Title: An Open-Label, Single Arm, Phase 2a Study of Bortezomib, Lenalidomide, Dexamethasone and Elotuzumab in Newly Diagnosed Multiple Myeloma

NCT Number: NCT02375555

IRB Approval Date: 04/08/2021

Protocol Version Date: November 10, 2020
NCI Protocol #: N/A
BMS Protocol #: CA204-130
Local Protocol #: 14- 453

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Agents:
Lenalidomide - Celgene Corporation - commercial supply
Bortezomib - Millennium Pharmaceuticals, Inc. – commercial supply
Dexamethasone – commercial supply
Elotuzumab – Bristol-Myer Squibb (BMS) – investigational supply

SYNOPSIS

Title	An Open-Label, Single Arm, Phase 2a Study of Bortezomib, Lenalidomide, Dexamethasone and Elotuzumab in Newly Diagnosed Multiple Myeloma
Study Objectives	**Original Primary Objective** • To estimate the response rate after 4 cycles in subjects treated with elotuzumab plus bortezomib, lenalidomide and dexamethasone (E-RVD). **Original Secondary Objectives** • To estimate the proportion of subjects with successful stem cell mobilization after receiving 4 cycles of treatment with E-RVD. • To estimate the proportion of subjects requiring dose modification of any study drug during the first four cycles of E-RVD • To characterize safety in subjects who receive E-RVD • To provide preliminary information on the activity of E-RVD including best response, objective response rate (ORR), including ORR at end of 8 cycles for patients that complete 8 cycles of induction therapy, duration of response, time to response, progression free survival (PFS) and time to next treatment. **Original Exploratory Objectives** • For subjects who elect to undergo autologous stem cell transplant (ASCT), to characterize engraftment parameters The original objectives of the study have now been met as of October 2020. The new primary objective will be safety. The following information will be collected: • All SAEs. • All ≥Grade 2 AEs. • New primary malignancies. • Any AE resulting in dose modification or discontinuation of any study drug. • Any other AE that in the opinion of the investigator is a clinically significant event.
Study Design	This is an open-label Phase 2a study of E-RVD. The study will treat approximately 40 autologous stem-cell transplant (ASCT)-eligible subjects with newly diagnosed multiple myeloma (MM). **Induction Cycles 1 - 8:** Induction regimen will consist of a treatment cycle every 21 days with: • Elotuzumab at 10 mg/kg IV on Days 1, 8, and 15 in Induction Cycles 1 and 2 and 10 mg/kg IV on Days 1 and 11 in Induction Cycles 3 through 8. • Bortezomib at 1.3 mg/m^2 subcutaneous (SQ) injection on Days 1, 4, 8, and 11 followed by a 10-day rest period of cycles 1 – 8.

- Lenalidomide as a single daily oral dose of 25 mg on Days 1 - 14 of Cycles 1 - 8 followed by 7-day rest period. (Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline).
- Dexamethasone as a single daily oral dose of 20 mg/day on Days 2, 4, 5, 9, 11, and 12 during cycles 1 and 2.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1, 8, and 15 of Induction Cycles 1 and 2.
- Dexamethasone as a single oral dose of 20 mg/day on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 3 and 4.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of Induction Cycles 3 and 4.
- Dexamethasone 10 mg as a single oral dose of 10 mg on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 5 through 8.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of induction Cycles 5 through 8.

Stem cell mobilization: Stem cell mobilization will be performed for all subjects at the end of Induction Cycle 4. Stem cell mobilization will be performed with either cyclophosphamide 2500 mg/m^2 and filgrastim or filgrastim with or without plerixafor according to institutional guidelines. If stem cell mobilization using this approach is unsuccessful, a second attempt at collection can be undertaken within one month of the first attempt at mobilization. Subjects who attain at least a partial response (PR) may elect to stop E-RVD at the end of Induction Cycle 4 and proceed to autologous SCT as per the institutional guidelines. Subjects who do not proceed to SCT may receive a full 8 cycles of the induction therapy.

The decision whether subjects will proceed to SCT will be made on the basis of treating physician recommendations and patient preference. Physician recommendations are typically based on disease response and on how well subjects are tolerating treatment. The kind of decision making process related to SCT is considered nowadays standard of care in the multiple myeloma field.

Maintenance: Subjects who receive 8 cycles of the induction regimen will be allowed to continue treatment on a maintenance schedule, if they have at least stable disease and are eligible to receive maintenance treatment. Additionally, subjects who received SCT at the end of Induction Cycle 4 will forego Cycles 5 to 8 of therapy and will be allowed to continue treatment directly on a maintenance schedule after recovery from SCT.

Maintenance therapy will continue until disease relapse, unacceptable toxicity, withdrawal of consent or until the treating physician determines treatment discontinuation is in the best interest of the patient. Subjects unable to tolerate any of the individual drugs (eg, elotuzumab, lenalidomide, bortezomib or dexamethasone) during the maintenance phase may stop those individual drugs and continue on the remaining drugs, at the investigator's discretion.

Maintenance therapy will be administered to all patients, with the specific maintenance regimen determined by risk category. Each Maintenance cycle is 28 days.

