MM 61

A Phase 2 Study to Assess the Feasibility and Tolerance of the Combination of Elotuzumab, Lenalidomide, and Dexamethasone (ERd) in the Induction, Consolidation, and Maintenance Treatment of Transplant-Eligible Patients Newly Diagnosed with Multiple Myeloma (MM)

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	MM 61
BRISTOL-MYERS SQUIBB STUDY NUMBER:	CA204-154
STUDY DRUG:	Elotuzumab
SPONSOR:	Sarah Cannon Development Innovations 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Jesus Berdeja, MD Sarah Cannon Research Institute 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI
DATE FINAL:	10 May 2016
AMENDMENT NUMBER 1:	05 July 2016
AMENDMENT NUMBER 2:	07 December 2016

SARAH CANNON
Development Innovations

Clinical Study Statement of Compliance

A Phase 2 Study to Assess the Feasibility and Tolerance of the Combination of Elotuzumab, Lenalidomide, and Dexamethasone (ERd) in the Induction, Consolidation, and Maintenance Treatment of Transplant-Eligible Patients Newly Diagnosed with Multiple Myeloma (MM)

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **The US Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Clinical Study Signature Approval Page

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	MM 61
BRISTOL-MYERS SQUIBB STUDY NUMBER:	CA204-154
STUDY DRUG(S):	Elotuzumab
DATE FINAL:	10 May 2016
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Jesus Berdeja, MD

Study Chair **Sarah Cannon Research Institute**	**Study Chair Signature**	**Date**

Sheetal Khedkar, MD, MSPH

Sponsor Representative **Sarah Cannon Development Innovations, LLC**	**Sponsor Representative Signature**	**Date**

Clinical Study Principal Investigator Signature Form

A Phase 2 Study to Assess the Feasibility and Tolerance of the Combination of Elotuzumab, Lenalidomide, and Dexamethasone (ERd) in the Induction, Consolidation, and Maintenance Treatment of Transplant-Eligible Patients Newly Diagnosed with Multiple Myeloma (MM)

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

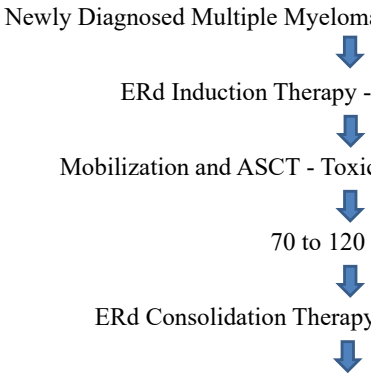
Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Charlotte Avenue, Suite 800
Attention: MM 61 Study Team
Nashville, TN 37203

MM 61 PROTOCOL SYNOPSIS

Title of Study:	A Phase 2 Study to Assess the Feasibility and Tolerance of the Combination of Elotuzumab, Lenalidomide, and Dexamethasone (ERd) in the Induction, Consolidation, and Maintenance Treatment of Transplant-Eligible Patients Newly Diagnosed with Multiple Myeloma (MM)	
Sarah Cannon Development Innovations Study Number:	MM 61	
Bristol-Myers Squibb Study Number	CA204-154	
Sponsor:	Sarah Cannon Development Innovations, LLC, Nashville, Tennessee	
Study Duration:	The total duration of the study is planned to be 2 years for enrollment and up to 3.5 years maximum follow up per patient to complete the full treatment plan.	**Phase of Study:** 2
Study Centers:	This study is planned to be conducted at 8 centers in the United States.	
Number of Patients:	Approximately 53 patients are planned to be enrolled in this study. Recruitment will end when 48 patients are evaluable for the primary endpoint (have completed 4 cycles of induction treatment with ERd and are able to start ASCT).	
Objectives:	**Primary objective** The primary objective of this study is to: • Evaluate the feasibility of using the combination of elotuzumab, lenalidomide, and dexamethasone (ERd) as induction therapy (induction feasibility rate [IFR]) and the ability of the combination to facilitate the start of autologous stem cell transplantation (ASCT) in transplant-eligible patients newly diagnosed with MM. **Secondary objectives** The secondary objectives of this study are to: • Evaluate the efficacy of the combination of ERd as induction, consolidation, and maintenance therapy in transplant-eligible patients newly diagnosed with MM • Evaluate the safety and tolerability of the combination of ERd as induction, consolidation, and maintenance therapy in transplant-eligible patients newly diagnosed with MM. **Exploratory objectives** The exploratory objectives of this study are to: • Determine minimal residual disease (MRD) by multi-parameter-flow cytometry per institutional guidelines • Evaluation of gene expression profiling (GEP) at diagnosis per institutional guidelines and correlation of outcomes.	

MM 61 PROTOCOL SYNOPSIS

Study Design:	This is a multi-center, open-label, Phase 2 study to assess the feasibility and tolerance of the combination of ERd in the induction, consolidation, and maintenance treatment of transplant-eligible patients newly diagnosed with MM according to the following schema: 
Study Drugs, Doses, and Modes of Administration:	**Induction** All patients will undergo four 28-day cycles of the following induction treatments: • Cycles 1 and 2 – Elotuzumab 10 mg/kg IV on Days 1, 8, 15, and 22 – Lenalidomide 25 mg orally on Days 1 through 21 – Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Days 1, 8, 15, and 22. – H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab. • Cycles 3 and 4 – Elotuzumab 10 mg/kg IV on Days 1 and 15 only – Lenalidomide 25 mg orally on Days 1 through 21 – Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Days 1 and 15 – Dexamethasone 40 mg orally on Days 8 and 22 – H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab. **Mobilization and ASCT** If a patient is unable to proceed to transplant, but the treating Investigator believes he/she would benefit from continued study treatment, the patient will be allowed to continue uninterrupted on to consolidation and maintenance without transplant. Toxicity evaluations are suspended during the stem cell procedure. **Consolidation** Consolidation is to begin 70 to 120 days following ASCT. All patients will undergo four 28-day cycles of the following consolidation treatment: • Cycles 5 through 8 – Elotuzumab 10 mg/kg IV on Days 1 and 15 – Lenalidomide 15 mg orally on Days 1 through 21 ▪ Lenalidomide can be escalated as tolerated to the maximum-tolerated dose

	administered during induction.
Study Drugs, Doses, and Modes of Administration (continued):	▪ Lenalidomide can continue with dose unchanged from induction in patients who remain on study, but do not proceed to transplant. – Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab infusion) on Days 1 and 15 – Dexamethasone 40 mg orally on Days 8 and 22 – H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab. **Maintenance** All patients will proceed to 28-day cycles during maintenance to continue for up to 24 months: • Cycles 9+ – Elotuzumab 20 mg/kg IV on Day 1 – Lenalidomide 10 mg ±5 mg orally on Days 1 through 21 – Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Day 1 – H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab. Any patient who comes off elotuzumab for whatever reason, or completes the 24 months of maintenance allowed by the protocol, can continue therapy with FDA-approved therapies at the discretion of the treating physician, but will no longer be on study following their 60-day post maintenance safety follow-up.
Inclusion Criteria:	Patients must meet **all** of the following criteria in order to be included in the research study: 1. Newly diagnosed myeloma requiring systemic chemotherapy as per International Myeloma Working Group (IMWG) uniform criteria (Appendix A) and Diagnostic Criteria and Staging for Multiple Myeloma (Appendix B): – Ideally, no prior therapy, or – No more than 1 cycle of therapy for emergent control of disease prior to enrolling on study, including prior treatment of hypercalcemia, spinal cord compression, or active and/or aggressively progressing myeloma with corticosteroids or lenalidomide or bortezomib-based regimens (the treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period, or not more than 1 cycle) – Bisphosphonates are permitted. 2. Eligible and plan to undergo ASCT in first remission (refer to Section 5.1.2) 3. Measurable disease, prior to initial treatment as indicated by one or more of the following: – Serum M-protein ≥1.0 g/dL – Urine M-protein ≥200 mg/24 hours – Serum free light chain assay: involved free light chain level ≥10 mg/dL (≥100 mg/L) provided the serum free light chain ratio is abnormal.

	4. Males and females ≥18 years-of-age.
Inclusion Criteria (continued):	5. Ability to take aspirin or other venous thromboembolism (VTE) anticoagulant therapy 6. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 through 2 (see Appendix C) 7. Adequate hematologic function defined as: – Absolute neutrophil count (ANC) ≥1.0 x 10^9/L – Hemoglobin (Hgb) ≥8 g/dL – Platelets ≥75 x 10^9/L. Screening platelet count should be independent of platelet transfusions for at least 2 weeks. 8. Adequate liver function defined as: – Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) – Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin) 9. Adequate renal function defined as serum creatinine ≤1.5 x ULN OR calculated creatinine clearance ≥50 mL/min as calculated by Cockcroft and Gault Formula. 10. All study participants must be registered into the mandatory Revlimid REMS® program and must be willing and able to comply with the requirements of that program. 11. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. 12. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 28 days following last dose of study drugs. Male patients must also refrain from donating semen or sperm during their participation in the study. Details of mandatory contraception measures are presented in Appendix E. 13. Willingness and ability to comply with study and follow-up procedures. 14. Ability to understand the nature of this study and give written informed consent.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome 2. Plasma cell leukemia 3. Waldenström's macroglobulinemia or IgM myeloma 4. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated *in situ* carcinoma (i.e., non-invasive) are eligible, as are patients with a history of non-melanoma skin cancer.

	5. Radiotherapy to multiple sites or immunotherapy within 4 weeks before start of protocol treatment (localized radiotherapy to a single site at least 1 week before start is permissible)
Exclusion Criteria (continued):	6. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 7. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose of study treatment 8. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome) 9. Any of the following cardiac diseases currently or within the last 6 months: – Left ventricular ejection fraction (LVEF) <40% as determined by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan – Unstable angina pectoris – Congestive heart failure (New York Heart Association ≥ Grade 2, see Appendix D) – Acute myocardial infarction – Conduction abnormality not controlled with pacemaker or medication – Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible) – Valvular disease with significant compromise in cardiac function. 10. Known seropositive for or active viral infection with human immunodeficiency virus or hepatitis A, B, or C virus. Patients who are seropositive because of hepatitis B virus vaccine are eligible. 11. Any clinically significant medical disease or condition that, in the treating Investigator's opinion, may interfere with protocol adherence or a patient's ability to give informed consent 12. Pregnant or lactating females 13. Contraindication to any of the required concomitant drugs, including dexamethasone, H_1 and H_2 blockers, and acetaminophen, or if patient has a history of prior thrombotic disease, warfarin or low molecular weight heparin 14. No health coverage, or if the copay for lenalidomide is not acceptable to the patient 15. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
Correlative Studies:	Bone marrow aspirates collected as standard of care will be used for MRD analysis and GEP to correlate with response. Minimal residual disease analysis will be conducted per institutional guidelines at any

	time bone marrow is collected as standard of care. Gene expression profiling will be conducted per institutional guidelines on bone marrow collected as standard of care at diagnosis.
Statistical Considerations:	In order to test the null hypothesis of an IFR of 65% versus an alternative hypothesis with an IFR of 80%, 48 patients are required in order to have 85% power to test the null hypothesis using a one-sided exact binomial test at the 0.1 significance level. To allow for a possible 10% drop-out rate the sample size has been inflated to 53 patients. Primary endpoint: • IFR, defined as the percentage of patients successfully completing 4 cycles of induction treatment with ERd and able to start ASCT. Secondary endpoints: • Complete response rate (CRR), defined as the percentage of patients who achieve a complete response (CR) or near complete response (nCR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and European Group for Blood and Marrow Transplantation (EBMT) criteria • Overall response rate (ORR), defined as the percentage of patients who achieve at least a partial response (PR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and EBMT criteria • Progression-free survival (PFS), defined as the time from start of induction treatment to documented progressive disease (PD) or death from any cause up to 3 years post first study treatment • Overall survival (OS), defined as the time from start of induction treatment to 3 years post first study treatment or death from any cause, whichever comes first • Consolidation feasibility rate (CFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of consolidation • Maintenance feasibility rate (MFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of maintenance.

	• Safety endpoints including 1) treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths, and 2) clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Volume 4.03) and abnormal vital signs. Exploratory endpoint: • To evaluate MRD: defined as the proportion of patients who are MRD positive versus those who are MRD negative. All efficacy analyses will be performed using the response evaluation population. The IFR will be computed and presented together with the exact 90% confidence interval (CI) using the method of Clopper and Pearson. The null hypothesis of 65% IFR will be rejected if at least 36 patients are able to complete 4 cycles of induction treatment and start ASCT. The CRR, ORR, CFR, and MFR will be computed and presented together with the exact 90% Clopper and Pearson CIs. The Kaplan-Meier product limit method will be used to estimate PFS and OS. Median values and rates at clinically relevant time points will be provided with the 90% CIs. A Cox Proportional Hazards Model may also be utilized to estimate the effects of patient baseline characteristics or known prognostic factors on PFS and OS.

