy as well as in combination led to human trials. Although as monotherapy in heavily pretreated subject the best responses were SD, elotuzumab showed high response rates in combination with bortezomib or lenalidomide.
Elotuzumab was approved in November of 2015 for treatment of relapsed MM subjects with prior 1-3 lines of therapy. Please refer to the package insert and Investigator's Brochure for more information.

1.6. Study Rationale

Previous studies have indicated that the KRd combination (formerly CRd) is highly active in new myeloma; best response for all subjects on ITT (N=53) 98% PR, 87% VGPR, 72% ≥nCR, 64% CR, 55% sCR, and 51% MRD-negative rate, 3-year PFS of 79% (Jakubowiak, 2016) and is well tolerated in both new myeloma (Jakubowiak, 2016) as well is in relapsed myeloma (Stewart et al., 2015). Additionally, the combination of elotuzumab with lenalidomide and dexamethasone is more active than Rd and well tolerated in relapsed MM with no significant added or overlapping toxicity after an addition of elotuzumab (Lonial et al., 2015; Moreau, 2012; Moreau et al., 2012). Finally, the combination of elotuzumab with proteasome inhibitor (bortezomib) shows encouraging activity suggestive of additive effect and no significant overlapping toxicity (Jakubowiak et al., 2012a). We hypothesize that an addition of elotuzumab to KRd combination (E-KRd combination), which includes both proteasome inhibitor (carfilzomib), and immunomodulatory drug (lenalidomide) will further improve treatment outcome, including the rate of CR/sCR and rate of MRD-negative disease.

As recently reported, incorporation of autologous stem cell transplant into KRd treatment of newly diagnosed myeloma improves rates of CR and MRD-negative disease, and appears to further improve PFS (Jakubowiak, 2016) providing, as a proof of concept, evidence that KRd results can further be improved. Since the achievement of CR and MRD negative status is associated with improved long term-control of the disease (Dytfeld et al., 2011; Harousseau et al., 2010), and elotuzumab in particular improves time to event in combination with IMiD and PI, this regimen may further improve overall treatment outcome in myeloma.

We hypothesize that treatment with E-KRd will improve the rate of sCR and/or the rate of negative MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) at the end of 8 cycles among non-transplant candidates or transplant candidates who agreed to defer transplant compared to historical results of KRd alone. We would like to investigate this in the proposed study, in subjects who are newly diagnosed and who are transplant ineligible or those who are transplant-eligible, and choose to delay transplant. The primary efficacy endpoint will be the rate of sCR and/or the rate of negative MRD by NGS at the end of 8 cycles among non-transplant candidates and/or transplant candidates who agreed to defer transplant.

Among secondary objectives, we propose to evaluate the status of MRD disease at established landmark time-points, and to use MRD status to determine the duration of E-KRd treatment. We anticipate that E-KRd treatment will result in a statistically improved rate of MRD-negative disease compared to the MRD rate observed in subjects who were treated with KRd in the historical trial.

Based on the results from the IMF study (Avet-Loiseau et al., 2015) we propose to use different durations of E-KRd treatment using MRD status as the modifying criteria. There will be 3 possible outcomes:

1) Subjects who have MRD-negative disease at the completion of 8 and 12 cycles of E-KRd will receive a shorter duration of E-KRd treatment (for a total of 12 cycles) and continue on E-Rd maintenance until disease progression.
2) Subjects that are MRD-positive after cycle 8 but transform to MRD-negative after 12 cycles of E-KRd will receive an additional 6 cycles of E-KRd and then continue on E-Rd maintenance until disease progression.
3) Subjects that are MRD-positive after 8 and 12 cycles, will receive an additional 12 cycles of E-KRd and then continue on E-Rd maintenance until disease progression.

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.

1.7. **Study Population and Sample Size**

A total of 40, non-transplant candidates, and/or transplant candidates who agreed to defer transplant will be enrolled. Since the study does not plan to exclude transplant candidates who do not wish to defer transplant, additional 15 subjects who discontinue E-KRd treatment and proceed to transplant are planned to be enrolled to generate additional tolerability and toxicity data, bringing the total number of subjects to be enrolled to 55. Subjects that continue to transplant will be removed from the study and censored at the end of 4 cycles. These subjects will not be followed up or further analyzed. Intention to go on ASCT will be required at the time of enrollment with 15 subjects planned in this category per study design. Subjects who were assigned to the 'non-ASCT' or 'deferred ASCT' category who proceed to ASCT for reasons other than disease progression or toxicity, will be replaced (up to 5 subjects).

For 40 non-transplant candidates and/or transplant candidates who agreed to defer transplant, we hypothesize that treatment with E-KRd will improve the rate of sCR at the end of 8 cycles among non-transplant candidates or transplant candidates who agreed to defer transplant compared to historical results of KRd alone.

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 near complete response (or very

good partial response when nCR cannot be determined). A serum sample from blood at landmark timepoints (after C4, 8, 12, and 18, 24 months after C1D1, and yearly after) will be required for banking at the University of Chicago for later M-spike analysis with a new elotuzumab interference assay. This assay will use mass spectrometry and is not commercially available. This assay is proprietary to BMS, which will receive banked samples and perform this assay. Assay results will not be used for clinical decision-making, but rather to assess and confirm the primary endpoint of stringent CR.

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. Subjects who achieve SD, PR, or CR will continue therapy until disease progression. Subjects with disease progression will discontinue the treatment regimen and be removed from protocol.

2. OBJECTIVES

2.1. Primary Objective

- The primary efficacy endpoint will be the rate of sCR and/or the rate of negative MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) at the end of 8 cycles among non-transplant candidates and transplant candidates who agreed to defer transplant

2.2. Secondary Objectives

- To evaluate the safety and tolerability of elotuzumab in combination with KRd, when administered to subjects with newly diagnosed multiple myeloma.
- Determine the rate of MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) and by multi-color flow cytometry (MFC) at the end of Cycle 4, 8,and 12 for all subjects, and end of C18 (for subjects who are MRD+ at the end of C8 but MRD- at the end of C12 only), 24 months after C1D1, and yearly after that.
- Estimate time to event, including duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS).

2.3. Exploratory Objectives

- GEP, proteomics, and gene sequencing to evaluate the correlation between treatment outcome and pre-treatment subject profile.
- Immunologic correlative studies including FcγRIIIa V genotype.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

- To determine the rate of sCR and/or the rate of negative MRD by NGS at the end of 8 cycles per IMWG criteria.

3.2. **Secondary Endpoints**

- Evaluate the safety and tolerability of elotuzumab in combination with KRd by monitoring AE rate, classification, and relation to study drug
- Compare rates of MRD between MFC and NGS at the end of cycles 4, 8,and 12 for all subjects, and end of C18 (for subjects who are MRD+ at the end of C8 but MRD- at the end of C12 only), 24 months after C1D1, and yearly after that.
- Estimate the time to event including duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS)

3.3. **Tertiary/Exploratory Endpoints**

- Conduct GEP, Proteomic, and gene sequencing studies to evaluate the correlation between treatment outcome and pre-treatment subject profile
- Conduct immunologic correlative studies including FcγRIIIa V genotype

4. INVESTIGATIONAL PLAN

4.1. **Overview of Study Design and Dosing Regimen**

This is a Phase 2, open-label, multicenter study studying the safety and tolerability to the combination therapy of elotuzumab, lenalidomide, carfilzomib, and dexamethasone for newly diagnosed subjects with multiple myeloma requiring systemic chemotherapy.

Subjects will receive treatment until disease progression or unacceptable toxicity (whichever occurs first). The primary endpoint of this Phase 2 study is to determine the rate of sCR and/or the rate of negative MRD by NGS at the end of 8 cycles per IMWG criteria and to evaluate the safety and tolerability of elotuzumab in combination with KRd, when administered to subjects with newly diagnosed multiple myeloma.

4.2. **Study Procedures**

On cycles 1 and 2, subjects will receive elotuzumab weekly on days 1, 8, 15, and 22 of a 28-day cycle at 10mg/kg. From cycle 3 onward, elotuzumab will be dosed every other week on days 1 and 15 at 10mg/kg..

Carfilzomib will be dose escalated on cycle 1 as follows: 20 mg/m^2 on day 1, 56mg/m^2 on day 8, and 56mg/m^2 on day 15. Between cycles 2-8, carfilzomib will be given on days 1, 8, and 15 of a 28-day cycle at 70 mg/m^2. From cycle 9 onward, carfilzomib will be given at the best-tolerated dose on days 1 and 15 of a 28-day cycle. Splitting carfilzomib dose to 27 mg/m^2 on days 8, 9 and 36 mg/m^2 on days 15, 16, and in subsequent cycles on days 1, 2, 8, 9, 15, 16 – as in the original KRd 2-day weekly schedule – will be allowed based on discussion with the lead PI.

Lenalidomide will be given initially at 25mg per dose daily on days 1-21 of a 28-day cycle for cycles 1-8. From cycle 9 onward, lenalidomide will be dosed at last tolerated dose daily on days 1-21 of a 28-day cycle.

Dexamethasone will initially be give 40 mg weekly (cycles 1-4), which in the first cycle will be split into two doses as follows: 20mg of dexamethasone will be given IV on days 1, 8, and 15 no more than 3 hours prior to elotuzumab infusion and 20mg on days 2, 9, and 16 will be taken PO. If in the course of dose modification carfilzomib is split, dex will be given prior to carfilzomib. However, most pts will not be given carfilzomib on days 2, 9, and 16. On Day 22 of cycle 1,

40mg dexamethasone will be given IV no longer than 3 hours prior to elotuzumab. In cycles 2-4 40mg dexamethasone will be taken PO (or IV) on days 1, 8, 15, and 22. On days when dexamethasone coincides with elotuzumab, dexamethasone will be taken no longer than 3 hours prior to elotuzumab infusion. For cycles 5+ dexamethasone will be reduced to 20 mg PO or IV weekly.

Dose modifications will be mandated based on aggressive schedule of dose modification for toxicities as per specific guidelines. Otherwise, subjects will continue at their best tolerated dose of lenalidomide on days 1-21 and their best tolerated dose of carfilzomib on days 1, 8, 15 in cycles 1-8 and days 1, 15, in cycles 9-12 (in subjects with MRD- disease at the end of cycle 8 and 12) or cycles 9-18 (in subjects with MRD+ disease at the end of cycle 8 but MRD- at the end of cycle 12) or cycles 9-24 (in subjects with MRD+ disease at the end of cycle 8 and 12). See section 1.7.