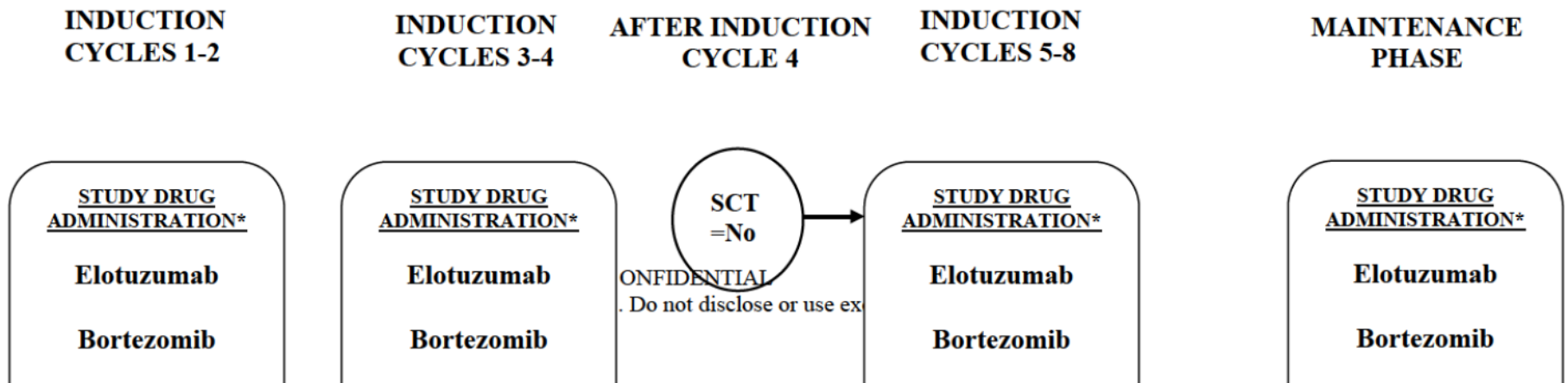
	Patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance with: • Elotuzumab 20 mg/kg on Day 1 of each 28 day cycle; • Lenalidomide 10 mg Days 1 – 21; • Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ; • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab). **Patients undergoing ASCT who are ISS I or II without high-risk** cytogenetics will receive maintenance with: • Elotuzumab 20 mg/kg Day 1 of each 28 day cycle; • Lenalidomide 10 mg Days 1 – 21; and • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab). **Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage II or III and/or have high-risk cytogenetics** including t(4;14), t(14;16); or del17p will receive maintenance with: • Elotuzumab 20 mg/kg on Day 1 of each 28 day cycle; • Lenalidomide at the dose tolerated during induction Days 1 – 21; • Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ; and • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab). **Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage I without high-risk cytogenetics** will receive maintenance with: • Elotuzumab 20 mg/kg Day 1 of each 28 day cycle; • Lenalidomide at the dose tolerated during induction Days 1 – 21; and • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab).
Study Procedures	Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (ODQ) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied. See Section 4 of the protocol for details.
Participant Sample	41 participants have been enrolled on this protocol.

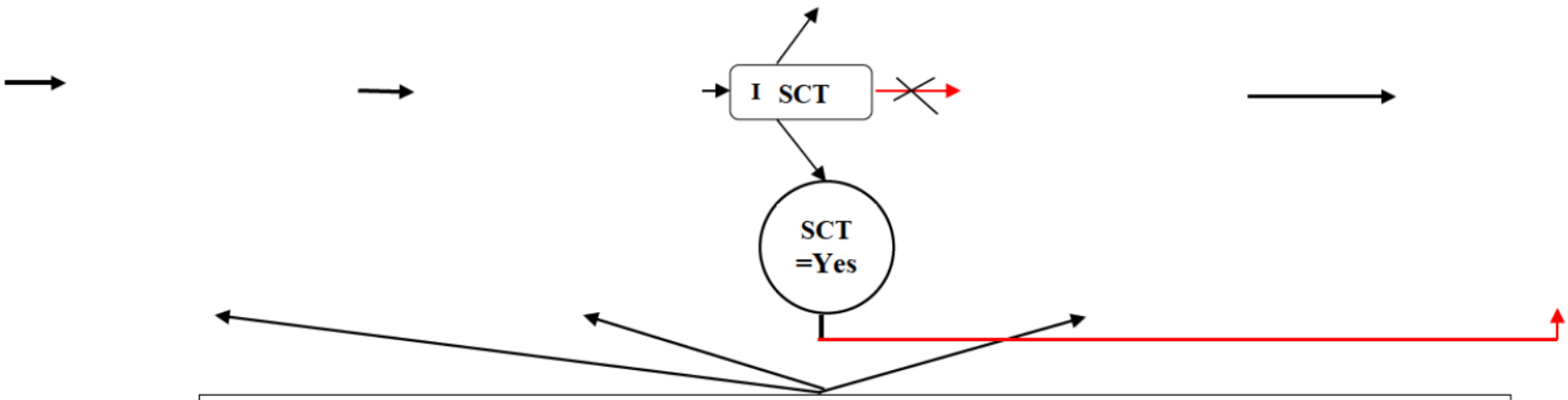
Treatment and Dosage	**Induction (Cycles 1 - 8):** • Elotuzumab at 10 mg/kg IV on Days 1, 8, and 15 in Induction Cycles 1 and 2 and 10 mg/kg on Days 1 and 11 in Induction Cycles 3 through 8. • Bortezomib at 1.3 mg/m^2/ SQ injection on Days 1, 4, 8, and 11 of Cycles 1 - 8, followed by a 10-day rest period. • Lenalidomide as a single daily oral dose of 25 mg on Days 1 - 14 of Cycles 1 - 8 followed by 7-day rest period. (Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline). • Dexamethasone as a single daily oral dose of 20 mg/day on Days 2, 4, 5, 9, 11, and 12 during Cycles 1 and 2. • Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1, 8, and 15 in during Induction Cycles 1 and 2. • Dexamethasone as a single oral dose of 20 mg/day on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 3 and 4. • Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of Induction Cycles 3 and 4. • Dexamethasone 10 mg as a single oral dose of 10 mg on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 5 through 8. • Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of induction Cycles 5 through 8. **Maintenance:** The maintenance schedule will start after completion of 8 cycles of the induction regimen or after recovery from SCT Maintenance therapy will be administered to all patients, with the specific maintenance regimen determined by risk category. **Patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics** including t(4;14), t(14;16); or del17p will receive maintenance with: • Elotuzumab 20 mg/kg on day 1 of each 28 day cycle; • Lenalidomide 10 mg Days 1 – 21; • Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ; • IV dexamethasone 8 mg on Day 1. **Patients undergoing ASCT who are ISS I or II without high-risk** cytogenetics will receive maintenance with: • Elotuzumab 20 mg/kg Day 1 of each 28 day cycle; • Lenalidomide 10 mg Days 1 – 21; and