MM 61 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
CBC	Complete blood count
CFR	Consolidation feasibility rate
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response/remission
CRF	Case Report Form
CRP	C-reactive protein
CRR	Complete response rate
CS1	CD2-subset-1, also known as CRACC and SLAMF7
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMBT	European Group for Blood and Marrow Transplantation
ERd	Elotuzumab, lenalidomide, and dexamethasone
FDA	US Food and Drug Administration
FISH	Fluorescence in-situ hybridization
GCP	Good Clinical Practice
GEP	Gene expression profiling
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IFR	Induction feasibility rate
IgG1	Immunoglobulin G 1
IMiD	Immunomodulatory drugs
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LVEF	Left ventricular ejection fraction
MFR	Maintenance feasibility rate
MM	Multiple myeloma
MRD	Minimal residual disease
MTD	Maximum-tolerated dose
MUGA	Multi-gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate

LIST OF ABBREVIATIONS

OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PO	*per os* (orally)
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin
PR	Partial response/remission
PT	Prothrombin time
QA	Quality assurance
RBC	Red blood cell
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SFLC	Serum-free light chains
SLAMF7	Signaling lymphocyte activation molecule family 7
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
VTE	Venous thromboembolism

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1. INTRODUCTION

1.1 Background

Multiple myeloma (MM), a B-cell tumor of malignant plasma cells within the bone marrow, is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and commonly results in anemia, bone marrow failure, bone destruction, hypercalcemia, renal failure, and increased susceptibility to infections. The disease accounts for approximately 1.4% of all new cancer cases in the United States (US) and approximately 13% of hematologic cancers worldwide (Palumbo and Anderson 2011). There are approximately 24,000 new cases of MM diagnosed in the US each year with over 11,000 deaths annually due to the disease (Howlader et al 2014).

1.2 Treatment for multiple myeloma

Although MM is considered fatal, survival has dramatically improved over the last 2 decades with the introduction of more effective treatment options. Multiple myeloma is sensitive to a number of cytotoxic drugs (e.g., alkylating agents and anthracyclines) and corticosteroids that are commonly used for initial treatment and for relapsed disease. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with autologous stem cell transplantation (ASCT). In addition, the introduction of novel agents such as proteasome inhibitors and immunomodulatory drugs (IMiDs) has revolutionized treatment and improved survival rates for this disease.

Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), lenalidomide (Revlimid®), elotuzumab (EMPLICITI™), and their combinations with and without corticosteroids. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, 10% to 30% of patients fail to respond to the primary therapy, and almost all patients eventually relapse, with a median OS of 44.8 months (Kumar et al 2008).

1.3 Elotuzumab

On 30 November 2015, the U.S. Food and Drug Administration (FDA) approved elotuzumab (EMPLICITI, Bristol-Myers Squibb Company) in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received 1 to 3 prior therapies. The full package insert can be viewed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf.

Elotuzumab is a humanized IgG1 monoclonal antibody that specifically targets the SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7) protein. SLAMF7 is expressed on myeloma cells independent of cytogenetic abnormalities, and is also expressed on natural killer cells, plasma cells, and at lower levels on specific immune cell subsets of differentiated cells within the hematopoietic lineage.

Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity. In preclinical models, the combination of elotuzumab and lenalidomide resulted in enhanced activation of natural killer cells that was greater than the effects of either agent alone and increased anti-tumor activity *in vitro* and *in vivo*.

1.3.1 Summary of non-clinical experience

The expression of the elotuzumab target, SLAMF7, is restricted to malignant myeloma cells and subsets of normal leukocytes in humans (natural killer, natural killer-like T cells, a subset of CD8+ T cells, and tissue plasma cells). No significant expression was detected in resting CD4+ T cells, B cells, resting monocytes, neutrophils, and granulocytes. Elotuzumab binding was not observed on epithelia, vessels, or smooth muscle cells of any of the organs examined.

No SLAMF7 expression was noted with immunohistochemical staining in a variety of normal and neoplastic tissues. Except for infiltrating cells, no SLAMF7 expression was noted in brain, breast, colon, heart, kidney, liver, lung, ovary, pancreas, prostate, skin, small intestine, spleen, stomach, testis, tonsil, uterus, and urinary bladder. Additionally, no SLAMF7 expression was noted in tumor samples, including ductal breast adenocarcinoma, lobular breast adenocarcinoma, renal cell carcinoma, prostate carcinoma, endometrial adenocarcinoma, gastric adenocarcinoma, urothelial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, ovarian carcinoma, testicular germ cell tumor, head and neck squamous cell carcinoma, melanoma, and pancreatic adenocarcinoma (Hsi et al 2008).

Elotuzumab only recognizes human SLAMF7 protein and does not appear to bind SLAMF7 from other species, including chimpanzee, cynomolgus monkey, dog, mini pig, mouse, rabbit, rat, and rhesus monkey. Due to the lack of species-specific cross-reactivity, there are no relevant animal species in which to conduct toxicological studies. Therefore, the nonclinical studies consisted primarily of *in vitro* safety assessments and selected *in vivo* biological activity assessment to address the selectivity of elotuzumab and potential toxicities. In addition, a limited non-Good Laboratory Practice exploratory single-dose intravenous (IV) toxicity and toxicokinetics study in rhesus monkeys was conducted and no potential non-target effects were identified.

Elotuzumab (100 and 200 μg/mL) *in vitro* had no effect on lymphocytes, CD3, CD4, CD8, and B cell counts in blood samples from healthy human donors. The natural killer cell counts were decreased on average by 20% at both doses of elotuzumab. The observed decline was variable between donors and ranged between 0% and 45%.

Elotuzumab, at concentrations up to 500 μg/mL, did not adversely affect the ability of human bone marrow-derived hematopoietic stem cells to differentiate down the erythroid and myeloid pathways.

In nonclinical models, elotuzumab plus either bortezomib or lenalidomide had greater antitumor activity than either agent alone. In addition, elotuzumab plus mAbs that enhance natural killer cell function either by antagonizing a negative regulatory molecule, KIR2DL3, or by agonizing

the immune cell costimulatory molecule, CD137, had greater antitumor activity than either agent alone.

Significant antibody-dependent killing of MM cells was observed when elotuzumab was incubated with L363 or OPM2 human MM cells in the presence of human PBMCs isolated from the blood of healthy donors or from the blood of patients with MM. No complement-dependent cytotoxicity was detected.

Elotuzumab treatment of mice bearing human xenograft MM tumors resulted in significant antitumor activity and eradication of tumors in many of the treated mice.

Experiments using an *in vivo* mouse xenograft model suggest that, while maximal antitumor activity is reached at elotuzumab serum levels of 70 to 430 µg/mL, minimal biological activity is seen at 2 to 13 µg/mL. *In vitro* experiments suggested that the elotuzumab concentration required to achieve saturation of SLAMF7 on PBMCs from healthy donors was approximately 20 µg/mL.

1.3.2 Summary of relevant clinical experience

The first 3 elotuzumab clinical trials were Phase I studies in patients with relapsed MM with elotuzumab as monotherapy or combined with bortezomib or lenalidomide.

Results of the monotherapy Phase I trial (Zonder et al 2012) demonstrated acceptable safety with no maximum tolerated dose (MTD) identified up to 20 mg/kg. The most common adverse events (AEs), regardless of attribution, were cough, headache, back pain, fever, and chills. Adverse events were generally mild to moderate in severity, and AEs attributed to elotuzumab were primarily infusion-related. Stable disease was reported for 27% of the 35 patients treated. Plasma elotuzumab levels and terminal half-life increased with dose whereas clearance decreased, suggesting target-mediated clearance.

Results of the Phase I trial of the combination of elotuzumab with bortezomib/dexamethasone demonstrated adequate safety with no MTD observed up to 20 mg/kg. Twenty-eight patients were treated: each were treated with the 2.5-, 5.0-, and 10-mg/kg dose cohorts, and 19 subjects were treated with the 20-mg/kg cohort. Objective responses were obtained in 48% of treated patients.

Results of a Phase I trial of the combination of elotuzumab with lenalidomide/dexamethasone demonstrated acceptable safety with no MTD observed up to 20 mg/kg (Lonial et al 2012). Twenty-eight patients were treated: 3 each in the 5.0- and 10-mg/kg cohorts, and 22 in the 20-mg/kg cohort. No dose-limiting toxicities were observed up to the maximum proposed dose of 20 mg/kg. The most frequent Grade 3 to 4 toxicities were neutropenia (36%) and thrombocytopenia (21%). Two patients experienced a serious infusion reaction during the first treatment cycle. Objective responses were obtained in 82% (23 of 28) of treated patients. After a median of 16.4 months follow-up, the median time to progression was not reached for patients in the 20-mg/kg cohort who were treated until disease progression. This trial also included a Phase 2 portion that is ongoing. Preliminary data from this portion of the trial demonstrated an objective response rate of 84% among all 73 treated patients, 92% among the 36 subjects treated with 10 mg/kg of elotuzumab. Median PFS was 33 months with the 10 mg/kg dose and 18.6 months with the 20-mg/kg dose.

In a randomized portion of a Phase Ib/II trial, the combination of elotuzumab with lenalidomide/dexamethasone was studied in patients with relapsed MM who were randomly assigned to either 10-mg/kg (36 patients) or 20-mg/kg (37 patients) doses of elotuzumab plus oral lenalidomide/dexamethasone (Richardson et al 2015). Of the 73 patients randomized, 61 (84%) achieved an objective response (33 [92%] with 10 mg/kg, 28 [76%] with 20 mg/kg); 31 (42%) a very good partial response (17 [47%] with 10 mg/kg, 14 [38%] with 20 mg/kg); and 20 (27%) a partial response (10 [28%] with 10 mg/kg, 10 [27%] with 20 mg/kg). The most common treatment-emergent AEs of any grade were diarrhea (48 [66%]), muscle spasms (45 [62%]), and fatigue (41 [56%]). Fifty-seven (78%) patients had Grade 3 or 4 events, the most common of which were lymphopenia (15 [21%]) and neutropenia (14 [19%]).

In a randomized, open-label Phase III clinical trial, patients with previously treated MM were assigned to receive either 10 mg/kg elotuzumab plus lenalidomide/dexamethasone (elotuzumab group) or lenalidomide/dexamethasone alone (control group) (Lonial et al 2015, EMPLICITI). Overall, 321 patients were assigned to the elotuzumab group and 325 to the control group. After a median follow-up of 24.5 months, the rate of PFS at 1 year in the elotuzumab group was 68%, as compared with 57% in the control group; at 2 years, the rates were 41% and 27%, respectively. Median PFS in the elotuzumab group was 19.4 months versus 14.9 months in the control group (hazard ratio for progression or death in the elotuzumab group, 0.70; 95% confidence interval, 0.57 to 0.85; $P<0.001$). The overall response rate in the elotuzumab group was 79% versus 66% in the control group ($P<0.001$). Common Grade 3 or 4 AEs in the 2 groups were lymphocytopenia, neutropenia, fatigue, and pneumonia. Infusion reactions occurred in 33 patients (10%) in the elotuzumab group, and were Grade 1 or 2 in 29 (88%) patients. The conclusion derived from these results was that patients with relapsed or refractory MM receiving a combination of elotuzumab, lenalidomide, and dexamethasone had a significant relative reduction of 30% in the risk of disease progression or death over those who received lenalidomide and dexamethasone alone.

Precautions and risks with elotuzumab are presented in Section 8.1.4.

1.4 Lenalidomide and dexamethasone

Lenalidomide is an immunomodulatory derivative of thalidomide and has both immunomodulatory and anti-angiogenic properties that are considered to confer anti-tumor effects. Two pivotal randomized Phase 3 trials established that lenalidomide in combination with high-dose dexamethasone produced a significant improvement in ORR and time to progression (TTP) versus high-dose dexamethasone alone in patients with relapsed MM who had had up to 3 prior therapies (Dimopoulos et al 2007, Weber et al 2007).