All subjects will have weekly visits for toxicity assessments in the first cycle and then monthly from cycles 2+. Disease assessments will start on Cycle 1 Day 15 and then will be done on clinic visits on day 1 of each cycle. Treatment will continue on protocol for up to 24 months or if elotuzumab, carfilzomib and lenalidomide are permanently discontinued. Toxicity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. Subject who complete 12 cycles (who are MRD-negative at the end of cycle 8 and 12), 18 cycles (who were MRD-positive at the end of cycle 8 but MRD-negative at the end of cycle 12), or 24 cycles (who were MRD-positive after cycle 8 and 12) of E-KRd, will then continue elotuzumab, lenalidomide, dexamethasone (E-Rd) maintenance.. 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 8 and 12 to determine the course of treatment (either move to ERd maintenance at the end of 12, 18, or 24 cycles of E-KRd. See section 1.7). MRD analysis will be performed using the most recent Spanish protocol by multiparameter flow cytometry (10-color) and by Next Generation Sequencing (NGS). MRD will be assessed in all bone marrow samples at the beginning of the study, after cycles 4, 8, 12, and 18 (when applicable), 24 months after C1D1, yearly after that, and at any time a bone marrow biopsy is completed to assess response for suspected nCR (or VGPR when nCR assessment is not possible). From the time nCR (or VGPR) is established, MRD analysis should continue at 12-month intervals from randomization up to 6 years in subjects with ongoing sCR. If a confirmatory BM for nCR is scheduled within 2 months of a hallmark BM, it is acceptable to wait until the hallmark timepoint. All flow cytometry analysis will be performed at the University of Chicago, 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 Adaptive Biotechnologies using clonoSEQ® platform after processing at the University of Chicago site. For this purpose, sites will be required to provide a fresh screening BM sample at all timepoints. At screening only, alternatively, non-decalcified slides from the BM aspirate, or FFPE clot slides can be used to establish a baseline for MRD samples analyzed by Adaptive Biotechnologies. Decisions to change treatment at indicated time points will be based primarily on MRD results by NGS. Only if NGS testing is not successful (i.e. either at the calibration or measurement step), flow-based results will be used for decision about duration of E-KRd treatment.

Treatment responses will be assessed by serum and urine monoclonal protein electrophoresis and immunofixation and serum free light chains (SFLC) and where needed by serum protein immonglobulins at Cycle 1 Day 15, then at Cycle 2 Day 1 and then at the beginning of each subsequent cycle. A serum sample from blood at landmark timepoints (after C4, 8, 12, and 18, 24 months after C1D1, and yearly after) will be required for banking at the University of Chicago for later M-spike analysis with a new elotuzumab interference assay. The analysis of banked samples by elotuzumab interference assay will be performed using Mass Spectrometry by BMS

Subjects with stable disease or better will continue treatment until disease progression or the development of unacceptable toxicities. All subjects will then undergo a final visit (end of treatment visit) within 30 (+/-7) days of last dose of study medication.

4.2.1. **MRD Detection Methods**

The tests used Minimal Residual Disease (MRD) after cycles 8 and 12 is considered experimental and has not been approved by the US Food & Drug Administration (FDA) for use in evaluating MRD disease in multiple myeloma.

The flow cytometry analysis procedure used to determine MRD is performed on a NAVIOS FLOW CYTOMETER SYSTEM manufactured by BECKMAN COULTER, INC., using a laboratory developed assay. The Premarket Notification 510(k) (Number K130373) for the device can be found using the following link.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K130373.

4.2.2. **Number of Centers**

A total of 5 centers in the US will participate.

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

Each treatment cycle is 28 days. The study is planned to start in Q4 2016 with respect to first subject in (FSI). With an expected accrual rate of 2-4 subjects per month across 5 centers, and a total number of 40-55 subjects planned, the anticipated enrolment period is 12 -18 months. Hence the last subject in will be included not prior to Q4 2017. The length of treatment period will be up to 24 months. Subjects will be followed for survival for up to 6 years since their enrollment or until death, whichever occurs first.

4.2.4. **Treatment Phase**

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

4.2.5. **End of Treatment Visit**

Subjects that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, 30 (+/-7) days after the last dose of study medication.

4.2.6. **Long Term Follow Up**

Subjects will be followed up every 3 months for progression and survival after the end of treatment. Subjects will be followed for survival for up to 6 years after enrollment or until death, whichever occurs first. The follow up will be done over the phone.

5. SUBJECT 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. Newly diagnosed, previously untreated myeloma requiring systemic chemotherapy

a. Prior treatment of hypercalcemia or spinal cord compression or active and/or aggressively progressing myeloma with corticosteroids and/or lenalidomide and/or bortezomib/PI-based regimens does not disqualify the subject. The corticosteroid treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period or not more than 1 cycle of lenalidomide and/or PI-based therapy. A higher total dose of corticosteroid is allowed for the management of cord compression at the discretion of the PI, as long as the subject does not exhibit any steroid related toxicities at the initiation of study treatment.

2. Both transplant and non-transplant candidates are eligible.
3. Diagnosis of symptomatic multiple myeloma as per current IMWG uniform criteria prior to initial treatment
4. Monoclonal plasma cells in the BM 10% or presence of a biopsy-proven plasmacytoma
5. Measurable disease, prior to initial treatment as indicated by one or more of the following:
    a. Serum M-protein ≥ 1 g/dL
    b. Urine M-protein ≥ 200 mg/24 hours
    c. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative immunoglobulin levels are acceptable (≥ 1 g/dL)
    d. Involved serum free light chains ≥ 10 mg/dL provided that free light chain ratio is abnormal

6. Screening laboratory values must meet the following criteria and should be obtained within 21 days prior to enrollment
    i. WBC ≥ 2000/μL
    ii. Platelets ≥ 75 x10^3/μL
    iii. ANC >1000/μL
    iv. Hemoglobin > 8.0 g/dL
    v. Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 50 mL/min
        a) Use the Cockcroft-Gault formula below):
            - *Female* CrCl = (140 - age in years) x weight in kg x 0.85
                - 72 x serum creatinine in mg/dL
            - *Male* CrCl = (140 - age in years) x weight in kg x 1.00
                1. 72 x serum creatinine in mg/dL

b) Alternatively to Cockroft-Gault formula of CrCl, 24hr urine CrCl can be used

vi. AST/ALT ≤ 3 x ULN

vii. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) or ≤ 2 x ULN if lenalidomide is being prescribed.

7. Males and females ≥ 18 years of age
8. ECOG performance status of 0-1
9. Females of childbearing potential (FCBP) must have 2 negative pregnancy tests (sensitivity of at least 25 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**

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

1. Non-secretory or hyposecretory multiple myeloma, prior to initial treatment defined as <1.0 g/dL M-protein in serum, <200 mg/24 hr urine M-protein, and no measurable disease as per IMWG by Freelite.
2. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
3. Geriatric assessment score of ≥2 as defined by Palumbo et al.
4. Known or suspected Amyloidosis
5. Plasma cell leukemia
6. Within 4 weeks since any plasmapheresis
7. Within 3 weeks of any corticosteroids except per inclusion criteria #2
8. Waldenström's macroglobulinemia or IgM myeloma
9. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ($t_{1/2}$) prior to first dose, whichever time is greater
10. Subjects not able to tolerate elotuzumab, lenalidomide, carfilzomib, or dexamethasone
11. Peripheral neuropathy ≥ Grade 2 at screening
12. Prior CVA with persistent neurological deficit

13. Diarrhea > Grade 1 in the absence of antidiarrheals
14. Corrected calcium ≥ 11.5 mg/dL within 2 weeks of randomization
15. CNS involvement
16. Pregnant or lactating females
17. Radiotherapy within 14 days before randomization. Seven days may be considered if to single area
18. Major surgery within 3 weeks prior to first dose
19. Subject has clinically significant cardiac disease, including:
    - myocardial infarction within 1 year before Cycle 1 Day 1, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV
    - uncontrolled cardiac arrhythmia (NCI CTCAE Version 4 Grade 2:2) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec
20. Uncontrolled HTN 14 days prior to enrollment
21. Prior or concurrent deep vein thrombosis or pulmonary embolism
22. Rate-corrected QT interval of electrocardiograph (QTc) > 470 msec on a 12-lead ECG during screening
23. Uncontrolled hypertension (defined as average systolic blood pressure ≥140 or average diastolic blood pressure ≥90, with blood pressure measured ≥3 times in the two weeks prior to enrollment) or diabetes
24. Acute infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose
25. Active infection
26. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Subjects who are seropositive because of hepatitis B virus vaccine are eligible.
27. 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
28. 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

5.3 SUBJECT ENROLLMENT AND REGISTRATION

5.3.1 Registration Process

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

Registration will be done centrally at University of Chicago. All subjects who have signed consent, regardless of if they are enrolled or 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.

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

When a potential subject has been identified, notify the University of Chicago CRA via phone or email to ensure a reservation on the study: (773) 702-2052 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 subject's eligibility is confirmed by the CRA will be considered the subject's "Enrolled/On Study Date." The subject'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).

6. TREATMENT PLAN

Please refer to the Study Calendar (Appendix 6 for an overview).

After screening, eligibility determination and enrollment, subjects will receive elotuzumab, carfilzomib, lenalidomide, and dexamethasone, 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 6 years total from the time of enrollment.

6.1. **Treatment Regimen**

Please refer to the Study Calendar (Appendix 6 for an overview).

After screening, eligibility determination and enrollment, subjects will receive elotuzumab, carfilzomib, lenalidomide, and dexamethasone, 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 6 years total from the time of enrollment.

Cycles 1 – 2

Agent	Premedication and Precautions	Schedule	Dose	Route
Elotuzumab	Please refer to Section 6.3	Days 1, 8, 15, 22	10 mg/kg	Intravenous-See appendix B for more details
Carfilzomib	Please refer to Section 6.3			
Lenalidomide	None	Days 1-21 of each cycle	25 mg	Oral
Dexamethasone	Take with food; recommended to be taken in the morning	Days 1, 8, 15 Days 2,9, 16	20 mg 20 mg	IV Oral
		Day 22	40 mg	Oral

Cycles 3 – 4

Agent	Premedication and Precautions	Schedule	Dose	Route
Elotuzumab	Please refer to Section 6.3	Days 1 and 15	10 mg/kg	Intravenous-See appendix B for more details
Carfilzomib	Please refer to Section 6.3			
Lenalidomide	None	Days 1-21 ofeach cycle	25 mg	Oral
Dexamethasone	Take with food;recommended to be taken in the morning	Days 1, 8,15, 22	40 mg	Oral

Cycles 5+

Agent	Premedicationand Precautions	Schedule	Dose	Route
Dexamethasone	Takewithfood; recommended to be taken in the morning	Days1, 8,15,22	20 mg	Oral

6.2. **Study Procedures**

6.2.1.**Screening Procedures**

The screening period is 21 days in length. The screening period starts on the date that the subject signs the Informed Consent Form. Refer to the study calendar (Appendix 6)

Signed written informed consent Obtained prior to any study specific assessments

Demographics and medical history
- Age, gender, ethnic background
- Details on myeloma diagnosis
- Previous and concurrent relevant diseases
- Current symptoms and/ or residual toxicities from prior therapies

Skeletal Survey	May be within 3 months of planned treatment start (does not need to be repeated if within 3 months). 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.
Cardiac evaluation	12-lead ECG
Echocardiogram	Required
Physical examination and vital signs	• Body height and weight • BSA • ECOG Performance Status (Appendix 2) • Blood pressure, pulse, temperature, respiration • Physical examination
Hematology (CBC)	Hemoglobin, WBC with complete differential, RBCs, platelet count, absolute neutrophil and lymphocyte counts. WBC differential may be automated or manual as per institutional standards.
Serum chemistry	Sodium, potassium, chloride, creatinine, glucose, uric acid, phosphorus, magnesium, LDH, total bilirubin, CRP
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.
β2 microglobulin	Required

Myeloma Disease Assessment – laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • 24hr Urine • Serum Free Light Chains (SFLC) • Serum quantitative immunoglobulins (IgGs) All of the above assessments are required at screening regardless of the disease classification.
Bone Marrow Biopsy	The Screening BM aspirate and biopsy is SOC. Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for MRD analysis by flow and NGS, conventional cytogenetics, and fluorescent *in situ* hybridization. A BM aspirate sample at screening is required for calibration for NGS analysis. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at screening.
CT-PET	A CT-PET must be performed at screening.
Correlative Samples	For subjects who sign additional consent: peripheral blood and Buccal mucosa swab (screening only) will be collected
Adverse Events	AEs will be collected from the time of first study drug treatment through 30-days after end of study treatment Only SAEs considered related to study procedure need to be reported.