	• IV dexamethasone 8 mg on day 1 (45-90 minutes before elotuzumab). **Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage II or III and/or have high-risk cytogenetics** including t(4;14), t(14;16); or del17p will receive maintenance with: • Elotuzumab 20 mg/kg on Day 1 of each 28 day cycle; • Lenalidomide at the dose tolerated during induction Days 1 – 21; • Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ; and • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab). **Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage I without high-risk cytogenetics** will receive maintenance with: • Elotuzumab 20 mg/kg Day 1 of each 28 day cycle; • Lenalidomide at the dose tolerated during induction Days 1 – 21; and • IV dexamethasone 8 mg on Day 1(45-90 minutes before elotuzumab).
Duration of the Study	Participants who have stable or responding disease to treatment and have an acceptable toxicity profile will be allowed to continue treatment until disease relapses, unacceptable toxicity develops, the patient withdraws consent or until the treating physician determines treatment discontinuation is in the best interest of the patient.
Safety Parameters	Prior to enrollment each participant will have their medical history documented. The history will be updated at baseline (Cycle 1, Day 1), and throughout participation in the study as indicated by clinical symptoms. Participants will undergo physical examination (to include vital signs), query for adverse events and concomitant medication use, and clinical laboratory testing, according to the details outlined in Section 9. Assessment of peripheral neuropathy will occur on Day 1 of each cycle. Completion of the peripheral neuropathy questionnaire (FACT/GOG Ntx) will occur on Day 1 of odd cycles. Adverse experiences, including clinical laboratory and vital sign abnormalities, will be graded using CTEP Version 4.03 of the NCI Common Terminology for Adverse Events (CTCAE). Body surface area will be calculated prior to each cycle of bortezomib. The effect of elotuzumab has been studied extensively in combination with Lenalidomide and Bortezomib, and dosages of 10 mg/kg IV are used in all phase III and randomized phase II studies to date. Nonetheless, the four drug combination proposed in this study has not yet being evaluated in humans. Therefore, after the enrollment of 10 subjects in the study, further subject enrollment will be placed on hold to evaluate safety/toxicity data pertaining the 4 drug combination, and specifically regarding Elotuzumab.
Efficacy Parameters	It is recommended that disease assessments are performed per standard of care.

ENROLLMENT

Study Schema





Tumor assessments at the beginning of every cycle
(starting at Induction Cycle 2)
(Even if subject discontinues 1 or more study drugs, tumor assessment should continue until progression

DRA – disease response assessment; SCM – stem cell mobilization; SCT – stem cell transplant

*Induction cycles are 21 days and maintenance cycles are 28 days in length. *
Subjects who receive 8 cycles of the induction regimen will be allowed to continue treatment on a maintenance schedule and subjects who received SCT at the end of Induction Cycle 4 will forego Cycles 5 to 8 of therapy and will be allowed to continue treatment directly on a maintenance schedule after recovery from SCT.
Please refer to Table Section 5 for different dosages of drugs in Induction Cycles and Maintenance Phase
*Subjects who receive 8 cycles of the induction regimen will be allowed to continue treatment on a maintenance schedule and subjects who received SCT at the end of Induction

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Abbreviation	Definition
°C	degrees Celsius
°F	Degrees Farenheit
ADL	Activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
ATRA	All trans-retinoic acid
BM	Bone marrow
Bpm	beats per minute
BSA	body surface area
BMSC	Bone marrow stromal cells
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive heart failure
Cm	Centimeter
CR	Complete Response
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DAR	Drug accountability record
DF/HCC	Dana-Farber/Harvard Cancer Center
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DVT	Deep vein thrombosis
EBMT	European Group for Blood & Marrow Transplant
ECG	Electrocardiography
ECHO	Echocardiogram

Abbreviation	Definition
ECM	Extracellular matrix
ECOG	Eastern Cooperative Oncology Group
ERK	Extracellular signal-regulated kinase
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
FLC	Free light chain
G	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HIV	Human immunodeficiency virus
Ht	Height
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor
IL-6	Interleukin-6
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	International Staging System
IV	Intravenous
Kg	Kilogram
Lbs	Pounds
L	Liters
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
m^2	square meters
mm^3	Cubic millimeter
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
Mg	Milligrams
Ml	Milliliter
MM	Multiple myeloma
m-protein	Monoclonal protein
MR	Minimal response
MRI	Magnetic resonance imaging
Msec	Millisecond
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NC	No change
NCI	National Cancer Institute
nCR	near complete response
NF-κB	nuclear factor-κB
Ng	Nanogram
NK cell	Natural killer cell
nM	Nanomole
NYHA	New York Heart Association
OHRS	Office of Human Research Studies
p21	p21(ras) farnesyl-protein transferase
p53	tumor suppressor protein with molecular weight of 53 kDa
PBMC	Peripheral blood mononuclear cell
PC	Plasma cells
PCP	Pneumocystis carnii pneumonia
PD	Progressive disease
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
ODQ	Quality Assurance for Clinical Trials
QOW	Every other week

Abbreviation	Definition
QW	Every week
RNA	Ribonucleic acid
RR	Response rate
SAE	serious adverse event
sCR	Stringent Complete Response
SCT	Stem cell transplantation
SD	Stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOC	System organ class
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
SQ	Subcutaneous
TEN	Toxic epidermal necrosis
TFR	Tumor flare reaction
TIW	Three times a week
TLS	Tumor lysis syndrome
TSH	Thyroid-stimulating hormone
TTR	Time-to-response
ULN	Upper limit of normal
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
WBC	White blood cells
Wt	Weight

1 INTRODUCTION (BACKGROUND)

1.1 Multiple Myeloma (MM)

1.1.1 Epidemiology and pathogenesis

MM is a B-cell neoplasm characterized by the proliferation of clonal plasma cells and associated with a variety of clinical manifestations such as lytic bone lesions, hypercalcemia, renal impairment, and anemia. It accounts for 10-15% of hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow (McKenna, 2008). The high degree of immunoglobulin (Ig) heavy chain gene hypermutation present in MM cells suggests that tumor cells derive from a post-germinal center B-cell (Bakkus, 1992). Moreover, it is likely that mutations occurring during Ig receptor hyper-mutation and class switch are involved in the pathogenesis of MM. Indeed a substantial percentage of MM patients have chromosomal aberrations involving the Ig heavy chain gene at locus 14q32 (Fonseca, 2003). Partner genes in translocations involving the Ig heavy chain include cyclin D1 (chromosome 11q13), cyclin D3 (chromosome 6p21), FGFR3/MMSET (chromosome 4p16), and C-MAF (chromosome 16q23). It is believed that such mutations lead to dysregulated growth of the affected clone. C-MAF, for example, appears to augment MM cell proliferation and binding to surrounding bone marrow stromal cells (BMSCs) (Hurt, 2004). Inhibition of FGFR3, meanwhile, has been shown to promote plasma cell differentiation and induce apoptosis (Chauhan, 1995). Gain or loss of specific chromosomal regions is also frequently observed, including monosomy or partial deletion of chromosome 13, loss of the short arm of chromosome 17 (site of the tumor-suppressor gene TP53), and gains or amplification of chromosomal region 1q (Hanamura, 2006).