The combination of lenalidomide and high-dose dexamethasone has shown impressive activity in untreated disease. In a Phase 2 study of 34 patients with newly diagnosed MM, patients received lenalidomide (25 mg Days 1 to 21 of a 28-day cycle) and high-dose dexamethasone (40 mg Days 1 to 4, 9 to 12, and 17 to 20). The ORR was 91%, with 6% complete responders (CR), 32% near CR plus very good partial response (VGPR), and 53% partial responses (PR) (Arastu-Kapur et al 2008). However, when this regimen was compared with a more conventional delivery of dexamethasone (40 mg Days 1, 8, 15, and 22) in a 445-patient study, the more intensive dexamethasone schedule was associated with significantly shorter OS relative to the less intensive regimen (1-year survival rates 86% vs. 96.5%, respectively) (Kirk et al 2008). The

dexamethasone-intensive regimen was associated with higher incidences of thromboembolism and hyperglycemia, and higher incidences of Grades 3 and 4 toxicities overall. Clearly, better and safer combination regimens for newly diagnosed disease are warranted.

1.5 Rationale for the study

Despite many advances in the treatment of MM, the optimal front-line treatment and duration of treatment of transplant-eligible patients with MM remains controversial. It appears that the use of a triplet such as bortezomib, lenalidomide, and dexamethasone, and the incorporation of the newer generation of drugs such as carfilzomib, lenalidomide, and dexamethasone, can yield a higher percentage of CRs than seen with less aggressive therapies. It is also clear that the duration of therapy is important with respect to PFS and OS in the transplant-ineligible population, and likely the transplant-eligible population, as well. Thus, it is imperative to find a balance with an aggressive regimen that will result in good disease control to allow stem cell transplantation, but that will also be well tolerated so that it can translate to more prolonged treatment duration without significantly impacting patients' quality of life. The combination of 10 mg/kg elotuzumab, lenalidomide, and dexamethasone (ERd) is active, well-tolerated, and approved for patients with MM who have had prior treatments, based on data from a large randomized trial of elotuzumab in combination with lenalidomide and dexamethasone in newly diagnosed transplant-ineligible patients with MM (Lonial et al 2015). There are currently no studies looking at this combination in the transplant-eligible population.

In this study, we will determine the feasibility of incorporating ERd into the treatment paradigm of transplant-eligible patients with MM. All patients will undergo 4 cycles of induction therapy, followed by stem cell mobilization and collection. Patients will then undergo ASCT followed by consolidation therapy with ERd for 8 more cycles, and then maintenance with elotuzumab and lenalidomide for up to 2 years. Elotuzumab 10 mg/kg will be dosed every 2 weeks for all phases of the study with the exception of the maintenance phase. During maintenance, the frequency of elotuzumab dosing drops to once every 4 weeks. Therefore, the dose of elotuzumab is increased to 20 mg/kg for that phase to maintain as much of the receptor saturation as possible, as reflected by the PK data from the Phase I studies (Zonder et al 2012, Lonial et al 2012). The $t_{1/2}$ increased with an increased dose of elotuzumab from 0.5 mg/kg to 20 mg/kg, and saturation of the CS1 by elotuzumab on bone marrow target cells increased as the dose of elotuzumab increased. At doses of 10 mg/kg and 20 mg/kg elotuzumab, CS1 receptors on bone marrow–derived myeloma cells were consistently saturated. Lower dose groups exhibited more variation in the level of target cell saturation achieved. Since the 20-mg/kg dose of elotuzumab, both as monotherapy and in combination with lenalidomide and dexamethasone, has been shown to be well tolerated when dosed every 2 weeks, no increase in toxicity would be expected with the less frequent dosing schedule of once every 4 weeks. This maintenance strategy is being used in several large studies in front-line MM in both the transplant and non-transplant settings.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to:

- Evaluate the feasibility of using the combination of elotuzumab, lenalidomide, and dexamethasone (ERd) as induction therapy (induction feasibility rate [IFR]) and the ability of the combination to facilitate the start of autologous stem cell transplantation (ASCT) in transplant-eligible patients newly diagnosed with MM.

The primary endpoint is:

- IFR, defined as the percentage of patients successfully completing 4 cycles of induction treatment with ERd and able to start ASCT.

2.2 Secondary objectives

The secondary objectives of this study are to:

- Evaluate the efficacy of the combination of ERd as induction, consolidation, and maintenance therapy in transplant-eligible patients newly diagnosed with MM
- Evaluate the safety and tolerability of the combination of ERd as induction, consolidation, and maintenance therapy in transplant-eligible patients newly diagnosed with MM.

The secondary endpoints are:

- Complete response rate (CRR), defined as the percentage of patients who achieve a complete response (CR) or near complete response (nCR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and European Group for Blood and Marrow Transplantation (EBMT) criteria
- Overall response rate (ORR), defined as the percentage of patients who achieve at least a partial response (PR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and EBMT criteria
- Progression-free survival (PFS), defined as the time from start of induction treatment to documented progressive disease (PD) or death from any cause up to 3 years post first study treatment
- Overall survival (OS), defined as the time from start of induction treatment to 3 years post first study treatment or to death from any cause, whichever comes first
- Consolidation feasibility rate (CFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of consolidation
- Maintenance feasibility rate (MFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of maintenance.
- Safety endpoints including 1) treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths, and 2) clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Volume 4.03) and abnormal vital signs.

2.3 Exploratory objectives

The exploratory objectives of this study are to:

- Determine MRD by multi-parameter flow cytometry per institutional guidelines
- Evaluate gene expression profiling (GEP) at diagnosis per institutional guidelines and correlation of outcomes.

The exploratory endpoint is:

- To evaluate MRD defined as the proportion of patients who are MRD-positive versus those who are MRD-negative.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion criteria

Patients must meet **all** of the following criteria in order to be included in the research study:

1. Newly diagnosed myeloma requiring systemic chemotherapy as per International Myeloma Working Group (IMWG) uniform criteria (Appendix A) and Diagnostic Criteria and Staging for Multiple Myeloma (Appendix B):
    - Ideally, no prior therapy, or
    - No more than 1 cycle of therapy for emergent control of disease prior to enrolling on study, including prior treatment of hypercalcemia, spinal cord compression, or active and/or aggressively progressing myeloma with corticosteroids or lenalidomide or bortezomib-based regimens (the treatment dose should not exceed the equivalent of 160 mg of dexamethasone in a 4 week period, or not more than 1 cycle)
    - Bisphosphonates are permitted
2. Eligible and plan to undergo ASCT in first remission (refer to Section 5.1.2)
3. Measurable disease, prior to initial treatment as indicated by one or more of the following:
    - Serum M-protein ≥1.0 g/dL
    - Urine M-protein ≥200 mg/24 hours
    - Serum free light chain assay: involved free light chain level ≥10 mg/dL (≥100 mg/L) provided the serum free light chain ratio is abnormal.
4. Males and females ≥18 years-of-age
5. Ability to take aspirin or other venous thromboembolism (VTE) anticoagulant therapy
6. An ECOG Performance Status score of 0 through 2 (see Appendix C)
7. Adequate hematologic function defined as:

- Absolute neutrophil count (ANC) ≥1.0 x 10^9/L
- Hemoglobin (Hgb) ≥8 g/dL
- Platelets ≥75 x 10^9/L. Screening platelet count should be independent of platelet transfusions for at least 2 weeks.

8. Adequate liver function defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
9. Adequate renal function defined as serum creatinine ≤1.5 x ULN OR calculated creatinine clearance ≥50 mL/min as calculated by Cockcroft and Gault Formula.
10. All study participants must be registered into the mandatory Revlimid REMS® program and must be willing and able to comply with the requirements of that program.
11. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
12. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 28 days following last dose of study drugs. Male patients must also refrain from donating semen or sperm during their participation in the study. Details of mandatory contraception measures are presented in Appendix E.
13. Willingness and ability to comply with study and follow-up procedures.
14. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome
2. Plasma cell leukemia
3. Waldenström's macroglobulinemia or IgM myeloma
4. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated *in situ* carcinoma (i.e., non-invasive) are eligible, as are patients with a history of non-melanoma skin cancer.

5. Radiotherapy to multiple sites or immunotherapy within 4 weeks before start of protocol treatment (localized radiotherapy to a single site at least 1 week before start is permissible)
6. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
7. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose of study treatment
8. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome)
9. Any of the following cardiac diseases currently or within the last 6 months:
    - Left ventricular ejection fraction (LVEF) <40% as determined by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan
    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association ≥ Grade 2, see Appendix D)
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
    - Valvular disease with significant compromise in cardiac function
10. Known seropositive for or active viral infection with human immunodeficiency virus or hepatitis A, B, or C virus. Patients who are seropositive because of hepatitis B virus vaccine are eligible.
11. Any clinically significant medical disease or condition that, in the treating Investigator's opinion, may interfere with protocol adherence or a patient's ability to give informed consent
12. Pregnant or lactating females
13. Contraindication to any of the required concomitant drugs, including dexamethasone, H_1 and H_2 blockers, and acetaminophen, or if patient has a history of prior thrombotic disease, warfarin or low molecular weight heparin
14. No health coverage, or if the copay for lenalidomide is not acceptable to the patient.
15. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from study treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements (non-compliance)
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Lost to follow-up
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days and SAEs for 60 days, after their last dose of study drugs. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the patient's medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

After 24 months of maintenance therapy, patients who have no recorded disease progression or death can continue treatment with FDA approved therapies at the discretion of the treating physician. Patients who discontinue study treatment prior to the occurrence of disease progression will be followed for a total of up to 3 years post first study treatment or until they progress (see Section 7.5.1). Patients with documented disease recurrence or progression will be followed for survival status only for up to 3 years or until death (see Section 7.5.2).

4. STUDY REGISTRATION

The patient must willingly consent to participate in this study after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side effects, risks, and discomforts. Human protection committee (Institutional Review Board [IRB]) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study and sign the consent form will be enrolled into the study.

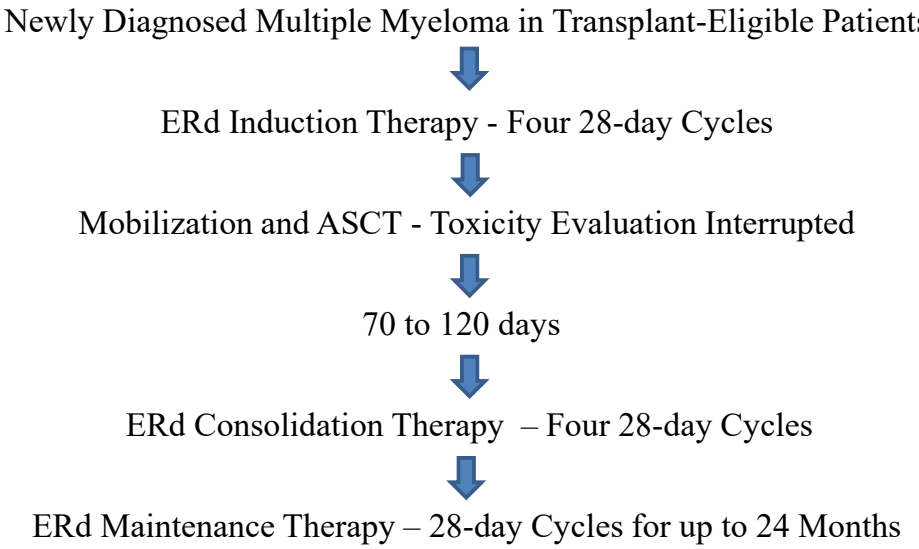
Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the Sarah Cannon Development Innovations Central Enrollment Desk. The enrollment desk may be reached by calling 877-MY-1-SCRI (877-691-7274). Registration may be done via fax 866-699-0258 Monday through Friday, 8:30 AM to 4:30 PM, Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This is an open-label, Phase 2 study to assess the feasibility and tolerance of the combination of ERd in the induction, consolidation, and maintenance treatment of transplant-eligible patients newly diagnosed with MM. The study is planned to be conducted at 8 centers in the United States.

This study will enroll approximately 53 patients in the pre-ASCT induction portion of the study with the anticipation that most of them will resume protocol treatment at the consolidation/maintenance therapy post ASCT. Recruitment will end when 48 patients are evaluable for the primary endpoint (have completed 4 cycles of induction treatment with ERd and are able to start ASCT). Patients who decline transplant for reasons other than toxicities will be replaced. The study schema is presented in Figure 1.

Figure 1 Study schema



5.1 Treatment plan

Instructions for initiation of a new cycle during induction, consolidation, and maintenance

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

- ANC $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 50 \times 10^9$/L
- Any other study drug-related adverse event must have resolved to grades as specified in protocol (see Section 6.2).

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

If either lenalidomide or dexamethasone 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 of lenalidomide and/or dexamethasone, as applicable (see Table 2 and Table 3, respectively).

5.1.1 Induction

All patients will undergo four 28-day cycles of the following induction treatments.