6.2.2. **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 nCR (or VGPR when nCR determination is not possible) or better is suspected. Hematology and Chemistry labs are required per SOC before Carfilzomib infusion on day 1, 8, and 15 of cycles 1-8, and on days 1, and 15 of cycles 9+. On cycles 9+ this evaluation should be done as clinically indicated .

Complete Physical examination and vital signs on Day 1	• Body weight • BSA • ECOG Performance Status • Blood pressure, pulse, temperature, respiration • Physical examination • Pulse oximetry to investigator discretion
Symptom-directed Physical Exam Days 8, 15, (and 22 on cycles 1-2)	

Vital signs on each treatment day with Carfilzomib and/or elotuzumab	
Hematology (Day 1,8 and 15 on cycles 1-8before infusion required. On cycles 9+ days 1 and 15 before infusion and as clinically indicated)	Hemoglobin, WBC with complete differential, RBCs, platelet count, absolute neutrophil and lymphocyte counts. WBC differential may be automated or manual as per institutional standards. Results must be reviewed before dosing.
Complete clinical chemistry (Day 1, 8, and 15 on cycles 1-8 before infusion required. On cycles 9+ days 8 and 15 before infusion and as clinically indicated)	Sodium, potassium, chloride, creatinine, glucose, uric acid, phosphorus, magnesium, LDH, total bilirubin, CRP Results must be reviewed before dosing in Cycles 1 and 2.
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 (Cycle 1 Day 15 and on Day 1 of every cycle from cycle 2+)	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation • Urine Protein Electrophoresis (UPEP) and immunofixation • 24hr Urine • 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. A serum sample from blood at landmark timepoints (after C4, 8, 12, and 18, 24 months after C1D1, and yearly after) will be required for banking at the University of Chicago for later M-spike analysis with a new elotuzumab interference assay. Analysis of banked samples via elotuzumab interference assay will be performed using Mass Spectrometry by BMS.
Bone Marrow Aspirate/biopsy	All BM aspirates and biopsies are SOC except the end of cycle 4 sample, which will only be SOC for subjects who proceed to transplant. Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for MRD analysis by flow and NGS. This is required at end of Cycle

	8 and end of cycle 12 for treatment decision making. Additionally, a BM aspirate and biopsy will be collected at the end of cycle 4. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at the time of the SOC BMA
CT-PET	A CT-PET must be performed to confirm MRD-negative disease per Standard of Care. Subjects who are MRD-positive do not need PET scans until suspected CR. If there is clinical need for assessment at cycles 8 and 12, a CT-PET should be performed at these timepoints as well.
Correlative samples	For subjects who sign additional consent: peripheral blood will be collected every time a Bone Marrow biopsy is performed as SOC
Adverse events	Assessed on an ongoing basis
Study Treatment	Section 6 and Appendix 6

6.2.3. End of Treatment Procedures and Long-Term Follow-Up

Subjects 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 treatment, subjects will be followed for survival for 6 years total since enrollment.

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

Physical examination and vital signs	• Body weight • ECOG • Blood pressure, pulse, temperature, respiration • Physical examination Pulse oximetry to investigator discretion
Hematology	Hemoglobin, WBC with complete differential, RBCs, platelet count, absolute neutrophil and lymphocyte counts. WBC differential may be automated or manual as per institutional standards.
Clinical chemistry	Sodium, potassium, chloride, creatinine, glucose, uric acid, phosphorus, magnesium, LDH, total bilirubin, CRP
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
Myeloma Disease Assessment– laboratory	M-protein determination: • Serum Protein Electrophoresis (SPEP) and immunofixation

	• Urine Protein Electrophoresis (UPEP) and immunofixation • 24hr Urine • Serum Free Light Chains • Serum quantitative immunoglobulins (Igs)
Bone Marrow Aspirate/biopsy	All BM aspirates and biopsies are SOC, except the end of cycle 4 sample, which will only be SOC for subjects who proceed to transplant. Quantify percent myeloma cell involvement, and obtain bone marrow aspirate for MRD analysis by flow and NGS. This is required at EOT (C12, C18 or C24), 24 months after C1D1, and yearly after that (for up to 6 years after enrollment). Additionally, a BM aspirate and biopsy is required at any time nCR is suspected and MRD will be tested at this time. If nCR (If nCR determination is not possible, then VGPR will be used to trigger a bone marrow biopsy. A Bone Marrow Biopsy to confirm nCR or VGPR will not be required if the subject is within 2 months of a landmark Bone Marrow Biopsy timepoint) is suspected within 3 months of EOT, it is acceptable to wait for the EOT BM biopsy. For subjects who sign consent for correlative samples, an additional aspirate sample should be collected at EOT
CT-PET	MRD-negative subjects will undergo a yearly PET until progression.
Correlative samples	For subjects who sign additional consent: peripheral blood will be collected every time a Bone Marrow biopsy is performed as SOC
Adverse events	Record through 30-days after last treatment. All SAEs considered related to treatment must be followed until resolution.

6.3. Pretreatment Preparation

6.3.1. 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.

6.3.2. **Concomitant Medications**

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.
-

Patients receiving multi-agent chemotherapy are inherently at greater risk of thrombosis and should follow the anticoagulation recommendations from International Myeloma Working Group (IMWG) guidelines. This includes LMWH 40 mg subcutaneously daily or warfarin target INR 2-3. As an alternative to LMWH or warfarin, we would accept prophylactic doses of direct oral anticoagulants (apixaban 2.5 mg twice daily or rivaroxaban 10 mg daily). If patient is unable to receive any of the previously listed options and has not risk of thrombosis/no prior thrombosis the patient may proceed with aspirin, preferably 325 mg, after discussing with the study overall PI.

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.

6.3.2.1. 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)
- The contraceptive requirement for Carfilzomib in Females of childbearing potential is at least 30 days after the last dose. Carfilzomib is prohibited in breast-feeding women.

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 30 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

6.3.3. **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 ≥ 4mg/day or prednisone > 20 mg/day are not permitted. Other investigational agents are not to be used during the study.

6.3.4. **Use of Blood Products**

Subjects may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects 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 subjects are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Subjects 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.

6.3.5. **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.

6.4. Study Drug Administration

6.4.1. *Elotuzumab Administration*

Elotuzumab for Injection is supplied as a lyophilized product in single-use 400mg and 300mg vials. Each vial of Elotuzumab for Injection, 400 mg/Vial and Elotuzumab for Injection, 300 mg/Vial should be reconstituted with sterile water for injection (SWFI) at the clinical compounding site. Once the reconstitution is completed, dilution with 0.9% sodium chloride injection (NS) is necessary to result in an elotuzumab concentration from 1.0 mg/mL to no higher than 6.0 mg/mL. The dose for C1D1 will be calculated using the screening weight. Dose adjustments do not need to be made for weight gains/losses of ≤ 10%.

Elotuzumab will be given as an IV infusion and should be initiated at a rate of 0.5mL/min. If well tolerated, the infusion rate may be increased in a stepwise fashion as described in the table below. The maximum infusion rate should not exceed 5mL/min.

- Cycle 1-2: 10mg/kg on days 1, 8, 15, and 22 of a 28-day cycle
- Cycles 3+: 10mg/kg on days 1 and 15 of a 28-day cycle

Infusion Rate for Elotuzumab

Cycle 1, Dose 1		**Cycle 1, Dose 2**		**Cycle 1, Dose 3 and 4** **And all subsequent Cycles**
Time Interval	**Rate**	**Time Interval**	**Rate**	**Rate**
0 - 30 min	0.5 mL/min	0 - 30 min	3 mL/min	
30 - 60 min	1 mL/min	≥30 min	4 mL/min[a]	5 mL/min[a]
≥60 min	2 mL/min[a]	-	-	

All subjects should have vital signs monitored at the start and end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

The sponsor may modify the infusion rates or the preinfusion medications (Section 6.1.3.1) prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines.

6.4.2. *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 20mg/m^2 dose level), 123.2mg of carfilzomib (at the 56mg/m^2 dose level), or 154 (at the 70mg/m^2 dose level).

Carfilzomib will be given as an IV infusion over 30 minutes on Days 1, 8, and 15 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 6-1 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. Missed doses will not be replaced during a cycle. Carfilzomib will be escalated from 20mg/m^2 (Cycle 1 Day 1) to 56mg/m^2 (Cycle 1 Day 8 and 15 - see below) and then further escalated to 70mg/m^2 (Cycle 2 Day 1) as long as the subject does not present with cytokine release symptoms (fever, rash, dyspnea, etc) after Cycle 1 Day 2.

- Cycle 1: 20 mg/m^2 Day 1; 56 mg/m^2 Day 8; 56mg/m^2 Day 15.
- Cycles 2 - 8: 70mg/m^2 if tolerated Days 1, 8, and 15
- Cycles 9+ (for up to 24 cycles max): 70mg/m^2 if tolerated Days 1 and 15

Subjects will continue on E-KRd regimen for 12 cycles. MRD results after cycles 8 and 12 will determine the course of action after C12 with 3 possible outcomes: 1) subjects who are MRD- at both instances will end E-KRd and will continue on E-Rd maintenance until disease progression. 2) Subjects who are MRD+ after cycle 8 but MRD- after cycle 12 will receive 6 additional E-KRd cycles (for a total of 18) and then continue on E-Rd maintenance until disease progression. 3) Subjects who are MRD+ at both instances will receive 12 additional E-KRd cycles (for a total of 24) and continue on E-Rd maintenance until disease progression.

6.4.3. *Lenalidomide Administration*

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.

Subjects will receive lenalidomide as follows in 28-day cycles:

- Cycle 1-8: 25 mg days 1-21
- Cycles 9+: 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.