The pathogenesis of MM is also driven by interactions between MM cells and the bone marrow microenvironment, which is composed of extracellular matrix proteins such as fibronectin, collagen, and laminin, along with cellular elements such as hematopoietic stem cells, immune cells, bone marrow endothelial cells, and bone marrow stromal cells (BMSCs). Adhesion of MM cells to ECM proteins and accessory cells leads to increased expression of factors such as IL-6, insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF), which in turn further stimulates growth and survival of the malignant clone (Chauhan, 1995; Podar, 2001). Various intracellular pathways are involved in this response, including the Ras-Raf-MAPK kinase, (MEK)-extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)-Akt, and the Janus kinase 2-signal transducer and activator of transcription 3 (STAT3) pathways (Hideshima, 2007).

1.1.2 Staging

Since 1975, the Durie-Salmon classification system has been widely used for disease diagnosis and staging. Stages I, II and III are defined by criteria for bone lesion status, hemoglobin, serum calcium, and monoclonal protein (M-protein) levels and subcategorized as A or B on the basis of renal function. A clear correlation between disease stage and survival duration has been demonstrated (Durie, 1986). The International Staging System (ISS) was established more recently (Greipp, 2005), and is based on the levels of serum β2M and albumin among MM patients at diagnosis. The ISS has been validated as a predictor of overall survival for MM patients.

1.1.3 Treatment

Patients with early stage, asymptomatic MM are typically observed without systemic chemotherapy (Alexanian, 1980; Kyle, 1980). Such patients are carefully monitored with appropriate clinical assessment, including laboratory studies, every two to three months. Treatment is indicated when significant disease-related symptoms or organ dysfunction develop. Historically, patients ineligible for stem cell transplantation (SCT) have been treated with the combination of melphalan and prednisone (MP) (Alexanian, 1969), while those eligible for SCT received the three-drug combination of vincristine, doxorubicin, and dexamethasone (Samson, 1989). MP produced a partial response (PR) in approximately 50% of patients, and a complete response (CR) in 3-5%. Efforts to augment chemotherapy sensitivity and improve patient outcomes led to the evaluation of various multidrug combinations, including vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) (Lee, 1974); carmustine, melphalan, cyclophosphamide, and prednisone (BMCP) (Cooper, 1986); and vincristine, doxorubicin, and dexamethasone (VAD) (Samson, 1989). However, while these agents produced higher rates of response than MP, they did not lengthen remission or prolong overall survival.

Over the past decade, the management of MM has changed dramatically with the introduction of new and more active therapies. These include the immunomodulatory agents, thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib. Thalidomide, the first of these drugs to be developed clinically, exerts its anti-MM activity through various mechanisms, including enchancement of T-cell and NK-cell mediated immunological response, alteration of the bone marrow microenvironment, induction of caspase-8 mediated apoptosis, and inhibition of angiogenesis (D'Amato, 1994). Initial clinical evaluation of thalidomide demonstrated the agent's significant activity even in heavily pretreated patients with relapsed and refractory disease (Singhal, 1999). In the setting of newly diagnosed MM, thalidomide plus MP has proven to be superior to MP alone in terms of both response and median overall survival (Facon, 2007; Palumbo, 2006).

Lenalidomide, an analogue of thalidomide, has more potent anti-MM activity than its parent compound and a more favorable toxicity profile. Following a series of early phase clinical trials, the clinical activity of lenalidomide in relapsed MM was confirmed in two large phase III trials comparing lenalidomide plus dexamethasone to dexamethasone alone (Weber, 2007; Dimopoulos, 2007). Several lenalidomide-based combinations, including lenalidomide plus dexamethasone and lenalidomide plus MP have proven to be effective in the treatment of patients with newly diagnosed MM (Rajkumar, 2009; Palumbo, 2009).

Bortezomib is a proteasome inhibitor that inhibits NFKB, induces caspase-8/9 mediated apoptosis, and disrupts IL-6 induced intracellular signaling pathways (Hideshima, 2003). In a landmark phase III trial, bortezomib was superior to high dose dexamethasone in relapsed MM (Richardson, 2005). The agent has also been associated with promising results in patients with newly diagnosed disease. In this setting the combination of bortezomib plus MP was superior to MP alone with respect to response, remission duration, and overall survival (San Miguel, 2008). More recently, subcutaneous (s.q.) bortezomib was compared to intravenous (i.v.) bortezomib in a randomized, phase III non-inferiority study involving patients with relapsed disease and found to be equivalent

in terms primary efficacy endpoints with significantly less therapy-induced peripheral neuropathy (Moreau, 2011).

Preclinical evidence of synergy between lenalidomide and bortezomib provided rationale for combination therapy with lenalidomide and bortezomib. A phase I multicenter study established the MTD of the regimen at lenalidomide 15 mg/d Days 1-14 and i.v. bortezomib 1 mg/m^2 Days 1, 4, 8, and 11 of a 21 day cycle (Richardson, 2009). Dexamethasone at either 20 or 40 mg on the day of and day following bortezomib was added for progressive disease after two cycles of treatment. Study participants had received a median of 5 prior lines of therapy, and 61% had previously undergone either autologous or allogeneic SCT. DLTs included grade 3 hyponatremia and herpes zoster reactivation, as well as grade 4 neutropenia. The most common grade 3/4 toxicities were neutropenia, thrombocytopenia, anemia, and leucopenia. The combination demonstrated significant activity, with 61% of patients achieving a minimal response (MR) or better, and 31% achieving at least a PR.