- Cycles 1 and 2
  - Elotuzumab 10 mg/kg IV on Days 1, 8, 15, and 22
  - Lenalidomide 25 mg orally on Days 1 through 21
  - Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Days 1, 8, 15, and 22
  - H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab (see Section 5.3.1.1).
- Cycles 3 and 4
  - Elotuzumab 10 mg/kg IV on Days 1 and 15 only
  - Lenalidomide 25 mg orally on Days 1 through 21
  - Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Days 1 and 15
  - Dexamethasone 40 mg orally on Days 8 and 22
  - H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab (see Section 5.3.1.1).

5.1.2 Mobilization/ASCT

Following completion of 4 cycles of induction therapy, all patients will undergo standard mobilization, collection of stem cells, and then ASCT using a melphalan conditioning regimen as per individual transplant institutional guidelines.

Mobilization with G-CSF should start 2 to 4 weeks from the last dose of lenalidomide (i.e., 2 to 4 weeks after Cycle 4 Day 21). In general, the scheduling of stem cell collection should

assure as limited a break as possible between the last dose of ERd treatment and ASCT, which should not exceed 6 weeks.

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

During the apheresis procedure, correction of cytopenias and electrolyte abnormalities will be performed as per institutional guidelines.

Conditioning chemotherapy will consist of melphalan 140 mg/m^2 or 200 mg/m^2 IV. Sites should follow their standard protocol for hydration and antiemetic prophylaxis prior to melphalan infusion, antibiotic prophylaxis, platelet and packed red blood cell transfusions, and standard laboratory testing. Administration of autologous peripheral stem cells will take place on Day 0 according to standard unit protocol. Patients will be monitored as per standard protocol until criteria for discharge from the transplant unit are met.

If a patient is unable to proceed to transplant, but the treating Investigator believes he/she would benefit from continued study treatment, the patient will be allowed to continue uninterrupted on to consolidation and maintenance without transplant.

All patients will be monitored and followed closely by the transplant team as per institutional guidelines during the stem cell procedure and full toxicity evaluations will resume with the onset of consolidation. Standard, expected hematotoxicity and gastrointestinal toxicities well known from high-dose melphalan treatment will not be collected. Any unexpected toxicity will be reviewed by the Medical Monitor in consultation with the Investigator and documented prior to a decision to proceed to the consolidation phase of treatment.

5.1.3 Consolidation

Consolidation is to begin approximately 70 to 120 days from transplant. Patients can begin consolidation if they have recovered from all transplant-related toxicities, do not have PD, and they meet the standards presented in Section 5.1.

All patients will undergo four 28-day cycles of the following consolidation treatment:

- Cycles 5 through 8
  - Elotuzumab 10 mg/kg IV on Days 1 and 15
  - Lenalidomide 15 mg orally on Days 1 through 21
    - Lenalidomide can be escalated as tolerated to the maximum-tolerated dose [MTD] administered during induction.
    - Lenalidomide can continue with dose unchanged from induction in patients who remain on study, but do not proceed to transplant.
  - Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab infusion) on Days 1 and 15
  - Dexamethasone 40 mg orally on Days 8 and 22

- H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab (see Section 5.3.1.1).

In order for a patient's data to be included in the calculation of CFR, they must have successfully completed all 4 consolidation cycles with or without dose reductions.

5.1.4 Maintenance

All patients who do not have PD will automatically be switched to maintenance therapy (28-day cycles) following successful completion of 4 cycles of consolidation therapy. Please note that the elotuzumab dose is increased here to 20 mg/kg from 10 mg/kg due to once per month dosing during this phase as opposed to twice a month dosing in the previous phases.

- Cycles 9+
  - Elotuzumab 20 mg/kg IV on Day 1
  - Lenalidomide 10 mg ±5 mg orally on Days 1 through 21
  - Dexamethasone 28 mg orally (3 to 24 hours prior to start of elotuzumab infusion) AND 8 mg IV (45 to 90 minutes prior to elotuzumab) on Day 1
  - H_1 blockers, H_2 blockers, and acetaminophen as pre-medications for elotuzumab (see Section 5.3.1.1).

Any patient who comes off elotuzumab for whatever reason, or completes the 24 months of maintenance allowed by the protocol, can continue treatment with FDA approved therapies at the discretion of the treating physician, but will no longer be on study following their 60-day post maintenance safety follow up.

5.2 Treatment duration

The end of the study is defined as the last visit of the last patient after 24 months of maintenance therapy. The total duration of the study is planned to be 2 years for enrollment and up to 3.5 years maximum follow up per patient to complete the full treatment plan.

Patients will be evaluated for toxicity at the start of each cycle according to procedures listed in Appendix G. Toxicity evaluation will be interrupted during the stem cell procedure and will resume with the onset of consolidation. Patients will continue on treatment until progression as defined in Appendix A, intolerance to side effects, or completion of 2 years of maintenance therapy.

After 24 months of maintenance therapy, patients who have no recorded disease progression or death can continue treatment with FDA approved therapies at the discretion of the treating physician. Patients who discontinue study treatment prior to the occurrence of disease progression will be followed for a total of up to 3 years post first study treatment or until they progress (see Section 7.5.1). Patients with documented disease recurrence or progression will be followed for survival status only for up to 3 years or until death (see Section 7.5.2).

5.3 Concomitant medications

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients will be instructed not to take any additional medications

during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of study drug treatment.

5.3.1 Permitted concomitant medications

5.3.1.1 Required premedication prior to administration of elotuzumab

Premedication is recommended prior to administration of elotuzumab, according to the following guidelines:

- Dexamethasone 28 mg orally (between 3 to 24 hours prior to the start of elotuzumab infusion OR as a split dose 12 to 24 hours and 3 hours prior to elotuzumab). If a dose of dexamethasone tablets is missed, it should be taken as soon as possible. If it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Two doses should not be taken at once.

  AND

- Dexamethasone 8 mg IV on the day of elotuzumab infusion 45 to 90 minutes prior to the start of infusion. If a dose of oral dexamethasone is missed, it is recommended that the IV still be administered.
- H_1 blocker: diphenhydramine (25 to 50 mg orally or IV), or equivalent, 45 to 90 minutes prior to the start of elotuzumab infusion
- H_2 blocker: ranitidine (50 mg IV), or equivalent, 45 to 90 minutes prior to the start of elotuzumab infusion
- Acetaminophen (650 to 1000 mg PO) 45 to 90 minutes prior to the start of elotuzumab infusion.

5.3.1.2 Premedication in patients with a prior infusion reaction

Patients with a prior infusion reaction must receive H_1, H_2 blockers, and acetaminophen at the **maximum doses** specified in Section 5.3.1.1.

In addition, dexamethasone premedication should be administered as per Table 1.

Table 1 Corticosteroid premedication[a] for previous infusion reactions

Prior infusion reaction	Corticosteroid premedication[b] prior to elotuzumab
None or only Grade 1 prior infusion reaction[c]	28 mg PO dexamethasone (3 to 24 hours prior to elotuzumab) AND 8 mg IV dexamethasone at least 45 to 90 minutes prior to elotuzumab
Prior Grade 2 infusion reaction[d]	28 mg PO dexamethasone (3 to 24 hours prior to elotuzumab) AND 10 mg IV dexamethasone at least 45 to 90 minutes prior to elotuzumab
Prior Grade 3 or recurrent Grade 2 infusion reaction	8 mg oral dexamethasone (12 to 24 hours prior to elotuzumab) AND 8 mg oral dexamethasone (at least 3 hours prior to elotuzumab) AND 18 mg IV dexamethasone at least 45 to 90 minutes prior to elotuzumab

a For prior infusion reactions, use maximum doses of H1, H2 blockers, and acetaminophen (see Section 5.3.1.1)

b At the discretion of the Investigator, the oral dexamethasone component may be given as a split dose 12 to 24 and 3 hours prior to elotuzumab
c Subjects with a prior Grade 1 infusion reaction may be premedicated as per Grade 2 infusion reactions.
d Subjects with prior Grade 2 infusion reactions may be premedicated as per Grade 3 infusion reactions

At the discretion of the investigator, the 28-mg oral dexamethasone component may be given as a split dose: 12 mg orally (12 to 24 hours prior to elotuzumab) AND 16 mg orally (3 hours prior to elotuzumab).

If a patient with a prior Grade 2 or 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 administered 45 to 90 minutes prior to elotuzumab.

Patients with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued.

5.3.1.3 Permitted concomitant medications for the maintenance of pre-existing conditions

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Patients may receive anti-emetics and antidiarrheal agents, as necessary.
- Colony-stimulating factors may be used if neutropenia occurs, but should not be given prophylactically.
- Patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, in accordance with institutional guidelines; however, the screening platelet count must be independent of platelet transfusions for at least 2 weeks. Patients who require repeated platelet transfusion support should be discussed with the Study Chair.
- Allopurinol (for use only in patients at risk for tumor lysis syndrome [TLS] due to high tumor burden) is optional and will be prescribed at the discretion of the treating Investigator. These patients may receive allopurinol 300 mg PO twice daily (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO once daily, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Patients who do not tolerate allopurinol and are at risk for TLS should be discussed with the Study Chair.
- Radiation therapy to a localized mass for patients on ERd therapy is acceptable with prior approval of the Study Chair.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose ≤4 mg/day or prednisone ≤20 mg/day are permitted.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited concomitant medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose >4 mg/day or prednisone >20 mg/day are not permitted.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

5.4 Correlative studies

Bone marrow aspirates collected as standard of care will be used for MRD analysis and GEP to correlate with response.

Minimal residual disease analysis will be conducted per institutional guidelines at any time bone marrow is collected as standard of care.

Gene expression profiling will be conducted per institutional guidelines on bone marrow collected as standard of care at diagnosis.

6. DOSE MODIFICATIONS AND PERMANENT DISCONTINUATION

6.1 Discontinuation of study treatments

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

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

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

Treatment doses of dexamethasone may be discontinued without the subject discontinuing the other study treatment(s). If treatment doses of dexamethasone must be discontinued, it is up to treating Investigator's discretion whether to continue with elotuzumab administration. If

dexamethasone prophylaxis is discontinued, however, elotuzumab administration should not be continued.

6.2 Dose modifications

The following sections and tables summarize dosing modifications of elotuzumab, lenalidomide, and dexamethasone to manage possible toxicity.

The criteria presented in this section for dose modification are meant as general guidelines, and they are based on current US standards of clinical practice. Local standards may differ and may be followed. Dose modification may occur in the setting of lower grade toxicity if the Investigator, in consultation with the Study Chair, believes that it is in the interest of patient safety.

6.2.1 Elotuzumab

No dose reduction is allowed for elotuzumab.

6.2.2 Lenalidomide

Dose adjustments, as summarized in Table 2, are recommended for the management of NCI CTCAE Grade 3 and 4 toxicities for thrombocytopenia, neutropenia or other toxicities that are judged by the Investigator to be related to lenalidomide.

Table 2 Dose reduction steps for lenalidomide

		Dose reduction[a]	
Lenalidomide PO	Starting dose level	Dose level -1	Dose level -2
Cycles 1 through 4	25 mg on Days 1 through 21	15	10
Cycles 5 through 12	15 mg[b] on Days 1 through 21	10	5
Cycles 13 and beyond	10±5 mg on Days 1 through 21	5	Stop lenalidomide

a Dose reduction should be based on the worst toxicity demonstrated.
b Lenalidomide can be escalated as tolerated to the MTD administered during induction.

In addition to dose reductions, administration of elotuzumab 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 the event resolves to the baseline value or to ≤ Grade 1 within 21 days; otherwise elotuzumab and lenalidomide will be permanently discontinued, unless continued administration is approved by the Study Chair.

6.2.3 Dexamethasone

Dose reduction levels of dexamethasone are presented in Table 3. Dexamethasone delay should be performed as clinically indicated at the discretion of the treating Investigator; however, it is recommended that both the dexamethasone oral and IV doses be administered as part of the premedication for elotuzumab, as indicated. Refer to Section 5.3.1.1 and Section 5.3.1.2 for further guidance on dexamethasone administration before elotuzumab administration and for

patients with a prior infusion reaction. If dexamethasone prophylaxis is discontinued, elotuzumab administration should not be continued.

If treatment doses of dexamethasone must be discontinued, it is up to treating Investigator's discretion whether to continue with elotuzumab administration.