6.4.4.*Dexamethasone Administration*

Dexamethasone will be administered no longer than 3 hours preceding elotuzumab and between 30 min and 4 hours prior to carfilzomib (on days that they coincide). When dexamethasone, carfilzomib and elotuzumab coincide, dexamethasone will be given first, followed by carfilzomib and finally elotuzumab will be infused:

- Cycle 1-2: 20 mg IV not longer than 3 hours prior to elotuzumab infusion and between 30 min and 4 hours prior to carfilzomib on Days 1, 8, and 15. 20mg PO will be taken on Days 2, 9, and 16 and 40mg PO will be taken as a single dose on Day 22 not longer than 3 hours prior to elotuzumab infusion.

- Cycles 3-4: 40 mg PO Days 1, 8, 15, 22. On days when dexamethasone coincides with elotuzumab, dexamethasone will be taken no longer than 3 hours prior to elotuzumab infusion. On days when carfilzomib is given, dexamethasone will be dosed between 30 min and 4 hours prior to carfilzomib

- Cycles 5+: 20mg PO Days 1, 8, 15, 22. On days when dexamethasone coincides with elotuzumab, dexamethasone will be taken not longer than 3 hours prior to elotuzumab infusion. On days when carfilzomib is given, dexamethasone will be dosed between 30 min and 4 hours prior to carfilzomib

Split weekly dosing on cycles other than cycle 1 (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 elotuzumab or carfilzomib (on cycles 3+ day 22) may be self-administered by the subject on an outsubject basis.

Missed doses of dexamethasone will not be made up.

6.4.5.**Maintenance treatment**

Subjects that complete 12 cycles (who were MRD-negative after cycles 8 and 12), 18 cycles (who were MRD-positive after cycle 8 but MRD-negative after cycle 12), or 24 cycles (who were MRD-positive after cycle 8 and 12) of E-KRd, will continue a regimen of E-Rd until disease progression. This regimen will have elotuzumab every four weeks, lenalidomide at best-tolerated dose (days 1-21), and low dose dexamethasone (weekly) in 28-day cycles until disease progression.

6.4.6. **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 empty drug containers to the research center at their next visit for destruction.

6.5. **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 elotuzumab, 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 site Lead Principal Investigator at the University of Chicago and the Co-Investigator at the treating institution.

6.6. **Dose-Modification Guidelines**

The following sections and tables summarize dosing modifications of elotuzumab, 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 elotuzumab, carfilzomib and lenalidomide will be held temporarily in the event of a treatment-related toxicity at the Treating Investigator's discretion. Study treatment may be reintroduced if resolution of the event to the baseline value or to ≤ Grade 1 within 21 days; otherwise study drug will be permanently discontinued. Any deviations from this plan must be approved by the Lead Principal Investigator.

If a subject's elotuzumab administration is delayed on day 1 of a cycle, carfilzomib, lenalidomide, and dexamethasone will also be delayed until the elotuzumab is resumed, which would then become the new day 1 of that cycle.
If a subject's elotuzumab is held in the middle of a cycle, carfilzomib, dexamethasone, and lenalidomide dosing will continue as scheduled. If the subject's elotuzumab is delayed during the cycle and is resumed within the designated window, (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond) the subject may receive the scheduled dose. If the elotuzumab is not resumed within the given window (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond), the subject is to omit that dose, and resume dosing at the next dosing time point.

If a study drug (except dexamethasone) is discontinued, the subject may continue on trial. However, if the discontinuation happens prior to the end of cycle 8 (1^{ary} endpoint), the subjects will

continue to be treated and will only be included on the intent to treat analysis.

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

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

Table 6-1 Carfilzomib Dose Adjustments

Nominal carfilzomib dose	Dose -1	Dose -2	Dose -3	Dose -4
70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2

Table 6-1 Lenalidomide Dose Adjustments

Nominal Lenalidomide Dose	Dose -1	Dose -2	Dose -3
25 mg Days 1-21	15 mg	10 mg	5 mg

Table 6-3 Dexamethasone Dose Adjustments

Nominal Dexamethasone Dose	Dose -1	Dose -2	Dose -3
40mg or 20 mg	Reduce dexamethasone by 50% from starting dose; however, the 20-mg IV dose of dexamethasone given before the infusion on the day of elotuzumab infusions must not be decreased.	Discontinue dexamethasone on the day when elotuzumab is not given.	Discontinue dexamethasone

*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

6-4 Elotuzumab Dose Adjustments

No dose reductions for elotuzumab are allowed. If Elotuzumab is held on Day 1 of a new cycle, treatment with carfilzomib/lenalidomide/dexamethasone will also be delayed. If elotuzumab is held during any cycle on days 8, 15, or 22, the treating investigator will decide if lenalidomide, carfilzominb, and/or dexamethasone will be held using recommended guidance for retreatment below. Treatment may be delayed for a maximum of 21 days (see section 6.5.2.1 for details).

6.6.1. **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.

6.6.1.1. Hematologic Toxicity

Table 6-5 Dose Modification Guidelines for Hematologic Toxicities

When Platelets:	**Lenalidomide**	**Carfilzomib**		**Elotuzumab**
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	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
		If evidence of bleeding or platelets < 10 x10^9/L	• Hold • With resolution restart at previous dose	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
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	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
		If evidence of bleeding or platelets < 10 x10^9/L	• Hold • With resolution restart at 1 dose decrement	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
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 6-5 Dose Modification Guidelines for Hematologic Toxicities

When ANC:	Lenalidomide	Carfilzomib		Elotuzumab
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 10^9/L	• Continue at full dose	• 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	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
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	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion
		If ANC < 0.5 x10^9/L	• Hold • Resume at 1 dose decrement when ANC returns to ≥ 0.5 x10^9/L	• Hold • Upon resolution elotuzumab can be restarted at the treating physician's discretion

6.6.1.2. Non-hematologic Toxicity

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
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	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Grade 4	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
Desquamating (blistering) rash – any grade	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Sinus bradycardia/ other cardiac arrhythmia			
≤ 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.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
≥ Grade 3	Discontinue lenalidomide study drug	Hold until ≤ Grade 1, reinstitute at current dose.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
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.	Discontinue
Grade 4	Discontinue	Discontinue	Discontinue

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
Tumor lysis syndrome (≥ 3 of the following: ≥ 50% increase in creatinine, uric acid, or phosphate;≥ 30% increase in potassium;≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold lenalidomide until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Infection Grade 3 or 4	Hold lenalidomide until systemic treatment for infection is completed. If no neutropenia, restart lenalidomide at full dose. If neutropenic, follow neutropenic instructions.	Hold carfilzomib until systemic treatment for infection is completed If no neutropenia, restart carfilzomib at full dose. If neutropenic, follow neutropenic instructions.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
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.	Hold When lesions are dry elotuzumab can be restarted at the treating physician's discretion
Grade 2 neuropathy with pain or any Grade 3 neuropathy	Hold until ≤ Grade 2. Then restart lenalidomide at 1 dose decrement	Withhold until toxicity is resolved or returned to baseline After resolution, consider if restarting CFZ at the same dose or at a reduced dose is appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Grade 4 neuropathy	Discontinue	Discontinue	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Renal dysfunction			
Serum creatinine > 2 mg/dL	Base dose reduction on calculated GFR (below)	Base dose reduction on calculated GFR (below)	Hold Upon resolution elotuzumab can be

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
			restarted at the treating physician's discretion
CrCl>60 mL/min	Full dose	Full dose	Full dose
CrCl <60 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	Full dose
CrCl< 30 mL/min	Reduce lenalidomide to 15 mg every 48 h	Hold carfilzomib until CrCl> 30 mL/min. If attributed to carfilzomib, restart at 1 dose decrement. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. If not attributed to carfilzomib, restart at dose used prior to the event. Frequent monitoring of renal function should then be implemented	Full Dose
CrCl< 30 mL/min requiring dialysis	5 mg once daily. On dialysis days the dose should be administered following dialysis.	Hold until resolved to ≤ Grade 2. Then restart carfilzomib at 1 dose decrement	Full Dose

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
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	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	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 tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.	Hold Upon resolution elotuzumab can be restarted at the treating physician's discretion
Hypertension including Hypertensive Crises	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 2. Resume at one level dose reduction	NA

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
Heart problems, including rapid, strong, or irregular heartbeat, heart attack, reduced blood flow to the heart, abnormal amount of fluid to the lining around the heart, and swelling/irritation of the lining around the heart	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction	NA
Pericardial Effusion	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	NA
Pericarditis	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	NA
Pulmonary Hypertension	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to baseline. After resolution consider if restarting CFZ at the same dose or reduced dose is appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	NA
Pulmonary Toxicities: Interstitial Lung Disease (inc. pneumonitis), Acute Respiratory Failure, and Adult Respiratory Distress Syndrome (ARDS), cough and cough with phlegm	NA	≥ Grade 2 for Pneumonitis ≥ Grade 3 for ARDS ≥ Grade 4 for Respiratory Failure Carfilzomib attribution, hold drug until resolved to ≤Grade 1. Resume at one level dose reduction	NA

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
Blood clot in the lungs, fluid in the lungs, bleeding in the lungs	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction	NA
Gastrointestinal Perforation	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction	NA
Hepatic Toxicities (≥ Grade 3 elevation of AST or ALT, Bilirrubin, or other ≥ Grade 3 liver abnormalities)	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented.	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented.	Hold treatment and restart when toxicity has resolved to ≤ Grade 1 or baseline
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	Full dose

Table 6-6 Dose Modifications for Non-hematologic Toxicity

Recommended Action			
Non-heme toxicity	**Lenalidomide**	**Carfilzomib**	**Elotuzumab**
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Full dose	Hold carfilzomib dose until toxicity resolves to ≤ Grade 1 or baseline. After resolution, consider if restarting CFZ at the same dose or at a reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	Full dose
Other non-hematologic toxicity assessed as elotuzumab-related ≥ Grade 3	Full dose	Full dose	Hold Upon resolution, restart at the treating physician's discretion
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	Hold treatment and restart when toxicity has resolved to ≤ Grade 1 or baseline

Table 6-8 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	Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms

	> Grade 2 (interfering with function +/- interfering with activities of daily living)	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.

6.6.2. Guidelines for Elotuzumab Infusion and pre-medication in Subjects with Infusion Reactions

Required Treatments

Dexamethasone

On weeks without elotuzumab administer the weekly dose of 40 mg (Cycles 3-4) or 20mg (Cycles 5+) dexamethasone orally on Day 1, 8, 15, and 22 (-1 to +3 days). At the investigator's discretion, the oral dexamethasone may be given as a split dose over 2 consecutive days each week.

At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 – 24 hours and 3 hours prior to elotuzumab.

Premedication Before Elotuzumab:

1. Dexamethasone 20 mg IV (C1 and 2), 40mg PO (C3-4), or 20mg (C5+) not longer than 3 hours prior to the start of elotuzumab infusion when they coincide, and 20mg PO the day after elotuzumab infusion (C1-2 only).