1.1.4 Elotuzumab: Mechanism of Action

Elotuzumab is a humanized IgG1 mAb targeted against Signalling Lymphocyte Activation Molecule (SLAMF7, also called CS1), a glycoprotein expressed on myeloma and Natural Killer cells but not on normal tissues. Elotuzumab binding to SLAMF7 directly activates NK cells, but not myeloma cells. Elotuzumab bound to myeloma cells via SLAMF7 further activates NK cells via a CD16 mediated pathway thereby enabling selective killing of myeloma cells with minimal effects on normal tissue. SLAMF7 expression is restricted to malignant myeloma and normal plasma cells and subsets of normal leukocytes in humans (NK, NK-like T-cells [NKT], a subset of CD8 positive T-cells and tissue plasma cells).

Through both direct activation and engagement of Natural Killer cells, Elotuzumab selectively targets and kills SLAM F7 expressing myeloma cells. While analysis of mRNA indicates that CS1 has a similar expression pattern in nonhuman primates T-cells and tissue plasma cells).

1.1.5 Combination of elotuzumab with lenalidomide, bortezomib and dexamethasone

Lenalidomide is an oral immunomodulatory agent, a derivative of thalidomide with a distinct side effect profile. Currently, it is approved in combination with dexamethasone for the treatment of relapsed MM. The anti-myeloma activity of lenalidomide is mediated by multiple mechanisms of action, which target both the malignant cell and its microenvironment. This drug has also been shown to induce immune responses, enhance activity of immune cells, and inhibit inflammation. For instance, lenalidomide may enhance the activation of T cells and NK cells, induce production of interleukin-2, and inhibit pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin 1-beta. Since lenalidomide may enhance the activity of NK cells, which are central to the main biological activity of elotuzumab, the two drugs underwent preclinical testing in combination to determine the extent of potential synergy. Elotuzumab-mediated ADCC against

primary myeloma cells was significantly enhanced when the PBMC effector cells (which include NK cells) from the same subject were pretreated with lenalidomide (Investigator Brochure – Elotuzumab).

Dexamethasone, a glucocorticoid that is used extensively for the treatment of MM in combination with lenalidomide, as well as with most other anti-myeloma therapies, has been shown to directly induce apoptosis of myeloma cells by activation of caspases. The effect of combining dexamethasone with elotuzumab was also tested using an in vivo human myeloma xenograft model. Results indicated an additive anti-tumor effect in combination with elotuzumab.

Bortezomib is a small-molecule proteasome inhibitor approved for the treatment of MM as well as for mantle-cell non-Hodgkin lymphoma after at least one prior treatment. Bortezomib appears to have anti-tumor activity against a wide spectrum of human neoplasms and its mechanism of action may vary depending on tumor type. In MM inhibition of nuclear factor □B (NF □B) and attenuation of interleukin-6-mediated growth appear to be among the primary mechanisms of action, possibly further augmented by an anti angiogenic effect. In addition, a down-modulation of cell-surface expression of MHC Class 1—an inhibitor of NK function—was recently demonstrated following bortezomib treatment of myeloma cells. This finding lends further support to the hypothesis that treatment of myeloma cells with bortezomib may render them more susceptible to elotuzumab-mediated ADCC.

In vitro testing of the bortezomib/elotuzumab combination using ADCC assays showed enhanced elotuzumab-mediated ADCC against OPM2 cells using NK effector cells from healthy donors. In separate experiments, patient-derived NK cells induced approximately 20% specific lysis of autologous myeloma cells in the presence of elotuzumab (10 μg/mL) alone at a ratio of 30 NK cells to 1 MM cell with a dose-dependent increase in specific lysis with the addition of bortezomib.

In vivo experiments with OPM2 tumor-bearing mice demonstrated profound reduction in the rate of tumor growth from the addition of bortezomib to elotuzumab and activity that was significantly superior to bortezomib or elotuzumab alone.

1.2 Elotuzumab Development Background

Non-clinical as well as clinical studies, as reviewed in subsequent sections of this protocol, have provided evidence for synergistic antitumor activity between elotuzumab, bortezomib, and lenalidomide. Furthermore, elotuzumab-based combinations have been shown to be safe and well tolerated. In the current protocol, the combination of bortezomib, lenalidomide, and dexamethasone (also referred to as RVD) is used at doses adopted for Phase 3 development, which were found to be highly effective and safe in the Phase 1/2 setting (Richardson 2010). This RVD triplet is administered in combination with elotuzumab (E-RVD). In view of the demonstrated efficacy of the RVD regimen—a current standard of care with a reported response rate of 74% at 12 weeks (Richardson 2010)—and evidence for synergy between its components and elotuzumab, a rapid response to this regimen is expected in at least 90% of subjects.
In addition to assessing the efficacy of E-RVD, this study will explore the ability of subjects treated with four cycles of E-RVD as induction therapy to undergo successful stem cell mobilization. This

secondary objective remains critically important considering the important role of autologous stem cell transplant (ASCT) in the management of subjects with MM who are eligible for the procedure.

1.2.1 Non-clinical Toxicology

Elotuzumab only recognizes human SLAMF71 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 in vivo biological activity evaluation to address the selectivity of elotuzumab and potential toxicities.

Elotuzumab (100 and 200 mcg/mL) in vitro had no effect on lymphocytes, CD3+, CD4+, CD8+, and B cell counts in blood samples from healthy donors. NK 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 mcg/mL did not adversely affect the ability of bone marrow-derived hematopoietic stem cells to differentiate down the erythroid and myeloid pathways.

1.2.2 Clinical Experience with Elotuzumab in Multiple Myeloma

1.2.2.1 HuLuc63-1701, a Phase 1 Elotuzumab Monotherapy Study

In this Phase 1 study, escalating doses (0.5 - 20 mg/kg) of elotuzumab monotherapy were administered IV every 2 weeks for a total of 4 doses in subjects with advanced MM (Zonder 2012). Subjects with stable disease or better had the option to receive additional doses of elotuzumab. As of 03-Jul-2009, the study is complete. A total of 35 subjects were enrolled: 3 in the 0.5 mg/kg cohort, 4 in the 1.0 mg/kg cohort, 6 in the 2.5 mg/kg cohort, 4 in the 5.0 mg/kg cohort, 4 in the 10 mg/kg cohort, and 14 in the 20 mg/kg cohort. One (1) subject in the 10 mg/kg cohort did not receive study drug. The primary objective of this study was to determine the MTD.