Table 3 Dose reduction steps for dexamethasone

		Dose reduction[a]	
Dexamethasone PO & IV	Starting dose level	Dose level -1	Dose level -2
Cycles 1 & 2	28 mg PO Days 1, 8, 15, and 22, AND	12 mg	0 mg
	8 mg IV on Days 1, 8, 15, and 22	No change to IV	No change to IV
Cycles 3 & 4	28 mg PO Days 1 and 15	12 mg	0 mg
	40 mg PO Days 8 and 22, AND	20 mg	12 mg
	8 mg IV on Days 1 and 15	No change to IV	No change to IV
Cycles 5 through 12	28 mg PO Days 1 and 15	12 mg	0 mg
	40 mg PO Days 8 and 22, AND	20 mg	12 mg
	8 mg IV on Days 1 and 15	No change to IV	No change to IV
Cycles 13 and beyond	28 mg PO on Day 1, AND	12 mg	0 mg
	8 mg IV on Day 1	No change to IV	No change to IV

a Dose reduction should be based on the worst toxicity demonstrated.

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

6.2.4 Dose modifications due to hematologic toxicity

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

Table 4 Dose modifications due to hematologic toxicities

Event	Elotuzumab	Lenalidomide
Neutropenia (ANC)		
ANC falls to <0.5 x 10^9/L or to <1.0 x 10^9/L with fever	Hold elotuzumab[a], add G-CSF if Grade 3 with fever or Grade 4, follow CBC with diff weekly.	Hold lenalidomide[a], add G-CSF if Grade 3 with fever or Grade 4, follow CBC with diff weekly.
ANC returns to 1.0 x 10^9/L (if neutropenia was the only toxicity noted)	Resume elotuzumab at full dose.	Resume lenalidomide at full dose.
ANC return to 1.0 x 10^9/L (if other toxicity noted)	Resume elotuzumab at full dose unless marked cyclical thrombocytopenia is present	Resume lenalidomide at 1 dose decrement.
ANC subsequently drops to <0.5 x 10^9/L or to <1.0 x 10^9/L with fever	Hold elotuzumab[a] treatments.	Hold lenalidomide[a] treatments.
ANC returns to 1.0 x 10^9/L	Resume elotuzumab	Resume lenalidomide at 1 dose decrement. Do not dose below 5 mg.
Thrombocytopenia[b]		
Platelets drop to <30 x 10^9/L	Hold elotuzumab[a] and follow CBC with diff weekly.	Hold lenalidomide[a] and follow CBC with diff weekly. Hold prophylactic ant-coagulation until platelets return to 30 x 10^9/L.
Platelets return to ≥30 x 10^9/L	Resume elotuzumab	Resume lenalidomide at 1 dose decrement.
Platelets subsequently drop to <30 x 10^9/L	Hold elotuzumab[a] and follow CBC with diff weekly.	Hold lenalidomide[a] and follow CBC with diff weekly.
Platelets return to ≥30 x 10^9/L	Resume elotuzumab	Resume lenalidomide at 1 dose decrement. Do not dose below 5 mg.

[a] Any patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating Investigator and the Study Chair agree that continued treatment at lower doses is in the best interest of the patient.

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

ANC = absolute neutrophil count, CBC = complete blood count, diff = differential; G-CSF = granulocyte colony-stimulating factor.

6.2.5 Dose modifications/management guidelines due to non-hematologic toxicities

6.2.5.1 Guidelines for infusion reactions

Grade 1 infusion reaction

Grade 1 elotuzumab infusion-related reactions by definition, require no intervention; however, increased monitoring is recommended.

Grade ≥2 infusion reaction

For a Grade ≥ 2 elotuzumab infusion-related reaction, 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.

Patients with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued. These subjects should continue to receive lenalidomide and dexamethasone per protocol.

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 a maximum of 2 mL/minute or the rate at which the infusion reaction occurred. Patients 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 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 as described in Table 1.

If a Grade ≥ 2 infusion reaction occurs following 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, H_2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Subjects with prior Grade 2 or higher infusion reactions should have the next infusion started at 0.5 mL/minute and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes to a maximum of 2 mL/minute). If there is no recurrence of a Grade >2 infusion reaction, the next infusion may be initiated at 1.0 mL/minute. The infusion rate may be escalated by 1.0 mL/minute to a maximum rate of 2 mL/minute, if the subject does not experience an infusion reaction within 30 minutes. Once a subject has received 3 consecutive infusions initiated at 1.0 mL/minute without a Grade >2 infusion reaction, subsequent infusions may be initiated at a maximum rate of 2.0 mL/minute and maintained at that rate.

The dose reduction guidelines for other non-hematologic toxicities are shown in Table 5.

Table 5 Dose reductions for non-hematologic toxicities other than infusion reactions

Toxicity Grade	Elotuzumab	Lenalidomide
Non-blistering rash		
Grade 3	Hold (if treating Investigator's opinion is possibly related to elotuzumab) until ≤ Grade 1, then resume dose.	Hold and follow weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 28 of the current cycle, restart at 1 dose decrement, and continue the cycle until Day 28 of the current cycle.
Grade 4	Hold until ≤ Grade 1, then resume dose.	Discontinue
Desquamating (blistering) rash – any grade	Hold until ≤ Grade 1, then resume dose.	Discontinue
Erythema multiforme ≥ Grade 3	Hold until ≤ Grade 1, then resume dose.	Discontinue
Sinus bradycardia/ other cardiac arrhythmia		
Grade 2	Hold until ≤ Grade 1, then resume dose.	Hold and follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 28, restart at 1 dose decrement and continue the cycle until Day 28.
≥ Grade 3	Hold until ≤ Grade 1, then resume dose.	Discontinue
Allergic reaction/hypersensitivity		
Grades 2 to 3	Hold until ≤ Grade 1, then resume dose.	Hold lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 28, restart at 1 dose decrement and continue the cycle until Day 28.
Grade 4	Discontinue	Discontinue

Table 5 Dose reductions for non-hematologic toxicities other than infusion reactions

Toxicity Grade	Elotuzumab	Lenalidomide
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 until all abnormalities in serum chemistries have resolved. Reinstitute at full dose.	Hold until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection Grades 3 or 4	Hold until systemic treatment for infection is completed. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.	Hold until systemic treatment for infection is completed. If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex Any grade	Hold until lesions are dry. Reinstitute at full dose.	Hold until lesions are dry. Reinstitute at full dose.
Neuropathy		
Grade 2 with pain or Grade 3	Hold until ≤ Grade 2, then restart at full dose.	Hold until ≤ Grade 2, then restart at 1 dose decrement.
Grade 4	Discontinue	Discontinue
Renal dysfunction		
Serum creatinine >2 mg/dL		Base dose reduction on calculated GFR
CrCl >50 mL/min		Full dose
CrCl <50 mL/min and >30 mL/min		Reduce to 10 mg every 24 hours; may reinstate prior dose if, after 2 cycles, CrCl normalizes.
CrCl <30 mL/min		Reduce to 15 mg every 48 hours
CrCl <30 mL/min requiring dialysis		5 mg. Once daily. On dialysis days, the dose should be administered following dialysis.
Venous thrombosis/embolism ≥ Grade 3	No adjustment required	Hold dose and adjust anticoagulation regimen; re-start at treating Investigator's discretion at full dose.

Table 5 Dose reductions for non-hematologic toxicities other than infusion reactions

Toxicity Grade	Elotuzumab	Lenalidomide
Congestive heart failure (CHF)	Any subject with symptoms of CHF, whether or not elotuzumab-related, must have the dose held until resolution or 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 lenalidomide-related, must have the dose held until resolution or return to baseline. If CHF was felt to be lenalidomide-related, reinstate by 1 dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.
Other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3	Full dose	Hold dose, and follow at least weekly. If the toxicity decreases to ≤ Grade 1 before Day 28 of the current cycle, restart at 1 dose decrement, and continue until Day 28 of the current cycle.
Other non-hematologic toxicity assessed as elotuzumab-related ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline and restart at full dose.	Full dose
Other non-hematologic toxicity assessed as drug-related ≥ Grade 3	Hold treatment and restart at full dose 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.

CHF = congestive heart failure; GFR = glomerular filtration rate

6.2.6 Dose modifications due to dexamethasone toxicity

The dose reduction guidelines for toxicities known to be related to dexamethasone are shown in Table 6. If dexamethasone must be discontinued, it is up to treating Investigator's discretion whether to continue with elotuzumab administration.

Table 6 Dose modifications due to dexamethasone toxicity

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

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix G. The baseline medical history, physical examination with vital signs, ECOG performance status, 12-lead electrocardiogram (ECG), complete blood count (CBC), including 3-part differential and platelets, comprehensive metabolic profile (CMP plus magnesium and phosphorus), prothrombin time (PT)/activated partial thromboplastin time (aPTT)/ International Normalized Ratio (INR), lactate dehydrogenase (LDH) and uric acid, and C-reactive protein (CRP) should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1, they do not have to be repeated on that day.

For women of childbearing potential, pregnancy counseling and 2 serum or urine pregnancy tests must be performed; one 10 to 14 days prior to initiation of study treatment and one within 24 hours of initiation of study treatment.

Disease assessments should be performed ≤28 days prior to initiation of treatment, with the exception of the bone marrow aspirate/biopsy and the skeletal survey, which should preferably be performed ≤28 days prior to initiation of treatment, but for which ≤60 days prior to Cycle 1 Day 1 is acceptable.

7.2 Baseline study assessments (screening)

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any other study-related procedures
- Register patient into Revlimid REMS® program and prescribe lenalidomide
- Medical history
- Physical examination, including a neurological evaluation and assessment for peripheral neuropathy (see questionnaire in Appendix F), measurements of height (first visit), weight, and vital signs (resting heart rate, systolic and diastolic blood pressure, respiratory rate, and oral temperature)
- ECOG performance status (see Appendix C)
- 12-lead ECG
- Concomitant medication review
- CBC, including hemoglobin, hematocrit, white blood cells with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin plus magnesium and phosphorus.

- Coagulation analysis: PT/aPTT/INR (not repeated if normal at baseline)
- LDH and uric acid
- Two serum or urine pregnancy tests for women of childbearing potential are required, one 10 to 14 days prior to starting treatment and another within 24 hours prior to start of treatment
- CRP
- Disease assessments:
  - Urine protein electrophoresis (UPEP) and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - Serum-free light chain (SFLC)
  - Serum β2-microglobulin
  - Quantitative immunoglobulins (IgG, IgA, IgM)
  - Bone marrow aspirate/biopsy (including flow cytometry, cytogenetics, fluorescence in-situ hybridization (FISH) to include 1q amplification, 13 del, 1p del, t(4;14), t(11;14), t(14;16) and 17p del, and GEP preferably via the MyPRS assay as per institutional guidelines
  - Aspirate should be sent for MRD evaluation according to institutional guidelines. Fresh or archival tissue can be used for MRD evaluation only.
  - Plasmacytoma evaluation, ONLY for patients with a known plasmacytoma that has been imaged before enrolling on study.
  - Skeletal survey including lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low dose CT scans can be substituted for skeletal survey as per institutional guidelines.

7.3 Study treatment assessments

7.3.1 ERd Induction Cycles 1 and 2, Day 1

The following information will be collected and procedures will be performed:

- Medical history
- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status
- AE evaluation
- Concomitant medication review

- CBC
- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential
- Disease assessments (for Cycle 1 Day 1, only if >14 days from baseline disease assessments):
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Plasmacytoma evaluation, if necessary (Cycle 2 only).
- Study drug administration (see Section 5.1.1 and Appendix G)
- Study drug compliance.

7.3.2 ERd Induction Cycles 1 and 2, Days 8, 15, and 22

The following information will be collected and procedures will be performed:

- Vital signs
- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential: weekly during Cycle 1, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.
- Study drug administration (see Section 5.1.1 and Appendix G)
- Study drug compliance.

7.3.3 Restaging

Restage every cycle (4 weeks): response will be evaluated after completion of 1 treatment cycle as per IMWG and European Group for Blood and Marrow Transplantation (EBMT) criteria (Appendix A). Thereafter, restaging must be done within a window of -7 to Day 1 of the next cycle.

7.3.4 ERd Induction Cycles 3 and 4, Day 1

The following information will be collected and procedures will be performed:

- Medical history
- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status
- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential.
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Plasmacytoma evaluation, if necessary (Cycle 4 only)
- Study drug administration (see Section 5.1.1 and Appendix G)
- Study drug compliance.

7.3.5 ERd Induction Cycles 3 and 4, Day 15

The following information will be collected and procedures will be performed:

- Vital signs
- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- Serum or urine pregnancy test for women of childbearing potential who have irregular menstrual cycles. Pregnancy counseling for all women of child-bearing potential.
- Study drug administration (see Section 5.1.1 and Appendix G).