   AND

2. H1 blocker: diphenhydramine (25 - 50 mg PO or IV) or equivalent (45-90 minutes prior to the start of infusion)

3. H2 blocker: ranitidine (50 mg IV) or equivalent (45-90 mins prior to the start of infusion)

4. Acetaminophen (650 - 1000 mg PO), (45-90 mins prior to the start of infusion

Premedication Regimen in Subjects With a Prior Infusion Reaction

Subjects with prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified above.

Table 6-9 Elotuzumab infusion in subjects with infusion reactions

Prior Infusion Reaction	Corticosteroid premedication prior to elotuzumab
None or Only Grade 1 infusion reaction	no change
Prior Grade 2 infusion reaction	Split dexamethasone dose on days of elotuzumab; e.g. for dose level 40 mg to 28 mg prior to carfilzomib and 12 mg prior to elotuzumab
Prior Grade 3 or recurrent Grade 2 infusion reaction	8 mg oral dexamethasone (12 - 24 hrs prior to elotuzumab) AND 8 mg oral dexamethasone (at least 3 hrs prior to elotuzumab) AND 24 mg IV dexamethasone at least 45-90 min prior to elotuzumab

At the discretion of the investigator, the 40 mg oral dexamethasone component may be given as a split dose: 20 mg PO (12–24 hours prior to elotuzumab) AND 20 mg PO (3 hours prior to elotuzumab).
If a subject with a prior Grade 2-3 infusion reaction also requires dose reduction of dexamethasone, the weekly dexamethasone on the days of elotuzumab infusion should be no lower than 8 mg IV (on the day of elotuzumab infusion at least 45 minutes prior to elotuzumab).
Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued. Additionally, subjects who have a recurrence of ≥ Grade 2 infusion reactions with subsequent doses and subjects who have a true hypersensitivity reaction at ≥ Grade 2 should have elotuzumab permanently discontinued (but may continue on KRd).

6.6.2.1. Elotuzumab Dose Delay or Interruption

If toxicity is considered to be related to elotuzumab, elotuzumab should delayed, interrupted, or discontinued (please refer to tables 6-5 and 6-6 for further guidelines). However, if dexamethasone is delayed or discontinued, the administration of elotuzumab should be based on clinical judgment (ie, risk of hypersensitivity).

If a ≥Grade 2 infusion reaction occurs during elotuzumab administration, the infusion must be interrupted. Upon resolution to ≤Grade 1, elotuzumab should be restarted at 0.5 mL/min and may be gradually increased at a rate of 0.5 mL/min every 30 minutes as tolerated to the rate at which the infusion reaction occurred. If there is no recurrence of the infusion reaction, the escalation regimen can be resumed (Table 6-9).

Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the infusion reaction recurs, the elotuzumab infusion must be stopped and not restarted on that day. Very severe infusion reactions may require permanent discontinuation of elotuzumab therapy and emergency treatment.

If a subject's elotuzumab administration is delayed on day 1 of a cycle, carfilzomib, lenalidomide, and dexamethasone will also be delayed until the elotuzumab is resumed, which would then become the new day 1 of that cycle.

If a subject's elotuzumab is held in the middle of a cycle, carfilzomib, dexamethasone, and lenalidomide dosing will continue as scheduled. If the subject's elotuzumab is delayed during the cycle and is resumed within the designated window, (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond) the subject may receive the scheduled dose. If the elotuzumab is not resumed within the given window (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond), the subject is to omit that dose, and resume dosing at the next dosing time point.

6.7. Response Evaluation

The first response assessment should be completed at Cycle 1 Day 15. 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
- 24hr Urine

	• Serum Free Light Chains • Serum quantitative immunoglobulins (Igs) A serum sample from blood at landmark timepoints (after C4, 8, 12, and 18, 24 months after C1D1, and yearly after) will be required for banking at the University of Chicago for later M-spike analysis with a new elotuzumab interference assay. The analysis of banked samples by elotuzumab interference assay will be performed using Mass Spectrometry by BMS.
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 8 and 12, EOT, 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.

6.8. **Study Termination**

Any Grade 5 toxicity related to study treatment will prompt stopping of the trial until further review is completed. Additionally, development of Grade 4 of non-hematologic toxicities in 2 or more patients will prompt the DSMB to stop the study for review to determine whether the trial should be terminated due to excessive toxicity.

6.9. **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).

Subjects 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 as well that due to Congestive Heart Failure unresolved for > 28 days the treatment shall be discontinued (see table 6-7)
- 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 subject decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The Treating Investigator should contact the subject to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made, with an explanation of why the subject is withdrawing from the study.

6.9.1. **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 up to 6 years from enrollment.

6.10. 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 subjects. 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.

6.10.1. **Elotuzumab Infusion Reactions**

The first dose of elotuzumab will be administered following pre-medications to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5mL per minute (30 mL/hour). If the subject does not have an infusion reaction within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an infusion reaction within 30 minutes, escalate the infusion rate to a maximum of 2 mL per minute (120 mL/hour).

The second dose of elotuzumab should be initiated at an infusion rate of 3 mL per minute if no infusion reactions were reported with the first elotuzumab infusion. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate by 1.0 mL per minute to a maximum infusion rate of 4 mL per minute.

The third and fourth dose of elotuzumab should be initiated at an infusion rate of 5 mL per minute if no infusion reactions were reported with previous elotuzumab infusions.

Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

Grade 1 Infusion Reaction: Grade 1 elotuzumab infusion-related reactions by definition do not require intervention; however, increased monitoring is recommended

Grade 2 or 3 Infusion Reaction: Infusion reactions during the elotuzumab infusion: For a Grade 2 or 3 elotuzumab infusion-related reactions, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or

interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred. If no recurrence of the infusion reaction, the escalation regimen can be resumed. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 1 or 2 hours after the end of the elotuzumab infusion (as clinically indicated). If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication.

Infusion reactions after the completion of elotuzumab infusion: Should a Grade 2 or 3 infusion reaction occur following the completion of an elotuzumab infusion, the subject should be treated as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodialators, or other supportive measures as indicated.

Elotuzumab infusions on subsequent weeks after a prior Grade 2 or 3 infusion reaction: Subjects with a prior Grade 2 or 3 infusion reactions should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred. If no Grade ≥2 infusion reaction occurs, the escalation regimen may be resumed, and the next infusion may be initiated as planned per regimen.

Grade 4 Infusion Reaction: Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued.

6.10.2. 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 6.3.2). 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.

6.10.3. Tumor Lysis Syndrome

TLS, which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some subjects with MM who have been treated with carfilzomib. All subjects should follow the hydration guidelines outlined in Section 6.3.2. 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. 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.

6.10.4. **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 6-7 for guidance regarding dose reduction in subjects with compromised renal function.

7. SAMPLES FOR MRD EVALUATION AND CORRELATIVE STUDIES

Bone marrow samples for MRD evaluation are required and as per the standard of care and will be collected prior to initiation of treatment (screening), at the completion of 4 (non-SOC for subjects who do not continue to ASCT), 8, 12, and 18 (for subjects who are MRD+ at the end of C8 but MRD- at the end of C12 only) cycles of E-KRd, 24 months after C1D1 for all subjects, and then yearly or at the time of near complete response (nCR determination is not possible, then VGPR will be used to trigger a bone marrow biopsy. A Bone Marrow Biopsy to confirm nCR or VGPR will not be required if the subject is within 2 months of a landmark BMBX timepoint) if more than 2-3 months from scheduled evaluation, and/or progression/relapse.

MRD evaluation will be done centrally at the University of Chicago (by Flow) and at Adaptive Biotechnologies (by NGS). For this purpose, two BM samples must be shipped at each timepoint.

Additionally, provided that the subject consents, correlative samples will be collected and banked for further research studies.

Shipping locations will be as follows:

Samples Shipped to University of Chicago Hematology Lab:

- Screening, cycle 4, cycle 8, cycle 12, cycle 18 (when applicable), 24 months after C1D1, yearly after that, and at the time of nCR (or VGPR if nCR determination is not possible)

Samples Shipped to Adaptive Biotechnologies directly:

- End of cycle 12 for quick turnaround for treatment decision

Samples Shipped to University of Chicago MM lab:

- Screening, cycle 4, cycle 8, cycle 18 (when applicable), 24 months after C1D1, yearly after that,, and the time of nCR, or VGPR when nCR determination is not possible (MRD only for batch shipping to Adaptive)
- Screening, cycle 4, cycle 8, cycle 12, cycle 18 (when applicable), 24 months after C1D1, and at the time of nCR, or VGPR when nCR determination is not possible (all correlative samples)

Shipment time points are outlined below.

Table 7-1 MRD and correlative sample shipment schema

MRD sample	Correlative Sample	Time Points
Bone Marrow Aspirate	Bone Marrow Aspirate	Screening/Pre-treatment, after 4, 8 and 12, and 18 (when applicable) cycles, 24 months after C1D1,, yearly after that, and at the time of near complete response (or VGPR if nCR determination is not possible) Progression/Relapse*
	Peripheral Blood	
	Plasma/Serum	
	Buccal Swab	Screening only

* Correlative sample only

All bone marrow procedures, except end of cycle 4 for subjects who do not go into ASCT (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) and MRN
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 to the University of Chicago Hematology lab (for MRD by flow)

1. Specimens should be delivered to the Hematology Laboratory within 24 hours of collection.
2. The delivery information should be on the outside of package.
3. Specimens cannot be accepted on Saturday or Sunday. NO FRIDAY SHIPMENTS PLEASE
4. Packages should be delivered to:

Julie Leanse, MS, MT (ASCP)
Hematology Laboratory
Room TW-051 / MC0008
5841 S. Maryland Ave.
Chicago, IL 60637
Phone: 773-702-1314

Shipping Instructions to the University of Chicago MM lab (for batch shipping to Adaptive and correlative samples):

1. An inventory sheet including a complete list of samples shipped (subject number and MRN, 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 773-702-9268
Email: myeloma-lab@bsd.uchicago.edu

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

8. ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***nonserious adverse event*** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events deemed to be related to study drug combination should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Unexpected AEs

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 also 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 considered 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 subject'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

All SAEs will be collected by the UC CRA and reviewed by the Lead Principal Investigator. Only those determined to be SUSARs by the Lead Principal Investigator will be distributed to all participating sites (using the completed MedWatch 3500 form). To ensure subject safety, each serious adverse event must be reported to the Lead Principal Investigator and the University of Chicago Comprehensive Cancer Center via paper submission via fax or email within 24 hours of learning of its occurrence. 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 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 IRB in accordance with local regulations. Additionally, the Lead Principal Investigator is responsible for reporting SAEs to BMS and Amgen as described in section 8.4.

8.3.1. **Serious Adverse Event Definition**

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- 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 insubject 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.
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

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 MUST be reported to the Lead Principal Investigator and to the University of Chicago Comprehensive Cancer Center (UC CCC), via 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-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 to the University of Chicago

Use the UC CCC protocol number and the protocol-specific subject 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 occurring at the University of Chicago as well as other sites, 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 and other US sites, according to regulations (see below).

The responsible Research Nurse or other designated individual at the treating site 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 unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event.