In the 2.5 mg/kg cohort, 1 out of the first 3 subjects dosed experienced a dose-limiting toxicity of (DLT) Grade 3 increase in blood creatinine levels leading to Grade 4 acute renal failure and that cohort was then expanded to include another 3 subjects. No further DLTs occurred in the 2.5 mg/kg cohort and dosing continued up to the 20 mg/kg cohort. In the 20-mg/kg cohort, 1 out of 14 subjects experienced a DLT of Grade 3 hypersensitivity. Therefore, the MTD was not reached in this study. A total of 31 SAEs were reported in 15 subjects. Six (6) of the SAEs were assessed as related to elotuzumab which included Grade 4 acute renal failure, Grade 2 chills, Grade 2 pyrexia, Grade 3 hypersensitivity, Grade 2 bradycardia, and Grade 2 chest discomfort. The most common treatment-emergent AEs (TEAE) overall during the study were chills (13 [38.2%] subjects), fatigue (13 [38.2%] subjects), pyrexia (13 [38.2%] subjects), cough (10 [29.4%] subjects), headache (10 [29.4%] subjects), and anemia (9 [26.5%] subjects). The most common treatment-related AEs were chills (11 [32.4% subjects), pyrexia (6 [17.6%] subjects), and flushing (4 [11.8% subjects). There was no apparent dose response relationship with respect to the incidence of AEs overall or treatment related TEAEs. Most TEAEs and treatment-related TEAEs were Grade 1 or Grade 2.

A secondary objective of this study was assessment for preliminary activity. Nine (9) subjects had a best response of stable disease. Although no subject had a confirmed response, this study was 1) conducted in heavily pre-treated subjects with likely compromised immune systems (ie, compromised NK cell function), 2) did not include bortezomib or immune activating myeloma therapies such as lenalidomide; and 3) half of the subjects were treated at doses lower than the Phase 3 dose of 10 mg/kg of elotuzumab.

1.2.2.2 HuLuc63-1702, a Phase 1 Elotuzumab + Bortezomib Study

This is a Phase 1 study of elotuzumab in combination with bortezomib (plus dexamethasone if applicable) in subjects with MM who have had 1 to 3 prior therapies (Jakubowiak 2012). Escalating doses (2.5 - 20 mg/kg) of elotuzumab (dosed Days 1 and 11) are administered in combination with 1.3 mg/m2 bortezomib (dosed Days 1, 4, 8, and 11) in a 21-day cycle. Subjects with disease progression at the end of Cycle 2 or 3 also received an oral dose of 20 mg dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle thereafter.

Data are preliminary as of 25-Mar-2011, 28 subjects with relapsed and relapsed and refractory MM have been treated; 3 each at 2.5, 5, and 10 mg/kg and 19 at 20 mg/kg of elotuzumab respectively. Twenty-eight (28) subjects in the intent-to-treat (ITT) population received at least 1 dose of elotuzumab and all 28 subjects (100%) experienced at least 1 AE. No DLT was observed in the study and MTD was not established up to the planned highest dose of 20 mg/kg. There were 23 (82.1%) subjects with an elotuzumab related AE. The most common AEs (in 45% or higher, regardless of causality) include Grade 1 to 3 fatigue, diarrhea, anemia, thrombocytopenia, nausea, hyperglycemia, lymphopenia, leukopenia, neutropenia, constipation, and peripheral neuropathy.

Grade 3 or higher AEs occurred in 22 (78.6%) subjects of whom 7 (25%) subjects experienced Grade 3 or higher AEs assessed as related to elotuzumab (lymphopenia, thrombocytopenia, gastroenteritis, chest pain, fatigue, and hypersensitivity). SAEs occurred in 10 (35.7%) subjects.

Additionally, 6 (21.4%) subjects, 2 in the 5.0 mg/kg and 4 in the 20.0 mg/kg cohorts, withdrew from treatment due to an AE (neuropathy peripheral [2 subjects], acute myocardial infarction, gastroenteritis, sepsis and pain in extremity [1 subject each]). No deaths have been reported due to AEs. Overall there does not appear to be a dose relationship with the incidence of AEs.

As of 25-Mar-2011, the best clinical response (≥ minimal [minor] response [MR]) and the best response rate (≥ partial response (PR)) by the combined European Group for Blood and Marrow Transplantation and uniform criteria (Blade 1998) in 27 response evaluable subjects compare favorably to the historical, Phase 3 clinical trial of bortezomib monotherapy (APEX) in a similar population (Richardson 2005). The clinical response rate was 63% in Study 1702 compared to 46% in APEX and the objective response rate was 48% in Study 1702 compared to 38% in APEX. Finally, the median time to progression (TTP) was 9.5 months compared to 6.2 months in APEX.

1.2.2.3 HuLuc63-1703, a Phase 1/2 Lenalidomide/dexamethasone + Elotuzumab (LdE) Study

This Phase 1b/2, multicenter, open-label, dose-escalation study is evaluating the combination of elotuzumab with lenalidomide and dexamethasone in subjects with relapsed MM. Elotuzumab was administered by IV infusion at escalating dose levels in a 3 plus 3 design, ranging from 5 to 20

mg/kg in combination with orally administered doses of 25 mg lenalidomide plus 40 mg dexamethasone (Lonial 2012) .

The primary objective of the Phase 1 portion of the study was to identify the MTD of elotuzumab given in combination with lenalidomide and dexamethasone in subjects with MM who have at least 1 prior relapse. As no MTD was established, the Phase 1 cohort defining the highest dose studied (20 mg/kg) included 7 subjects, to which an additional 15 subjects were added as part of the expansion phase.

The Phase 2 portion of this study is ongoing, and has randomized subjects with measurable disease who have had 1 to 3 prior relapses and 1 to 3 prior therapies to 10 versus 20 mg/kg elotuzumab in combination with lenalidomide and low-dose dexamethasone. The primary objective of this phase is to compare efficacy and safety between 10 and 20 mg/kg elotuzumab and determine a dose for the Phase 3 studies.

Subjects receive elotuzumab, lenalidomide, and dexamethasone in 28-day cycles unless discontinued earlier due to disease progression. Subjects receive elotuzumab on Days 1, 8, 15, and 22 for the first 2 treatment cycles and on Days 1 and 15 for subsequent cycles. Lenalidomide is given orally once daily on Days 1 through 21 followed by a 7-day rest period for each cycle. Dexamethasone is given on Days 1, 8, 15, and 22 of each cycle. Subjects are evaluated at 30 and 60 days after the last dose of study drug.