7.3.6 End of Cycle 4 through start of mobilization

The following information will be collected and procedures will be performed:

- Vital signs
- AE evaluation
- Concomitant medication review
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Bone marrow aspirate/biopsy including flow cytometry, cytogenetics, FISH, and MRD, per institutional guidelines
  - Plasmacytoma evaluation, if necessary (every other cycle).
- Women of child-bearing potential should be reminded to follow approved birth control practices while off study treatment.
- Study drug compliance.

7.3.7 Post ASCT evaluation (at 70 to 120 days following transplant) – preference would be to perform evaluation on the earlier side (Day 70) and initiate consolidation shortly thereafter.

The following information will be collected and procedures will be performed:

- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status
- CBC
- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential. Note: women of child-bearing potential were to continue to use appropriate birth control methods while off study treatment.
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins

- Bone marrow aspirate/biopsy including flow cytometry, cytogenetics, FISH, and MRD, per institutional guidelines
- Plasmacytoma evaluation, if necessary (every other cycle)
- Skeletal survey or alternate imaging as per institutional guidelines.

7.3.8 ERd Consolidation Cycles 6 through 8, Day 1

Cycle 5 Day 1 assessments are not necessary unless there has been >21 day delay from the Day 70-120 evaluation and the start of consolidation.

The following information will be collected and procedures will be performed:

- Medical history
- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status
- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Bone marrow aspirate/biopsy including flow cytometry and MRD only to confirm nCR or CR as per standard of care
  - Plasmacytoma evaluation, if necessary (every other cycle).
- Study drug administration (see Section 5.1.3 and Appendix G)
- Study drug compliance.

7.3.9 ERd Consolidation Cycles 5 through 8, Day 15

The following information will be collected and procedures will be performed:

- Vital signs

- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential who have irregular menstrual cycles
- Study drug administration (see Section 5.1.3 and Appendix G)
- Study drug compliance.

7.3.10 End of Cycle 8

The following information will be collected and procedures will be performed:

- Vital signs
- AE evaluation
- Concomitant medication review
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Bone marrow aspirate/biopsy including flow cytometry, cytogenetics, FISH, and MRD, per standard of care as clinically indicated
  - Plasmacytoma evaluation, if necessary
  - Skeletal survey or alternate imaging as per institutional guidelines, per standard of care as clinically indicated.
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential
- Study drug compliance.

7.3.11 Maintenance Cycles 9+, Day 1

The following information will be collected and procedures will be performed:

- Medical history
- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status

- AE evaluation
- Concomitant medication review
- CBC
- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential
- Disease assessments (every 3 months: Cycles 12, 15, 18, 21, 24, etc.):
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Plasmacytoma evaluation, if necessary (every other cycle).
  - An evaluation for MRD should be sent to the laboratory for any bone marrow aspirate performed as standard of care outside of study assessments, such as at 1 year and 2 years post-transplant.
- Study drug administration (see Section 5.1.4 and Appendix G)
- Study drug compliance (beginning with Cycle 14).

7.3.12 Maintenance Cycles 9+, Day 15

- Serum or urine pregnancy test, including pregnancy counseling, for women of childbearing potential who have irregular menstrual cycles.

7.4 End-of-treatment visit

After patients are discontinued from the study, they will visit the study center ≤30 days from the date of last dose of study drug for end-of-treatment assessments. Patients must be followed for AEs for 30 calendar days and for SAEs for 60 calendar days after the last dose of study drug.

The following information will be collected and procedures will be performed:

- Medical history
- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of weight and vital signs
- ECOG performance status
- AE evaluation
- Concomitant medication review
- CBC

- CMP plus magnesium and phosphorus
- LDH and uric acid
- Serum or urine pregnancy tests, including pregnancy counseling, for women of childbearing potential. For those with irregular menses, pregnancy tests are required at 14 and 28 days after treatment discontinuation of lenalidomide.
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins
  - Bone marrow aspirate/biopsy including flow cytometry, cytogenetics, FISH, and MRD, per standard of care as clinically indicated
  - Plasmacytoma evaluation, if necessary
  - Skeletal survey or alternate imaging as per institutional guidelines, per standard of care as clinically indicated.
- Survival status
- Study drug compliance.

7.5 Follow-up visits

7.5.1 Off-study follow-up before disease progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) for a total of up to 3 years from initiation of treatment on the protocol or until they progress, whichever comes first.

The following information will be collected and procedures will be performed during outpatient visits:

- Physical examination, including a neurological evaluation and assessment of peripheral neuropathy (see questionnaire in Appendix F), measurements of vital signs
- CBC
- CMP plus magnesium and phosphorus
- Disease assessments:
  - UPEP and immunofixation requiring a 24-hour urine sample collection
  - SPEP and immunofixation
  - SFLC
  - Quantitative immunoglobulins

- Plasmacytoma evaluation, if necessary

- Survival status.

7.5.2 Off-study follow-up after disease progression

Patients with documented disease recurrence or progression will be followed every 3 months (±1 month) for survival status only (e.g., date and cause of death) for up to 3 years from initiation of treatment on the protocol or until death, whichever comes first. Patients may be contacted during outpatient visits or by telephone.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 Elotuzumab

Elotuzumab (BMS-901608, also known as HuLuc63) is a humanized recombinant monoclonal antibody targeted against SLAMF7, a cell surface glycoprotein expressed on myeloma and natural killer cells.

Investigational Product	Dosage Form and Strength	Manufacturer
Elotuzumab	400 and 300 mg/vial	Bristol-Myers Squibb

8.1.1 Labeling, packaging, and supply

Elotuzumab for injection has been developed to be used as an IV infusion for clinical studies and will be provided by BMS to the Sarah Cannon Central Pharmacy, which will dispense it to the sites. The drug product is a nonpyrogenic lyophilized powder that is a white to off-white, whole or fragmented cake contained in 20 mL Type I glass vials, closed with 20 mm stoppers and sealed with aluminum seals. Each vial of drug product contains the labelled amount of elotuzumab drug substance, sucrose, sodium citrate dihydrate, citric acid monohydrate, and polysorbate 80. The drug product will be reconstituted prior to administration.

The immediate packaging will contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: Caution New Drug - Limited by United States law to investigational use.

8.1.2 Preparation and administration of elotuzumab

Each vial of elotuzumab should be reconstituted with sterile water for injection at the clinical site. Prior to IV administration, the reconstituted solution is diluted with 0.9% sodium chloride for injection to result in an elotuzumab concentration from 0.9 mg/mL to no higher than 6.6 mg/mL in a polyvinyl chloride or polyolefin infusion bag. Alternatively, 5% dextrose injection may be used as a diluent in place of 0.9% sodium chloride injection.

The infusion is to be administered through a sterile, non-pyrogenic, low-protein-binding in-line filter using an automated infusion pump. 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 should be started at 0.5 mL/minute and increased according to Table 7. Please note that infusion rate increases to the next higher level are permitted only if no infusion reactions are encountered.

Table 7 Elotuzumab infusion rates

Infusion rate	Duration of infusion	Volume delivered	Volume remaining[a]
Cycle 1 Dose 1	Approximate Total Duration: 2 hours 50 minutes		262 mL
0.5 mL/min	30 minutes	15 mL	247 mL
1.0 mL/min	30 minutes	30 mL	217 mL
2.0 mL/min	110 minutes	217 mL	0 mL
Cycle 1 Dose 2	Approximate Total Duration: 1 hour 13 minutes		262 mL
3.0 mL/min	30 minutes	90 mL	172 mL
4.0 mL/min	43 minutes	172 mL	0 mL
Cycle 1 Doses 3 & 4	Approximate Total Duration: 53 minutes		262 mL
5 mL/min	53 minutes	262 mL	0 mL
Cycle 2+	Approximate Total Duration: 53 minutes		262 mL
5 mL/min	53 minutes	262 mL	0 mL

a Volume for an 80 kg patient. Total volume varies according to patient weight.

8.1.3 Storage and use of elotuzumab

All study drugs must be kept in a secure place under appropriate storage conditions.

Elotuzumab for injection should be stored refrigerated at 2°C to 8°C (36°F to 46°F).

The reconstituted and diluted solution of elotuzumab for injection is stable for up to 24 hours, under refrigerated conditions, 2°C to 8°C (36°F to 46°F). The drug solution should be equilibrated to room temperature (process takes 2 to 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.

The dose of elotuzumab to be administered to a patient will be calculated by multiplying the patient's weight (kg) by 10 mg/kg or 20 mg/kg. After the dose is diluted in 0.9% sodium

chloride injection, or 5% dextrose injection, it must be fully administered within 8 hours, if stored at room temperature.

8.1.4 Precautions and risks associated with elotuzumab

8.1.4.1 Infusion reactions

Elotuzumab can cause infusion reactions. Infusion reactions were reported in approximately 10% of patients treated with ERd in the randomized trial in patients with MM. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of patients. 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 patients required interruption of the administration of elotuzumab for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose.

Administer premedication consisting of dexamethasone, antihistamines (H_1 and H_2 blockers), and acetaminophen prior to elotuzumab infusion.

Interrupt elotuzumab infusion for Grade 2 or higher infusion reactions and institute appropriate medical management.

8.1.4.2 Infections

In a clinical trial of patients with MM (N=635), infections were reported in 81.4% of patients in the ERd arm and 74.4% in the lenalidomide and dexamethasone (Ld) arm. Grade 3 to 4 infections were noted in 28% and 24.3% of ERd- and Ld-treated patients, respectively. Discontinuations due to infections occurred in 3.5% of ERd-treated and 4.1% of Ld-treated patients. Fatal infections were reported in 2.5% and 2.2% of ERd- and Ld-treated patients.

Opportunistic infections were reported in 22% of patients in the ERd arm and 12.9% of patients in the Ld arm. Fungal infections occurred in 9.7% of patients in the ERd arm and 5.4% of patients in the Ld arm. Herpes zoster was reported in 13.5% of patients treated with ERd and 6.9% of patients treated with Ld. Monitor patients for development of infections and treat promptly.

8.1.4.3 Second primary malignancies

In a clinical trial of patients with MM (N=635), invasive second primary malignancies have been observed in 9.1% of patients treated with ERd and 5.7% of patients treated with Ld. The rate of hematologic malignancies were the same between the ERd and Ld treatment arms (1.6%). Solid tumors were reported in 3.5% and 2.2% of ERd- and Ld-treated patients, respectively. Skin cancer was reported in 4.4% and 2.8% of patients treated with ERd and Ld, respectively. Monitor patients for the development of second primary malignancies.

8.1.4.4 Hepatoxicity

Elevations in liver enzymes (AST/ALT greater than 3 times the ULN, total bilirubin greater than 2 times the ULN, and ALP less than 2 times the ULN) consistent with hepatotoxicity were reported in 2.5% and 0.6% of ERd- and Ld-treated patients, respectively, in a clinical trial of

patients with MM (N=635). Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment. Monitor liver enzymes periodically. Stop elotuzumab upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

8.1.4.5 Interference with determination of complete response

Elotuzumab is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of CR and possibly relapse from CR in patients with IgG kappa myeloma protein.

8.2 Lenalidomide

Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys and drug shipment to the patient.

Lenalidomide is to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. Please refer to the US Package Insert (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf) for detailed information about administration.

Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program.

8.3 Dexamethasone

Dexamethasone is to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. In this study, dexamethasone will be administered both orally and intravenously. Commercial supplies will be used. Please refer to the US Package Inserts for detailed information on how to prepare and administer dexamethasone for injection (http://www.fda.gov/ohrms/dockets/dockets/07p0167/07p-0167-cp00001-02-Attachment-A-vol1.pdf) and how to administer dexamethasone tablets (http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Roxane/Dexamethasone/Dexamethasone+Tablets+Solution+and+Intensol.pdf).

8.4 Accountability for all study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

At the end of the study, all Sarah Cannon Development Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Sarah Cannon Development Innovations

Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact Sarah Cannon Development Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study as per IMWG and EBMT criteria (see Appendix A).

10. STATISTICAL CONSIDERATIONS

10.1 Statistical design

This is a multi-center, open-label, Phase 2 study to assess the feasibility and tolerance of the combination of ERd in the induction, consolidation, and maintenance treatment of transplant-eligible patients newly diagnosed with MM.