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 University of Chicago

The designated UC CCC Regulatory Manager will notify all participating sites of all SUSARs that occur on this clinical trial and which are reported to the UC Institutional Review Board (IRB). A copy of the completed Form 3500 (MedWatch) will be distributed to all participating sites.

8.4. Expedited Reporting by the Lead Principal Investigator to BMS and Amgen

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

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 to Bristol-Myers Squibb (BMS)
The Overall PI, as study sponsor, will be responsible for all communications with the BMS. With the exception of any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. The written report must be completed and supplied to BMS by facsimile or e-mail within 24 hours of Lead Principal Investigator knowledge of the event

- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (ie, CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (eg, delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs, laboratory tests, and other assessments.
- The Investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (worldwide.safety@bms). Frequency of reconcilliation should be on a quarterly basis and prior to the database lock or final data summary. BMS GPV&E will email upon request from the Investigator, the GPV&E reconcilliaton report. Requests for reconcilliation should be sent to aebusinessprocess@bms.com. The data elements listed on the GPV&E reconcilliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 60 days of discontinuation of dosing must be reported to BMS Worldwide Safety. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

SAE Reporting 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 of Lead Principal Investigator knowledge of the event.

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 subject identifiers (e.g., initials, subject 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. 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. 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. IRBs. The Lead Principal Investigator will support reconciliation of all ICSRs at the end of the study at a minimum.

The Amgen protocol number **(ISS # 20167383)** and the institutional protocol number should be included on SAE reports to Amgen.

Amgen Safety Contact Information:

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.

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 BMS and Amgen using expedited reporting procedures listed in Section 8.4 and 8.4.1.

Pregnancy Reporting by Lead Principal Investigator to BMS

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g. dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide.safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

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. Elotuzumab

9.1.1. Description

Elotuzumab (BMS- 901608; formerly known as HuLuc63) is a humanized recombinant monoclonal IgG1 antibody product directed to human CS1 (CD2-subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein that is highly expressed in MM cells.

9.1.2. Form

Elotuzumab for injection has been developed to be used as an intravenous (IV) infusion for the clinical studies. The drug product will be reconstituted prior to administration.

Product Description / Class and Dosage Form	Potency	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 mg/vial or 300mg/vial	Open Label	20 mL Vial/ Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2°C - 8°C

9.1.3. Storage and Stability

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

The lyophilized elotuzumab drug product should be stored at 2° to 8° C. Prior to administration the drug product must be reconstituted with Sterile Water for Injection, USP, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in section 9.1.6. After the dose is diluted in normal saline, it must be administered within 8 hours if stored at room temperature. If a delay is anticipated, the prepared dose may be refrigerated at 2° to 8° C for up to 24 hours. If stored under refrigerated conditions, the prepared study drug solution should be equilibrated to room temperature (process takes 2 - 2.5 hours) and the container must be gently inverted to mix well before administration. Do not use the accelerated warming method. If administration is delayed beyond the specified time, the prepared dose solution must be discarded, and the reason documented by the pharmacist in study drug accountability records.
The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg. The subject's pre-dose weight at screening will be used to calculate the dose for each cycle, unless there is a change in weight of ≥10%. Each dose should be infused as per instructions in Section 6.3.

9.1.4.**Handling**

The lyophilized elotuzumab drug product should be stored at 2° to 8°C. Prior to administration the drug product must be reconstituted with Sterile Water for Injection, USP, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Section 9.1.6.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

9.1.5.**Availability**

Bristol-Myers Squibb will supply elotuzumab. Elotuzumab is an investigational agent and will be supplied free-of- charge. Drug will be shipped to the pharmacy at the study site.

9.1.6.**Preparation**

Elotuzumab for Injection, 400 mg/vial and Elotuzumab for Injection, 300 mg/vial.

Each vial of Elotuzumab for Injection, 400 mg/Vial and Elotuzumab for Injection, 300 mg/Vial should be reconstituted with sterile water for injection (SWFI) at the clinical compounding site. The lyophilized powder should dissolve in less than 10 minutes. Once the reconstitution is completed, withdraw 16 mL from the 400 mg/vial presentation or 12 mL from the 300 mg/vial presentation for dilution with 0.9% sodium chloride injection (NS) to result in an elotuzumab concentration from 1.0 mg/mL to no higher than 6.0 mg/mL in a polyvinyl chloride or polyolefin infusion bag. Five percent (5%) Dextrose injection (D5W) may be used as a diluent in place of 0.9% sodium chloride injection. During drug product preparation, vigorous mixing or shaking is to be avoided. The infusion is to be administered through a sterile, non-pyrogenic, low protein binding in line filter (with a pore size of 0.2-µm to 1.2-µm) using an automated infusion pump. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain anti-microbial preservatives or bacteriostatic agents. A sufficient excess of drug product is included in each vial to account for withdrawal losses.

The infusion of the reconstituted and diluted solution of elotuzumab for injection prepared for dosing must be completed within 24 hours of reconstitution. If not used immediately, the infusion solution may be stored under refrigeration conditions, 2ºC to 8ºC (36ºF to 46ºF), and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours can be at room temperature, 20ºC to 25ºC (68ºF to 77ºF), and room light). The drug solution should be equilibrated to room temperature and the container must be gently inverted to mix well before administration.

9.1.7. **Administration**

Elotuzumab will be given cycle 1 & 2 at 10 mg/kg IV once a week (days, 1, 8, 15, and 22) in 28-day cycles.

From cycle 3 and beyond, elotuzumab will be given at 10mg/kg IV every two weeks (days 1 and 15) in 28-day cycles.

Elotuzumab should be initiated at an infusion rate of 0.5 mL per minute. If well tolerated, the infusion rate may be increased in a stepwise fashion as described in Table 5. The maximum infusion rate should not exceed 5 mL per minute. Please refer to section 6.3.1 for full infusion rate details for elotuzumab.

9.1.8. **Ordering**

The investigator or designee will order drug from Bristol-Myers Squibb, according to the ordering instructions provided by company.

9.1.9. **Accountability**

The investigator, or designee, is responsible for taking an inventory of each shipment of elotuzumab received, and comparing it with the accompanying accountability form. The Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study fill. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

9.1.10. **Destruction and Return**

IMP (those supplied by the sponsor or sourced by the site/investigator) are ideally to be destroyed on site. It is the Investigator's responsibility to ensure that arrangements have been made for the destruction, procedures for proper destruction have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the destruction have been documented. The unused IMPs can only be destroyed after being inspected and reconciled by the responsible site monitor.

Ideally used IMP should not be returned to the Sponsor but destroyed on site. All unused and/or partially used IMP may be destroyed on site providing the site has an appropriate standard operating procedure on file.

If required by local country/hospital regulations IMP can be returned to a BMS off-site IMP destruction vendor, but this should only be arranged by your site monitor. All IMP destruction must be documented. If on-site destruction occurs, then a Confirmation of Destruction must be available at the site, in accordance with the local laws, regulations and institutional requirements. If IMP is returned for destruction off site, the Investigational Product Return Form acts as the destruction certificate. All related documentation must be filed.

9.2. **Carfilzomib**

9.2.1. **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.

9.2.2. **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®).

9.2.3. **Storage**

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

9.2.4. **Accountability**

Amgen, Inc. 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.

9.3. **Lenalidomide**

9.3.1. **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.

9.3.2. **Supply**

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

9.3.3. **Storage Conditions**

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

9.3.4. **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.

9.3.5. Prescribing Information

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

9.3.6. Special Handling Instructions

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

9.4. Dexamethasone

Dexamethasone may be given IV or PO

9.4.1. 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.

9.4.2. Formulation

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

9.4.3. Storage conditions

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

9.4.4. 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

- The primary efficacy endpoint will be the rate of sCR and/or the rate of negative MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) at the end of 8 cycles among non-transplant candidates and transplant candidates who agreed to defer transplant

10.1.2. Secondary Objectives

- To evaluate the safety and tolerability of elotuzumab in combination with KRd, when administered to subjects with newly diagnosed multiple myeloma
- Rate of MRD by next generation gene sequencing (NGS) by clonoSEQ (Adaptive Biotechnologies) and by multi-color flow cytometry (MFC) at the end of Cycles 4, 8, 12, and 18 (for subjects who are MRD+ at the end of C8 but MRD- at the end of C12), 24 months after C1D1, and yearly after that.
- Estimate time to event, including duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS).

10.1.3. **Exploratory Objectives**

- GEP, proteomics, and gene sequencing to evaluate the correlation between treatment outcome and pre-treatment subject profile.
- Immunologic correlative studies including FcγRIIIa V genotype.

10.2. **Sample Size Justification & Analysis Plan**

A total of 40, non-transplant candidates, and/or transplant candidates who agreed to defer transplant will be enrolled. Since the study does not plan to exclude transplant candidates who do not wish to defer transplant, an additional 15 subjects who discontinue E-KRd treatment and proceed to transplant are planned to be enrolled to generate additional tolerability and toxicity data, which will bring a total number of subjects to be enrolled to 55. Subjects that continue to transplant will be removed from the study and censored at the end of 4 cycles. These subjects will not be followed up or further analyzed

10.2.1. **Primary Objective Sample Size Justification**

The primary endpoint is the sCR rate and/or the rate of MRD-negativity after 8 cycles of therapy. The rate of sCR for KRd treatment is established as the primary reference endpoint for statistical considerations by robust data (Jakubowiak et al., 2012b) Recognizing that the measurement of sCR has technical challenges when involving elotuzumab – which are anticipated to be resolved by the time it is needed – a co-primary endpoint of MRD-negative status by NGS is included in the primary efficacy assessment. This is based on the close correlation between MRD-negative status and sCR rate established in the ongoing KRd+transplant study (Jakubowiak et al. EHA 2016, Zimmerman et al. ASH 2016, both oral presentations). This primary endpoint incorporates also the new definition of MRD status, which requires sCR to confirm MRD negativity (Kumar et al., 2016). Therefore, an improvement from historical 30% (which is the sCR rate and the estimated MRD-negative rate by NGS in the KRd study without elotuzumab (Jakubowiak, 2016)) to 50% or higher sCR and/or MRD-negative status at the completion of 8 cycles, would be considered promising.

For 40 non-transplant candidates and/or transplant candidates who agreed to defer transplant, we will test the null hypothesis that the sCR and/or negative MRD status by NGS rate after 8 cycles is,≤30% against the alternative that it is,>30% using an exact one-sided binomial test at the alpha=0.10 significance level. The null hypothesis will be rejected if 17 or more sCR's and/or MRD-negative's responses are observed (≥42.5%). The sample size of n=40 response evaluable subjects provides a little over 85% power if the true sCR and/or negative MRD status rate by NGS is 50%. The sample size is selected to also allow for collection of sufficient data for toxicity and tolerability evaluation of the E-KRd regimen. The frequency of adverse events will be summarized by type, grade, and attribution to the study drugs.