In Phase 1 of the study, as of 08-Jul-2011, data are available for 29 subjects. During Phase 1, 28 of the 29 subjects were dosed: 3 in the 5-mg/kg cohort, 3 in the 10-mg/kg cohort, and 22 in the 20-mg/kg cohort. One additional subject in the 5-mg/kg cohort did not receive treatment. The study population consists of 15 women and 14 men, aged 41 to 83 years. In Phase 2, as of 15-Aug-2011, data are available for 73 subjects. All 73 subjects have been dosed: 36 in the 10-mg/kg cohort and 37 in the 20-mg/kg cohort. The study population consists of 30 women and 43 men, aged 39 to 82 years.

No DLTs have been observed by any subject treated with elotuzumab. There was one death in Phase 1 of the study, due to an adverse event in the 10 mg/kg cohort. There have been no deaths reported in Phase 2 of the study as of data cutoff.

Of the 29 subjects enrolled in Phase 1 of the trial as of 08-Jul-2011, 28 received study drug. All 28 treated subjects (100%) reported at least 1 AE, and 23 (82.1%) had AEs with a toxicity of Grade 3 or higher.

TEAEs related to elotuzumab that occurred in at least 2 subjects are presented in decreasing frequency in Table 1.2.2.3A. The most common elotuzumab-related TEAEs (as determined by the investigator) were anemia (35.7%), fatigue (28.6%), nausea (21.4%), and neutropenia (21.4%). The most common Grade $\geq$ 3 elotuzumab-related TEAEs were neutropenia (14.3%) and thrombocytopenia (10.7%).

The interim safety analysis revealed a key safety signal of elotuzumab-associated infusion reactions. These AEs included mostly Grade 1 and 2 nausea, dyspnea, chills, and headache. Two (2) subjects in the 20 mg/kg cohort discontinued due to infusion reactions, one Grade 4 SAE of anaphylaxis (related to elotuzumab) and one Grade 3 SAE of stridor (related to

elotuzumab/dexamethasone). Subsequent to these events, a new premedication regimen for the whole program has been instituted to minimize infusion reactions.

Table 1.2.2.3A: Study HuLuc63-1703 Phase 1 Treatment-emergent Related Adverse Events in ≥ 2 Dosed Subjects by Preferred Term and Cohort

Preferred Term	Dose (mg/kg) (number of subjects)			Any Grade: Total No. Subjects (N = 28)	No. Events Grade 3, 4, or 5
	5 (n = 3)	10 (n = 3)	20 (n = 22)		
Anemia	1 (33.3%)	2 (66.7%)	7 (31.8%)	10 (35.7%)	1 (3.6%)[a]
Fatigue	0	0	8 (36.4%)	8 (28.6%)	0
Nausea	0	1 (33.3%)	5 (22.7%)	6 (21.4%)	0
Neutropenia	2 (66.7%)	2 (66.7%)	2 (9.1%)	6 (21.4%)	4 (14.3%)[a]
Chills	2 (66.7%)	2 (66.7%)	0	4 (14.3%)	0
Constipation	0	0	4 (18.2%)	4 (14.3%)	0
Thrombocytopenia	1 (33.3%)	1 (33.3%)	2 (9.1%)	4 (14.3%)	3 (10.7%)[b]
Diarrhoea	0	1 (33.3%)	2 (9.1%)	3 (10.7%)	0
Headache	1 (33.3%)	0	2 (9.1%)	3 (10.7%)	0
Insomnia	1 (33.3%)	1 (33.3%)	1 (4.5%)	3 (10.7%)	0
Arthralgia	0	1 (33.3%)	1 (4.5%)	2 (7.1%)	0
Deep Vein Thrombosis	1 (33.3%)	0	1 (4.5%)	2 (7.1%)	1 (3.6%)[a]
Leukopenia	1 (33.3%)	0	1 (4.5%)	2 (7.1%)	0
Pruritus	1 (33.3%)	0	1 (4.5%)	2 (7.1%)	0
Rash	0	0	2 (9.1%)	2 (7.1%)	0
Urticaria	0	0	2 (9.1%)	2 (7.1%)	0

[a] Grade 3

[b] Grade 3,4

Source: preliminary data as of 08-Jul-2011

Of the 73 subjects enrolled in the Phase 2 portion of the trial as of 26-Oct-2011, all had been treated with elotuzumab and have data available. At least 1 AE was reported in 100% of subjects, and 72.6% experienced AEs with a toxicity of Grade 3 or Grade 4. AE reports were similar between the 2 doses of elotuzumab with numerically slightly higher rates of diarrhea, fatigue, nausea, upper respiratory tract infection, leukopenia, neutropenia, thrombocytopenia, lymphopenia, anemia, peripheral edema, and back pain at 10 mg/kg, and numerically slightly higher rates of muscle spasms, constipation, insomnia, hyperglycemia, and hypokalemia at 20 mg/kg. Given the sample size and interim status of this analysis, the rates of AEs appear to be generally similar between the

2 doses.

Of the 73 subjects enrolled, 51 (69.9%) subjects reported at least one elotuzumab-related TEAE (as assessed by the investigator). TEAEs related to elotuzumab that occurred in at ≥ 25% of dosed subjects are presented in decreasing frequency in Table 1.2.2.3B. The most common (≥ 40%) elotuzumab-related TEAEs were muscle spasms (55%), diarrhea (53%, fatigue (48%), constipation (45%), nausea (42%), and upper respiratory tract infection (41%). The most common ≥ Grade 3 elotuzumab-related TEAEs were lymphopenia, neutropenia, and thrombocytopenia (16% each).