10.2 Sample size considerations

In a study looking at a similar population with lenalidomide and dexamethasone as induction treatments prior to transplant, only 68% of patients were able to reach the first randomization, which occurred after induction and mobilization, but before transplantation (Palumbo et al 2014). In this study, the lowest accepted feasibility will be 65% with a target of 80%. In order to test the null hypothesis of an induction feasibility rate of 65% versus an alternative hypothesis with an induction feasibility rate of 80%, 48 patients are required in order to have 85% power to test the null hypothesis using a one-sided exact binomial test at the 0.1 significance level. The null hypothesis will be rejected if the induction treatment is deemed feasible in at least 36 patients. To allow for a possible 10% drop-out rate, the sample size has been inflated to 53 patients.

10.3 Analysis population

The following analysis populations will be used:

- Response evaluation population is defined as patients who have completed at least 1 cycle of therapy.
- Safety population is defined as all patients who provide informed consent and receive at least one dose of study treatment.

10.4 Data analysis

A comprehensive description of the statistical analyses and related activities for this study will be documented in a statistical analysis plan, which will be finalized prior to database lock.

10.4.1 Timing of analyses

The primary efficacy endpoint, IFR, will be analyzed when 48 patients have completed 4 cycles of induction therapy and are able to start ASCT.

Interim safety analyses are described in Section 10.4.4.

The final analysis of all study data will occur after all patients have been followed for 3.5 years or at death (whichever comes first).

10.4.2 Demographics and baseline characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, completed the treatment/study by stage, and withdrawn from treatment/study for any reasons will be presented overall.

10.4.3 Efficacy analysis

All efficacy analyses will be performed using the response evaluation population.

The primary efficacy endpoint is:

- IFR defined as the percentage of patients successfully completing 4 cycles of induction treatment with ERd and able to start ASCT.

The secondary efficacy endpoints are:

- Complete response rate (CRR), defined as the percentage of patients who achieve a complete response (CR) or near complete response (nCR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and European Group for Blood and Marrow Transplantation (EBMT) criteria
- Overall response rate (ORR), defined as the percentage of patients who achieve at least a partial response (PR) to treatment at each stage of the study, i.e., induction, ASCT, consolidation, end of study as per IMWG and EBMT criteria
- Progression-free survival (PFS), defined as the time from start of induction treatment to documented progressive disease (PD) or death from any cause up to 3 years post first treatment
- Overall survival (OS), defined as the time from start of induction treatment to 3 years post first treatment or death from any cause, whichever comes first
- Consolidation feasibility rate (CFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of consolidation
- Maintenance feasibility rate (MFR), defined as the percentage of patients starting induction treatment with ERd successfully completing treatment to end of maintenance.
- Safety endpoints including 1) treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths, and 2) clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03) and abnormal vital signs.

The exploratory endpoint is:

- To evaluate MRD defined as the proportion of patients who are MRD positive versus those who are MRD negative.

The IFR will be computed and presented together with the exact 90% confidence interval (CI), using the method of Clopper and Pearson 1934. The null hypothesis of 65% IFR will be rejected if at least 36 patients are able to complete 4 cycles of induction treatment and start ASCT.

The CRR, ORR, CFR, MFR will be computed and presented together with the exact 90% CIs, using the method of Clopper and Pearson 1934.

The Kaplan-Meier product limit method will be used to estimate PFS and OS. Median values and rates at clinically relevant time points will be provided with the 90% CIs. A Cox Proportional Hazards Model may also be utilized to estimate the effects of patient baseline characteristics or known prognostic factors on PFS and OS.

10.4.4 Safety analysis

Interim safety analyses

Significant toxicities for this protocol are based on the most common Grade 3 or greater AEs reported in Lonial et al 2015 and include: infusion reactions, fatigue, neutropenia, thrombocytopenia, diarrhea, or any unexpected toxicity.

After 10 patients have completed induction, an interim safety assessment will be performed. If 3 or more patients experience unexpected or significant toxicity, further accrual will occur only after discussions between the Study Chair and funding partners.

After 10 patients have completed consolidation, an interim safety assessment will be performed. If 3 or more patients experience unexpected or significant toxicity, further accrual will occur only after discussions between the Study Chair and funding partners.

After 10 patients have completed 4 cycles of consolidation, an interim safety assessment will be performed. If 3 or more patients experience unexpected or significant toxicity, further accrual will occur only after discussions between the Study Chair and funding partners.

Final safety analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE Version 4.03. A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term by stage of treatment for all patients in the safety population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by stage of treatment.

Other safety endpoints including laboratory results, vital signs, and ECG findings will be summarized for all patients in the safety population.

Concomitant medications will be coded using the World Health Organization Drug Dictionary and they will be listed and summarized by stage of treatment group.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs and SAEs to the Sarah Cannon Development Innovations Safety Department (see Section 11.1.5 and Section 11.2, respectively). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious adverse events

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**
- **Potential drug-induced liver injury (DILI) is also considered an important medical event--see the DILI section below for a definition of a potential DILI event.**
- **Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.1**

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected adverse reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

11.1.5 Recording and reporting of adverse events

11.1.5.1 Recording of adverse events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatments). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 4.03, and changes will be documented.

If the AE is serious, it should be reported immediately to Sarah Cannon Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that

are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

11.1.5.2 Reporting period for adverse events

All non-serious AEs considered unrelated to study treatments by the treating Investigator, spanning from the start of study treatment until **30** calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All non-serious AEs considered related to study treatments by the treating Investigator, spanning from the start of study treatment until **60** calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs assessed by the Investigator as treatment-related are to be reported. All SAEs, including deaths, will be reported from the start of study treatment through **60** days after completion of protocol-specific treatment.

11.1.6 Assessment of adverse events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria (if applicable), suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves

upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

NO: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious adverse event reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to Sarah Cannon Development Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Following the start of study treatment, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures, until 60 days after discontinuing study treatment. **The Sarah Cannon Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to Sarah Cannon Development Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

Sarah Cannon Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sarah Cannon Development Innovations Safety Department as soon as it is available; these reports should be submitted using the Sarah Cannon Development Innovations SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of the responsible IRB.

11.3 Recording of adverse events and serious adverse events

11.3.1 Diagnosis versus signs and symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate

on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per IMWG Uniform Response Criteria), should not be reported as an SAE.

11.3.2 Persistent or recurrent adverse events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal laboratory values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sarah Cannon Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, prolonged hospitalization, or surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE to the Sarah Cannon Development Innovations Safety Department.

11.3.6 Pre-existing medical conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, abortion, birth defects/congenital anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (see Appendix E) should be completed and faxed to the Sarah Cannon Development Innovations Safety Department. Sarah Cannon Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to Sarah Cannon Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Sarah Cannon Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form (see Appendix E) should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Elotuzumab overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sarah Cannon Development Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2).

11.4 Protocol-defined events of special interest

The following are events of special interest, and will need to be reported expeditiously (see Section 11.1.5). These events include the following:

Elotuzumab - Hypersensitivity, Infusion reactions

11.5 Serious adverse event reporting requirements to BMS

Sarah Cannon Development Innovations Safety Department will forward SAE information to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

within 1 business day of Sarah Cannon Development Innovations Safety Department personnel becoming aware of the SAE.

Sarah Cannon Development Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation guidelines, FDA regulations, and/or local regulatory requirements.

11.5.1 Bristol-Myers Squibb-specific requirements for adverse event reporting

Following the start of study treatment, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures, until 60 days after discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsies).

The Investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

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 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.

11.5.2 Sponsor assessment of unexpected

The Sponsor is responsible for assessing an AE or SAR as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the Investigator's Brochure
- Event(s) is not listed at the specificity or severity that has been observed
- Event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, or that have previously been observed under investigation

When applicable, an unexpected AE may also apply to an event that is not listed in the current US Package Insert, or an event that may be mentioned in the package insert, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events are suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure or package insert), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the package insert or current Investigator's Brochure (Elotuzumab 2014).

11.5.3 Sponsor reporting for clinical studies under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Sarah Cannon Development Innovations Safety Department must also be faxed to pharmaceutical company that is supporting the study with either funding or drug supply:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study monitoring, auditing, and inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board approval

The clinical study protocol, informed consent form, Investigator's Brochure, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients, and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB/EC for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/EC.

Safety updates for elotuzumab will be prepared by the Sponsor or its representative as required for distribution to the Investigators and submission to the relevant IRB.

13.2 Regulatory approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the

Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and staff information

Personal data of the Investigators and sub-Investigators may be included in the Sarah Cannon Development Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-Investigator, Sarah Cannon Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor, or its representatives. All amendments require review and approval of Bristol-Myers Squibb and the Study Chair supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, or addition or removal of new tests or procedures shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor, as applicable, and IRB approval obtained, specifically when an increase to dosing or

patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from the IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation required to initiate the study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Charlotte Avenue, Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB/EC approval of the study and the IRB/EC members list
- Current Curricula Vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of Sarah Cannon Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)

- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Study documentation and storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the Investigator's Brochure and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity, and batch/code or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last

marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records); all original, signed ICFs; and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor (Sarah Cannon Development Innovations) throughout the study, and will be held by the Sponsor at the conclusion of the study.

14.4 Data collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' statuses throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Sarah Cannon Development Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and publication policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

15. REFERENCES

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16. APPENDICES

Appendix A: Response Criteria for Multiple Myeloma

International Myeloma Working Group (IMWG) Criteria[1,2]	
Response Category	**Definition**
sCR **Stringent Complete Response**	CR criteria as defined below AND • Normal free light chain (FLC) ratio AND • Absence of clonal PCs by immunochistochemistry or 2-to 4-color flow cytometry
CR **Complete Response**	• Negative immunofixation on the serum and urine AND • Disappearance of any soft tissue plasmacytoma(s)AND • ≤5% plasma cells in bone marrow[b]. • In case the only measurable disease in a patient with CR at baseline is the serum FLC level, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR.
VGPR **Very Good Partial Response**	• Serum and urine M-protein detectable by immunofixation but not by electrophoresis (PEP) or ≥90% reduction from baseline serum AND urine M-protein level <100 mg/ 24 hours AND • In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytomas In case the only measurable disease in a patient with VGPR at baseline is the serum FLC level (i.e. no measurable disease in serum and urine PEP), a decrease of > 90% in the difference between involved and uninvolved FLC levels from baseline is required.
PR **Partial Response**	≥50% reduction from baseline in serum M-protein AND ≥90% reduction from baseline in 24h urinary M-protein OR urine M-protein <200 mg/24 hours If serum and urine M-protein are non-measureable at baseline, a ≥50% reduction form baseline 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 non-measurable, and serum free light assay is also non-measurable, ≥50% reduction from baseline in percent plasma cells in bone marrow is required instead of M-protein measurement, provided baseline plasma cells in bone marrow was ≥30%. AND In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in

	the SPD by ≥50% is required.

Appendix A: International Myeloma Working Group Uniform Response Criteria: Complete Response and Other Response Categories (continuation)

SD	Not meeting criteria for sCR, CR, VGPR, PR or PD
PD[c] **Progressive Disease**	Increase of ≥ 25% from the nadir in at least one of the following criteria: • serum M-protein (absolute increase must be ≥0.5 g/dL and absolute value must be ≥1 g/dL) • urine M-protein (absolute increase must be ≥200 mg/24h) • only in patients with non-measurable serum and urine M-protein levels: difference in involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • only in patients with non-measurable serum and urine M-protein levels and non-measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥10%) OR • definite development of new lytic bone lesions or increase from baseline in size of lytic bone lesion(s) OR • development of new soft tissue plasmacytoma(s) or definite increase from nadir in existing soft tissue plasmacytomas OR • development of hypercalcemia (corrected serum calcium >11.5 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will only be assessed due to the hypercalcemia criterion in case the corrected serum calcium level was ≤11.5 mg/dL post-baseline and increased thereafter beyond 11.5 mg/dL.

Additional Response Criteria for Specific Disease States (adopted from the European Group for Blood and Marrow Transplantation [EBMT] Criteria)[1,2,3,4]	
MR **Minor response in patients with relapsed and refractory myeloma**	• ≥25% but ≤49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% AND • If present at baseline, 25-49% reduction in the size of sort tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response
nCR **Near Complete Response**	• The absence of myeloma protein on electrophoresis, with positive immunofixation, stable bone disease, and a normal serum calcium concentration.
Immunophenotypic CR	• Stringent CR AND • 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 AND • Negative ASO-PCR (sensitivity 10^{-5})

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] At any point in this treatment, patients suspected of PD will have response assessed again to confirm disease progression (i.e. 2 sets of response assessments at least 1 week apart). The outcomes will be reviewed by the study chair before the patient is removed from the study

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
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4. Richardson et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Eng J Med. 352:2487-98, 2005

Appendix B: Diagnostic Criteria and Staging for Multiple Myeloma

This appendix contains both 2011 IMWG criteria and 2014 IMWG criteria. Please note the set of criteria used in the eCRF.