10.2.2. **Secondary Objective Sample Size Justification**

Since the rate of MRD-negative disease by NGS methodology at the end of 8 cycles is not established at this time, based on the ongoing evaluations, a rate of NGS MRD-negative disease of 50% or higher after 8 cycles will be considered promising. The rate of successful MRD testing at landmark time points (i.e, after cycles 4, 8, 12, 18 –when applicable- 24 months after C1D1, yearly after that, and/or when nCR is suspected), the rate of VGPR or better, and the rate of near complete responses or better will be estimated along with 90% confidence intervals. DOR, PFS, TTP, and OS will be estimated by the Kaplan-Meier method (Kaplan and Meier, 1958). DOR will be defined as the length of the interval from response to disease progression among responders. PFS will be defined as the time from first dose until disease progression or death from any cause. Subjects alive and without progression will be censored as of the date of the last negative exam.

TTP analyses will be similar to PFS except that subjects who die without a prior disease progression will be censored at the time of death. OS will be calculated as the time from first dose until date of death or date last known alive. In addition to the Kaplan-Meier curves, we will estimate the median time to event and 90% confidence intervals using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). The study population for PFS, TTP, and OS will be all subjects who receive at least one dose of study drug. The study population for DOR will be subjects who have responded to therapy.

Among all 55 subjects enrolled in the trial, including those who proceed to transplant, we will test the hypothesis that the sCR rate at the end of 4 cycles improves from a historical 8% rate to a higher value, using an exact binomial test at the 0.10 one-sided significance level. The total sample size of n=55 subjects will provide 85% power if the true rate is 19%, and the null hypothesis (≤8% rate) will be rejected if 8 or more of the 55 subjects respond. However, any subject who undergoes transplant prior to 4 cycles will be excluded, and the corresponding exact binomial test performed on the reduced sample size. (Thus, for example, if 6 subjects undergo transplant prior to 4 cycles, only 7 responders among the 49 would be needed to reject the null hypothesis.)

10.2.3. **Exploratory Objectives**

The association of exploratory biomarkers (GEP, proteomics, gene sequencing, and immunologic correlates) with outcomes will be analyzed using logistic regression for binary outcomes and Cox regression modeling for time-to-event endpoints (Cox, 1972).

11. DATA REPORTING

Data reporting will be performed utilizing the eVelos electronic data capture system for all subjects. The University of Chicago CRA will provide the applicable user registration information for all sub-sites.

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 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).

All case report forms must be completed by designated study personnel. Each screened subject (signed informed consent) is to be entered into eVelos within 48 hours of subject registration. In addition to direct data entry, providing supporting documentation is required as per Subject 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. Informed Consent

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

The Lead PI will provide all Site Investigators 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, subjects 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.

12.2. Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local health law and authority, and Institutional Review Board (IRB) requirements.

This study must have the approval of a properly constituted IRB. Before the investigational drug is shipped to the Site Investigator, the Lead Principal Investigator or designee will provide BMS and Amgen with a copy of the IRB 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 re-approval throughout the duration of the study, when necessary.

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

BMS will provide the Lead Principal Investigator with any expedited safety reports generated from any ongoing studies with elotuzumab, changes to the Investigator's Brochure, and any other safety

information which changes the risk/benefit profile of elotuzumab during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB, participating sites, and other Investigators participating in the study, when necessary.

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 IRB, participating sites, and other Investigators participating in the study, when necessary.

Upon completion of the trial, the Lead Principal Investigator must provide the IRB, BMS and Amgen with a summary of the trial's outcome.

12.3. 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 reviews, and FDA inspections. Identifiable data will be shared by the following collaborator: Adaptive Biotechnologies (to allow an IDE annual report to FDA).

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

12.4. 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 or designee are responsible for distributing all official protocols, amendments, and Unexpected Event Safety Reports to all participating institutions for submission to their applicable local IRBs as required.

13. ADMINISTRATION AND LEGAL OBLIGATIONS

13.1. Institutional Review Board (IRB) Approval and Consent

The investigator-sponsor will obtain, from the University of Chicago Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator-sponsor will promptly notify the University of Chicago IRB of the deviation.

The University of Chicago IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

Unless otherwise specified, each participating institution must obtain approval from a valid IRB before enrolling subjects on this study. It is expected that the IRB will have the proper representation and function in accordance with valid mandated regulations. The IRB 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 subject 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 regulations and local or state regulations. Once this essential information has been provided to the subject and the Treating Investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject 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' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the University of Chicago's Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

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

13.2. Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Dr. Andrzej Jakubowiak at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

13.3. Required Documentation

Before the study can be initiated at any 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.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation

- 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.

13.4. Protocol Amendments and Study Termination

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

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB 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 can authorize any modifications, amendments, or termination of the protocol.

13.4.1. Amendments to the Protocol at sub-Sites

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 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 header and/or 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.

13.5. Study Documentation and Archive

13.5.1. 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 will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report forms.

13.5.2. **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 subject 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 Study Lead Principal Investigator. 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 13.5.4), whichever is longer.

13.5.3. **Case Report Form Completion**

The data collected for this study will be entered into a secure database eCRF. The Lead PI will provide the applicable user registration information. Source documentation must be available to support the computerized subject 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 on eCRF completion. This will be done over a teleconference (see section 13.7 on Data Safety and Monitoring).

13.5.4. **Archival of Records**

According to 21 CFR 312.62I, the Lead Principal Investigator 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 Lead Principal Investigator retain these records until 15 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The Lead Principal Investigator must retain protocols, amendments, IRB approvals, copies of the FDA forms, 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.

13.6. **Clinical Monitoring Procedures**

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.

University of Chicago will be responsible for monitoring all sites and it 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

13.6.1. **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 subjects. 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.

13.6.2. **Protocol Deviations**

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu.

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) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB according to their policies and procedures.

13.7. **Data Safety and Monitoring**

Prior to subject recruitment, and unless otherwise specified, any participating 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.

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

Unless otherwise specified, this protocol will undergo bi-weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-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

13.8. **Quality Assurance & Auditing**

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of Investigator-initiated clinical trials 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 sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

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

REFERENCES

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.

Avet-Loiseau, H., Corre, J., Lauwers-Cances, V., Chretien, M. L., Robillard, N., Leleu, X., Hulin, C., Gentil, C., Arnulf, B., Belhadj, K.*, et al.* (2015). Evaluation of Minimal Residual Disease (MRD) By Next Generation Sequencing (NGS) Is Highly Predictive of Progression Free Survival in the IFM/DFCI 2009 Trial. Blood *126*.

Berenson, J. R., Cartmell, A., Bessudo, A., Lyons, R. M., Harb, W., Tzachanis, D., Agajanian, R., Boccia, R., Coleman, M., Moss, R. A.*, et al.* (2016). CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. Blood *127*, 3360-3368.

Boles, K. S., and Mathew, P. A. (2001). Molecular cloning of CS1, a novel human natural killer cell receptor belonging to the CD2 subset of the immunoglobulin superfamily. Immunogenetics *52*, 302-307.

Boles, K. S., Stepp, S. E., Bennett, M., Kumar, V., and Mathew, P. A. (2001). 2B4 (CD244) and CS1: novel members of the CD2 subset of the immunoglobulin superfamily molecules expressed on natural killer cells and other leukocytes. Immunol Rev *181*, 234-249.

Brookmeyer, R., and Crowley, J. (1982). A Confidence-Interval for the Median Survival-Time. Biometrics *38*, 29-41.

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.

Cox, D. R. (1972). Regression Models and Life-Tables. J R Stat Soc B *34*, 187-+.

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.

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.

Dytfeld, D., Griffith, K. A., Friedman, J., Lebovic, D., Harvey, C., Kaminski, M. S., and Jakubowiak, A. J. (2011). Superior overall survival of patients with myeloma achieving very good partial response or better to initial treatment with bortezomib, pegylated liposomal doxorubicin, and dexamethasone, predicted after two cycles by a free light chain- and M-protein-based model: extended follow-up of a phase II trial. Leuk Lymphoma *52*, 1271-1280.

Harousseau, J. L., Palumbo, A., Richardson, P. G., Schlag, R., Dimopoulos, M. A., Shpilberg, O., Kropff, M., Kentos, A., Cavo, M., Golenkov, A.*, et al.* (2010). Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood *116*, 3743-3750.

Hsi, E. D., Steinle, R., Balasa, B., Szmania, S., Draksharapu, A., Shum, B. P., Huseni, M., Powers, D., Nanisetti, A., Zhang, Y.*, et al.* (2008). CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Clin Cancer Res *14*, 2775-2784.

Jakubowiak, A. J., Benson, D. M., Bensinger, W., Siegel, D. S., Zimmerman, T. M., Mohrbacher, A., Richardson, P. G., Afar, D. E., Singhal, A. K., and Anderson, K. C. (2012a). Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. J Clin Oncol *30*, 1960-1965.

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.* (2012b). 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. R., N; Vij, R; Reece, D; Berdeja, J; Vesole, D; Jagannath, S; Cole, C; Faham, M; Nam, J; Stephens, L; Severson, E; Revethis, A; Wolfe, B; Rosebeck, S; Gurbuxani, S; Rosenbaum, C; Jasielec, J; Dytfeld, D; Griffith, K; Zimmerman, T (2016). Improved Efficacy After Incorporating Autologous Stem Cell Transplant (ASCT) into KRd Treatment with Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (DEX) in Newly Diagnosed Multiple Myeloma. Haematologica *Abstract S101*, 1-2.

Kaplan, E. L., and Meier, P. (1958). Nonparametric-Estimation from Incomplete Observations. J Am Stat Assoc *53*, 457-481.

Korde, N., Roschewski, M., Zingone, A., Kwok, M., Manasanch, E. E., Bhutani, M., Tageja, N., Kazandjian, D., Mailankody, S., Wu, P.*, et al.* (2015). Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. JAMA Oncol *1*, 746-754.

Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Blade, J., Mateos, M. V.*, et al.* (2016). International Myeloma Working Group consensus criteria

for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol *17*, e328-346.

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.

Lonial, S., Dimopoulos, M., Palumbo, A., White, D., Grosicki, S., Spicka, I., Walter-Croneck, A., Moreau, P., Mateos, M. V., Magen, H.*, et al.* (2015). Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med *373*, 621-631.

Moreau, P. (2012). A randomized phase II study of elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. J Clin Oncol *30*.

Moreau, P., Richardson, P. G. G., Jakubowiak, A. J., Jagannath, S., Raab, M., Facon, T., Vij, R., Reece, D. E., White, D., Benboubker, L.*, et al.* (2012). A randomized phase II study of elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. Journal of Clinical Oncology *30*.

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.

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.

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.

Tai, Y. T., Dillon, M., Song, W., Leiba, M., Li, X. F., Burger, P., Lee, A. I., Podar, K., Hideshima, T., Rice, A. G.*, et al.* (2008). Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. Blood *112*, 1329-1337.

Tassi, I., and Colonna, M. (2005). The cytotoxicity receptor CRACC (CS-1) recruits EAT-2 and activates the PI3K and phospholipase Cgamma signaling pathways in human NK cells. J Immunol *175*, 7996-8002.

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 subjects 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 subjects 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 subjects 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 subjects 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 subjects 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 subjects 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 subjects 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: Revlimid Prescribing and REMS information

Revlimid Risk Evaluation and Mitigation Strategy (REMS)™ Program

http://www.revlimidrems.com/pdf/REV_Prescriber_Guide.pdf

Revlimid Prescribing Information 2013

http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=5fa97bf5-28a2-48f1-8955-f56012d296be&type=pdf&name=5fa97bf5-28a2-48f1-8955-f56012d296be

APPENDIX 6: SCHEDULE OF EVENTS

Assessment	**Screening**	**Cycles 1-2**				**Cycles 3-8**				**Cycles 9-12, 9-18 or 9-24**				**End of Cycle 4**	**End of Cycle 8**	**End of Cycle 12**	**24 mo after C1D1 and yearly x4**	**Cycles 13+, 19+, or 25+ (after end of E-KRd)**				**EOT**[25]	**LTFU**[26,27]
Day	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**					**1**	**8**	**15**	**22**		
Informed Consent[1]	X																						
Demographics and Medical History[2]	X																						
Skeletal Survey[3]	X																						
CT/PET[28]	X														(X)	(X)	X					X	
ECG[4]	X																						
Echocardiogram[5]	X																						
Physical Exam/ ECOG[6]	X	X				X				X								X				X	
Vital Signs[7]	X	X	X	X	X	X	X	X		X		X						X				X	
Hematology[8]	X	X	X[8]	X[8]		X	X	X		X		X						X				X	
Serum Chemistry[9]	X	X	X[9]	X[9]		X	X	X		X		X						X				X	

Assessment	Screening	Cycles 1-2				Cycles 3-8				Cycles 9-12, 9-18 or 9-24				End of Cycle 4	End of Cycle 8	End of Cycle 12	24 mo after C1D1 and yearly x4	Cycles 13+, 19+, or 25+ (after end of E-KRd)				EOT[25]	LTFU[26,27]
Day	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**					**1**	**8**	**15**	**22**		
Pregnancy Test[10]	X	X		(X)[10]	(X)[10]	X				X								X				X	
Disease Assessment[11]																							
β2-microglobulin	X																						
SPEP and IFIX[12]	X	X		X[12,13]		X				X								X				X	
24 hour Urine: UPEP and IFIX[13;14]	X	X		X[14]		X				X								X					
SFLC	X	X		X		X				X								X				X	
Quantitative IgGs	X	X		X		X				X								X				X	
BM Aspirate/ biopsy, cytogenetics, FISH[15]	X													X	X	X	X					X	X
BM aspirate sample for MRD analysis[16]	X													X	X	X	X					X	X
Correlative Samples[17]	X													X	X	X	X					X	

Assessment	Screening	Cycles 1-2				Cycles 3-8				Cycles 9-12, 9-18 or 9-24				End of Cycle 4	End of Cycle 8	End of Cycle 12	24 mo after C1D1 and yearly x4	Cycles 13+, 19+, or 25+ (after end of E-KRd)				EOT[25]	LTFU[26,27]
Day	**-21 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**					**1**	**8**	**15**	**22**		
Adverse Events[18]		X																					
Treatment Schedule																							
Elotuzumab[19]		X	X	X	X	X		X		X		X						X					
Carfilzomib[20]		X	X	X		X	X	X		X		X											
Lenalidomide[21,22]		Days 1-21																					
Dexamethasone[23,24]		X[23]	X[23]	X[23]	X[23]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]	X[24]					X[24]	X[24]	X[24]	X[24]		

(X) As clinically indicated

1. Informed consent may be obtained within 30 days of start of treatment but must be obtained prior to any research-related activity
2. Includes baseline symptoms, neuropathy history and documentation of the CTCAE grade if peripheral neuropathy is present at baseline.
3. May be within 3 months 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 30-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 ≥ 50%. 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). Symptom-directed Physical Exam on Days 8, 15, (and 22 on cycles 1-2)
7. Systolic and diastolic blood pressure, pulse, respiration, temperature before and after elotuzumab infusion and approximately 1 hour before carfilzomib dosing on days where only carfilzomib is dosed.
8. Hemoglobin, WBC with complete differential, RBCs, platelet count, absolute neutrophil and lymphocyte counts. Results must be reviewed before dosing. On cycles 1-8, these tests will be required on days 1, 8, and 15 prior to infusion and on cycles 9+ they will be required on days 1 and 15 prior to infusion.
9. Full serum chemistry panel at screening, days 1, 8, and 15, and EoT for all subjects: sodium, potassium, chloride, creatinine, glucose, uric acid, phosphorus, magnesium, LDH, total bilirubin, C-Reactive Protein. Results must be reviewed before dosing. On cycles 1-8, these tests will be required on days 1, 8, and 15 prior to infusion and on cycles 9+ they will be required on days 1 and 15 prior to infusion.
10. 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. When applicable, females must have a pregnancy test at the EoT.
11. 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 1 Day 15 and on D1 of every cycle onwards.
12. 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. SPEP is required on Cycle 1 Day 15 for all subjects. A serum sample from blood at landmark timepoints (after C4, 8, 12, and 18, 24 months after C1D1, and yearly after) will be required for banking at the University of Chicago for later M-spike analysis with a new elotuzumab interference assay. BMS will perform this assay on banked samples, using using Mass Spectrometry.
13. Urine protein electrophoresis (UPEP), and urine protein immunofixation (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. For subjects whose disease is being monitored through UPEP, additional post baseline 24-hour urine collections are required as indicated. UPEP is required on Cycle 1 Day 15 for all subjects.

14. 24 hour urine is required on Cycle 1 Day 15 for all subjects.
15. 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 nCR (or VGPR when nCR determination is not possible) is suspected and as appropriate to confirm achievement of sCR, CR, or nCR. Bone marrow biopsy/aspirate performed outside of the 30-day window may be considered for inclusion. Please contact the Lead Principal 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.
16. All subjects are required to have a sample for MRD collected at screening, end of cycles 4, 8 12, 18 (if MRD+ at C8 but MRD- at C12), 24 months after C1D1, yearly after that, and at any other time a Bone Marrow biopsy/aspirate is collected as SOC. If nCR (or VGPR if nCR determination is not possible) is recorded between screening and EoT, a Bone Marrow Biopsy can be indicated. However, if nCR (or VGPR when nCR is not possible) is suspected within 2 months of a scheduled BM per protocol, it is acceptable to wait for the scheduled BM biopsy. Refer to lab manual for collection and shipping instructions. Central analysis includes MRD by multiparameter flow cytometry and MRD by gene sequencing. Non-decalcified FFPE or BMA slides from the subject at screening can be provided alternatively to fresh BM for calibration of MRD by gene sequencing.
17. For subjects who sign additional consent: peripheral blood and bone marrow aspirate samples collected at screening, end of cycle 4, 8, 12, and 18, 24 months after C1D1, yearly after that, and any time after enrollment that nCR or better is suspected or a BM is performed per protocol. Buccal mucosa swab will be collected at screening only. Please see the lab manual for specific instructions
18. AEs will be collected from the time of first study drug treatment through 30-days after end of study treatment.
19. Elotuzumab will be given IV at 10mg/kg weekly in 28-day cycles in cycles 1 and 2 starting on cycle 1 day 1. In cycles 3+, elotuzumab will dosed IV at 10mg/kg every two weeks in 28-day cycles starting on cycle 3 day 1. Refer to section 6.3.1 for elotuzumab infusion rates.
20. Carfilzomib days 1, 8, and 15 of cycles 1-8 and 1 and 15 of cycles 9+ at assigned dose. Cycle 1 step-up dosing is required: 20mg/m^2 Day 1; 56mg/m^2 Day 8; 56mg/m^2 Day 15. On Cycle 2 day 1, the dose of carfilzomib will be escalated to 70mg/m^2 and will continue to be dosed at this level. Hydration directions from section 6.3.2 must be followed
21. 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 subject and prescriber surveys, and drug shipment to subject.

22. Lenalidomide dosing Days 1-21. Cycles 1-8 Lenalidomide will be administered at 25 mg. From cycle 9+ Lenalidomide will be administered at best tolerated dose on days 1-21 of a 28-day cycle. Lenalidomide should be taken in the evening at approximately the same time each day.
23. On cycles 1-2, dexamethasone will be split into two doses as follows: 20mg of dexamethasone will be given IV on days 1, 8, and 15 no more than 3 hours prior to elotuzumab infusion and between 30min and 4 hours prior to carfilzomib, and 20mg will be taken PO on days 2, 9, and 16. On Day 22 of cycle 1, 40mg dexamethasone will be taken PO no longer than 3 hours prior to elotuzumab. When dexamethasone, carfilzomib and elotuzumab coincide, dexamethasone will be dosed first, followed by carfilzomib infusion, and finally elotuzumab will be infused.
24. On cycles 3-4 40mg dexamethasone will be taken PO on days 1, 8, 15, and 22. On days when dexamethasone coincides with elotuzumab, dexamethasone will be taken no longer than 3 hours prior to elotuzumab infusion. On days when dexamethasone coincides with carfilzomib, dexamethasone will be taken between 30min and 4 hours prior to carfilzomib infusion. When dexamethasone, carfilzomib and elotuzumab coincide, dexamethasone will be dosed first, followed by carfilzomib infusion, and finally elotuzumab will be infused.On cycles 5+ 20mg dexamethasone will be taken PO on days 1, 8, 15, and 22. On days when dexamethasone coincides with elotuzumab, dexamethasone will be taken no longer than 3 hours prior to elotuzumab infusion. On days when dexamethasone coincides with carfilzomib, dexamethasone will be taken between 30min and 4 hours prior to carfilzomib infusion. When dexamethasone, carfilzomib and elotuzumab coincide, dexamethasone will be dosed first, followed by carfilzomib infusion, and finally elotuzumab will be infused.
25. End of treatment will vary depending on MRD results post cycle 8 and 12. Subjects that are MRD negative after cycle 8 and 12, will go on E-Rd maintenance until disease progression, subjects that are MRD+ after cycle 8 but MRD- after cycle 12, will get another 6 cycles of Elo-KRd and go on E-Rd maintenance until disease progression; and subjects that are MRD+ at both instances will be given another 12 cycles of Elo-KRd and go on E-Rd maintenance until disease progression
26. Subjects will be followed for survival and development of any new cancers, at least every 3 months for up to 6 years from start of treatment. Reports of any death should include date of death and specific cause (disease under study or specify other cause).
27. Assessment for disease progression in subjects who did not progress during treatment. Every 3 months (+/- 30 days) from safety follow-up visit (28 days post-last study treatment or ASCT, if applicable) for up to 6 years from enrollment.
28. A CT-PET must be performed to confirm MRD-negative disease per Standard of Care. Subjects who are MRD-positive do not need PET scans until suspected CR. MRD-negative subjects will undergo a yearly PET until progression. If there is clinical need for assessment at cycles 8 and 12, a CT-PET should be performed at these timepoints as well.