International Myeloma Working Group Criteria for Diagnosis (2011)

The following criteria must be met, except as noted:

- clonal bone marrow plasma cells ≥10%
- presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma*) and
- evidence of end-organ damage, which can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - hypercalcemia: serum calcium ≥11.5 mg/dL
    - renal insufficiency: serum creatinine >2 mg/dL
    - anemia: normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or, a hemoglobin value of <10 g/dL
    - bone lesions: lytic lesions, severe osteopenia or pathologic fractures

*More than 10% clonal plasma cells are required for the diagnosis of nonsecretory myeloma

Dimopoulos., et al., Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. 2011 Blood J 117: 4701-4705

Revised International Myeloma Working Group Criteria for Diagnosis (2014)

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.

A: Durie and Salmon Staging System

Stage I

All of the following:

- Hemoglobin >10 g/dL
- Serum calcium <12 mg/dL
- Normal bone structure or solitary plasmacytoma on radiographs
- Low M component
  - IgG <5 g/dL
  - IgA <3 g/dL
  - Urine light chains <4 g/24 hours

Stage II

Fitting neither Stage I nor Stage III

Stage III

One or more of the following:

- Hemoglobin <8.5 g/dL
- Serum calcium >12 mg/dL

- Advanced lytic bone lesions
- Hyper M component
  - IgG >7 g/dL
  - IgA >5 g/dL
  - Urinary light-chain excretion >12 g/24 hours

Subclassification

A: serum creatinine <2.0 mg/dL

B: serum creatinine equal to or >2.0 mg/dL

B: International Staging System (ISS) for Myeloma

Stage I Serum $ß_2$-microglobulin <3.5 mg/L

Serum albumin ≥3.5 g/dL

Stage II Fitting neither Stage I nor III*

Stage III Serum ß2-microglobulin ≥5.5 mg/L

There are two categories for Stage II: serum $ß_2$-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum $ß_2$-microglobulin ≥3.5 mg/L and <5.5 mg/L irrespective of the serum albumin level.

Greipp P., et al., International staging system for multiple myeloma. 2005. JCO 23:3412-3420

Appendix C: ECOG and Karnofsky Performance Status Scales

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix D: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix E: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Females of reproductive potential must have 2 negative pregnancy tests prior to initiating therapy. The first test should be performed within 10 to 14 days, and the second test within 24 hours prior to administration of study therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception for at least 4 weeks before beginning study therapy, during therapy, during dose interruptions, and for 4 weeks following discontinuation of study therapy.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Lenalidomide is present in the semen of patients receiving the drug. Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of child-bearing potential must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide, during dose interruptions, and for 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

If pregnancy does occur during treatment, lenalidomide must be discontinued immediately.

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the **Sarah Cannon Development Innovations Safety Department** within 24 hours of learning of its occurrence using the pregnancy form at the end of this appendix. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented

evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

PREGNANCY FORM
Date of Report (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐
Investigative Site Name/ Number:
Clinical Study Number/ Protocol:
Patient Initial: ☐☐☐ Patient Number: ☐☐☐☐☐☐☐☐ Patient Date of Birth (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

PREGNANCY TEST RESULT	
☐ N/A (Female, post-menopausal/ surgically sterile)	
Result	Date of Test Result (DD/MMM/YYYY)
☐ Negative ☐ Positive ☐ Not Done	☐☐/☐☐☐/☐☐☐☐

PREGNANCY OUTCOME		
Date of Outcome (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐		
RESULT	☐ Carried to Term	☐ Ectopic Pregnancy
	☐ Spontaneous Abortion	☐ Congenital Abnormality
	☐ Elected Abortion	☐ Unknown

MOTHER COMPLICATIONS
Did the mother experience any complications during: *(check all that may apply)* ☐ Pregnancy ☐ Labor/ Delivery ☐ Postpartum

If yes, please explain:
_____

Intervention:
_____

Continuing: ☐ Yes ☐ No

PREGNANCY/ FETAL OUTCOME	
☐ Live Birth/ Full Term (>37 weeks)	☐ Spontaneous/ Missed Abortion, Gestational Age: _____
☐ Live Birth/ Premature (<37 weeks)	☐ Fetal Death in Utero/ Stillbirth, Gestational Age: _____
☐ Live Birth and Neonatal Death	☐ Post-Natal Death, Age:_____

Were congenital or chromosomal abnormalities detected? ☐ Yes ☐ No

If yes, please specify:
_____

Completed by: _____ Date: _____

Reviewed by: _____ Date: _____

Appendix F: Neurotoxicity Questionnaire

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

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

Instructions for Health Care Professionals

This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. There is no correlation between assessment scores and toxicity grades.

Appendix G: Schedule of assessments MM 61

ASSESSMENTS	Screen[a]	ERd Induction Cycles 1 through 4						End of Cycle 4 thru Start of Mobilization	70-120 Days Post Trans Plant[h]	ERd Consolidation[v] Cycles 6 through 8 (Start 70 to 120 days Following ASCT)		End of Cycle 8 1 yr Post ASCT FU Visit	ERd Maintenance 2 Years C 9+	End of Treatment Visit[s]	Off Study FU Before PD[t]	Off Study FU After PD[u]
		C 1&2				C 3&4										
Days	-28 to 1	1	8	15	22	1	15			1	15		1			
Informed consent	X															
Revlimid REMS® program[b]	X															
Medical history[a]	X	X				X				X			X	X		
Physical examination[a,c]	X	X				X			X	X			X	X	X	
Peripheral neuropathy questionnaire[a]	X	X				X			X	X			X	X	X	
Vital signs[a,d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status[a]	X	X				X			X	X			X	X		
12-lead electrocardiogram[a]	X															
AE and SAE evaluations[e]		X	X	X	X	X	X	X		X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X		X	X	X	X	X		
CBC, 3-part diff and platelets[a]	X	X	X	X	X	X	X		X	X	X		X	X	X	
CMP plus mag and phos[a,f]	X	X	X	X	X	X	X		X	X	X		X	X	X	
Coagulation tests[a,g]	X															
LDH and uric acid[a]	X	X				X			X	X			X	X		
Serum or urine pregnancy test and counseling [i]	X	X	X	X	X	X	X	X[i]	X	X	X	X	X	X		
C-reactive protein[a]	X															
Disease Assessments: **Restaging at the end of every cycle[j]**																
UPEP and immunofixation[j,k]	X	X[j]				X[j]		X	X	X[j]		X	X[o]	X	X	
SPEP and immunofixation[j,l]	X	X[j]				X[j]		X	X	X[j]		X	X[o]	X	X	
Serum-free light chain[j]	X	X[j]				X[j]		X	X	X[j]		X	X[o]	X	X	
Serum β2-microglobulin	X															
Quantitative Igs[j]	X	X[j]				X[j]		X	X	X[j]		X	X[o]	X	X	
BM aspirate/biopsy	X[m]							X[n]	X[n]	X[n]		X[n]		X[n]		
Gene expression profiling[m]	X															
MRD evaluation[n]	X							X[n]	X[n]	X[n]		X[n]	X	X[n]		
Plasmacytoma evaluation[p]	X	X[j]				X[j]		X	X	X[j]		X	X[o]	X	X	
Skeletal survey[q]	X								X			X		X[q]		
Survival status														X	X	X
Study Drug Administration																
Elotuzumab		X	X	X	X	X	X			X	X		X			
Lenalidomide		1 thru 21				1 thru 21				1 thru 21			1 thru 21			
Dexamethasone IV[r]		X	X	X	X	X	X			X	X		X			
Dexamethasone Oral		X	X	X	X	1, 8, 15 & 22				X	X		X			
Study drug compliance		X	X	X	X	X	X	X		X	X	X	X	X		

Appendix G: Schedule of Assessments (continued)

a Baseline procedures including medical history, physical examination (including a neurological evaluation and a peripheral neuropathy questionnaire), ECOG performance status, 12-lead ECG, CBC, CMP plus magnesium and phosphorus, prothrombin time (PT)/activated partial thromboplastin time (aPTT)/and International Normalized Ratio (INR), LDH and uric acid, and c-reactive protein (CRP) should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1, they do not have to be repeated.

b Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program.

c Physical examinations will include the measurement of height at the screening visit only. Patients should be weighed within 24 hours prior to elotuzumab dosing on Day 1 of each cycle, in order to calculate the correct dose. Measurement of weight is not required for visits occurring after completion of treatment. All physical examinations should include an assessment of peripheral neuropathy (see Appendix F).

d Vital signs will include resting heart rate, systolic and diastolic blood pressure readings, respiratory rate, and temperature.

e All events will be recorded from first study treatment. Non-serious AEs considered by the Investigator to be unrelated to study treatments will be collected for **30** days post last treatment, and non-serious AEs considered by the Investigator to be related to study treatments and all SAEs will be collected for **60** days post last treatment.

f CMP will include measurements of glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, magnesium, and phosphorus.

g Coagulation tests: PT, aPTT, and INR. If normal at baseline, they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

h Standard of care 70 to 120 day post-transplant visit before start of the first consolidation cycle (Cycle 5)

i Serum or urine pregnancy tests and pregnancy counseling are to be conducted in women of childbearing potential. For definition of childbearing potential, see Appendix E. Two serum or urine pregnancy tests must be performed; one 10 to 14 days prior to initiation of study treatment and one within 24 hours of initiation of study treatment. Serum or urine pregnancy tests, including pregnancy counseling, for women of childbearing potential will continue weekly during Cycle 1, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. For those with irregular menses, pregnancy tests are required at 14 and 28 days after treatment discontinuation of lenalidomide. From the end of Cycle 4 thru the start of mobilization, pregnancy tests are not required, but women of child-bearing potential should be reminded to follow approved birth control practices while off study treatment.

j Restage every cycle (4 weeks): response will be evaluated after completion of 1 treatment cycle. Thereafter, restaging must be done within a window of -7 to Day 1 of the next cycle. Disease assessments need only be done on Cycle 1 Day 1 if >14 days elapsed since baseline disease assessments.

k 24-hour urine total protein, urine protein electrophoresis (UPEP), and urine protein immunofixation. For patients whose disease is being monitored through UPEP, additional post baseline 24-hour urine collections are required, as indicated.

l Serum protein electrophoresis (SPEP): obtain blood for M-protein levels measured by SPEP and quantitative immunoglobulins for those patients in whom SPEP are felt to be unreliable (IgA type multiple myeloma), depending upon which studies were positive at baseline.

m Baseline bone marrow aspirate and biopsy are to be sent for flow cytometry, cytogenetics, and FISH for 1q amplification, 13 del, 1p del, t(4;14), t(11;14), t(14;16) and 17p del) per institutional guidelines. Sample should also be used for gene expression profiling (GEP) per institutional guidelines. Bone marrow aspirates/biopsies obtained ≤60 days prior to Cycle 1 Day 1 will be allowed.

n Bone marrow aspirates should be collected as clinically indicated. Anytime bone marrow is drawn for standard of care, such as 1-year and 2-years post-transplant, MRD analysis should be conducted per institutional guidelines.

o Beginning with Cycle 12 Day 1, restaging (SPEP, UPEP, plasmacytoma (if applicable), quantitative Igs [IgG, IgA, IgM], and SFLC) is to be conducted every 3 months during maintenance.

p Plasmacytoma: ONLY for patients with a known plasmacytoma that has been imaged before enrolling on study (to be done at baseline and every 2 cycles after that)

q Skeletal survey or alternate imaging as per institutional guidelines: should preferably be within 28 days of planned treatment start, but ≤60 days prior to Cycle 1 Day 1 is acceptable. This assessment includes lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Skeletal survey need only be repeated if clinically indicated (i.e., bone pain).

r Dexamethasone 8 mg IV is pre-medication on the day of elotuzumab infusion 45 to 90 minutes prior to the start of elotuzumab infusion (for all pre-medications, see Section 5.1.

s After patients are discontinued from the study, they will visit the study center ≤30 days from the date of last dose of study drug for end-of treatment-assessments. Patients must be followed for all AEs for **30** calendar days and for related AEs and SAEs for **60** calendar days after the last dose of study drug.

t Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) for a total of up to 3 years from initiation of treatment on the protocol or until they progress, whichever comes first.

u Patients with documented disease recurrence or progression will be followed every 3 months (±1 month) for survival status (e.g., date and cause of death) for up to 3 years from initiation of treatment on the protocol or death, whichever comes first. Patients may be contacted during outpatient visits or by telephone.

v Cycle 5 Day 1 assessments need to be done only if >21 days elapsed between the Day 70 to 120 evaluation and start of consolidation.