Table 1.2.2.3B: Study HuLuc63-1703 Phase 2 Treatment-Emergent Related Adverse Events in ≥ 25% of Dosed Subjects or Grade 3/4 ≥ 5% by Preferred Term and Cohort

	Elotuzumab Dose (mg/kg) (number of subjects)		Total No. Subjects (N = 73)	
	10 (N = 36)	20 (N = 37)	Any Grade	Grade 3/4
Preferred Term	n (%)			
Muscle spasms	19 (53)	21 (57)	40 (55)	2 (3)
Diarrhea	20 (56)	19 (51)	39 (53)	4 (5)
Fatigue	19 (53)	16 (43)	35 (48)	5 (7)
Constipation	14 (39)	19 (51)	33 (45)	0
Nausea	16 (44)	15 (41)	31 (42)	1 (1)
Upper respiratory tract infection	17 (47)	13 (35)	30 (41)	2 (3)
Pyrexia	14 (39)	14 (38)	28 (38)	1 (1)
Anemia	13 (36)	10 (27)	23 (32)	8 (11)
Insomnia	9 (25)	13 (35)	22 (30)	1 (1)
Peripheral edema	12 (33)	9 (24)	21 (29)	1 (1)
Back pain	11 (31)	8 (22)	19 (26)	2 (3)
Hyperglycemia	7 (19)	12 (32)	19 (26)	7 (10)
Neutropenia	11 (31)	8 (22)	19 (26)	12 (16)
Thrombocytopenia	11 (31)	7 (19)	18 (25)	12 (16)
Lymphopenia	10 (28)	7 (19)	17 (23)	12 (16)
Leukopenia	7 (19)	5 (14)	12 (16)	6 (8)
Hypokalemia	5 (14)	6 (16)	11 (15)	4 (5)

Fifty-one SAEs have been reported in subjects treated in Phase 2 of study HuLuc63-1703 as of 15-Aug-2011. Serious AEs that occurred in more than 1 subject are shown in Table 1.2.2.3C. Serious AEs of pneumonia reported in 4 (5.5%) subjects; bone pain, bronchitis, febrile neutropenia, neutropenia, pulmonary embolism, sepsis, syncope, and transient ischaemic attack were reported in 2 (2.7%) subjects each; all other SAEs have been reported in only 1 (1.4%) subject each.

Table 1.2.2.3C: Study HuLuc63-1703 Phase 2 Serious Adverse Events by Preferred Term and Cohort for All Treatment Cycles Combined Occurring in More than One Subject

	Elotuzumab Dose (mg/kg) (number of subjects)		Total No. Subjects (N = 73)	Grade
	10 (N = 36)	20 (N = 37)		
Preferred Term	n (%)			
Pneumonia	2 (5.6%)	2 (5.4%)	4 (5.5%)	1 Grade 2 3 Grade 3
Bone Pain	2 (5.6%)	0	2 (2.7%)	3
Bronchitis	1 (2.8%)	1 (2.7%)	2 (2.7%)	1 Grade 2 1 Grade 3
Febrile Neutropenia	1 (2.8%)	1 (2.7%)	2 (2.7%)	3
Neutropenia	1 (2.8%)	1 (2.7%)	2 (2.7%)	4
Pulmonary Embolism	1 (2.8%)	1 (2.7%)	2 (2.7%)	1 Grade 2 1 Grade 3
Sepsis	2 (5.6%)	0	2 (2.7%)	1 Grade 2 1 Grade 3
Syncope	2 (5.6%)	0	2 (2.7%)	3
Transient Ischemic Attack	1 (2.8%)	1 (2.7%)	2 (2.7%)	3

One of the secondary objectives of Study HuLuc63-1703 was to evaluate the efficacy of elotuzumab when given in combination with lenalidomide and low-dose dexamethasone (Ld). Table 1.4.2.3D presents the Phase 1 response rates in treated subjects. The overall response rate (ORR) (≥ PR) was assessed using IMWG criteria at 82.1% in all treated subjects who received elotuzumab/Ld and 93.8% in subjects who received prior thalidomide. In the subset analysis of subjects with no prior lenalidomide (n = 22), the ORR was 95.5%.

Table 1.2.2.3D: Response Rates in Study HuLuc63-1703 Phase 1 (Safety Population)

Efficacy Parameter	All Evaluable (N = 28)	No Prior Lenalidomide (N = 22)	Prior Lenalidomide (N = 6)	Prior Thalidomide (N = 16)	Refractory to Most Recent Line of Therapy (N = 12)
ORR (≥ PR)	23 (82.1%)	21 (95.5%)	2 (33.3%)	15 (93.8%)	10 (83.3%)
≥ VGPR	12 (42.9%)	11 (50.0%)	1 (16.7%)	7 (43.8%)	5 (41.7%)
sCR	0	0	0	0	0
CR	1 (3.6%)	1 (4.5%)	0	0	0
VGPR	11(39.3%)	10 (45.5%)	1 (16.7%)	7 (43.8%)	5 (41.7%)
PR	11 (39.3%)	10 (45.5%)	1 (16.7%)	8 (50.0%)	5 (41.7%)
No Confirmed Response	5 (17.9%)	1 (4.5%)	4 (66.7%)	1 (6.3%)	2 (16.7%)

Phase 2

Response rates in the Phase 2 portion of this study are shown in Table 1.4.2.3E. As of the efficacy data cutoff of 26-Oct-2011, the ORR (≥ PR) using IMWG criteria and in all 73 subjects was 82%. Although the study is not complete, the interim data analysis demonstrates 92% ORR at 10 mg/kg and 73% ORR at 20 mg/kg. Among the 16 subjects with 1 prior therapy who received the 10 mg/kg dose of elotuzumab, the ORR was 100%. This ORR is based on a median of 15 cycles. Responses were rapid, with a median time to response of approximately 1 month in evaluable subjects.

Table 1.2.2.3E: Response Rates in Study HuLuc63-1703 Phase 2 (Response Evaluable Population - IMWG Criteria)

Efficacy Parameter	Treatment Group (mg/kg)		Total No. Subjects (N = 73)
	10 (N = 36)	20 (N = 37)	
	n (%)		
ORR (≥ PR)	33 (92%)	27 (73%)	60 (82%)
CR/sCR	5 (14%)	4 (11%)	9 (12%)
VGPR	14 (39%)	11 (30%)	25 (34%)
PR	14 (39%)	11 (30%)	25 (34%)
< PR	3 (8%)	10 (27%)	13 (18%)

The Phase II cohort was reported at ASCO 2013 (Lonial 2013), the objective response rate (ORR) was 84%; 92% with 10 mg/kg (n=36) and 76% with 20 mg/kg (n=37). At a median follow-up of 20.8 months, median progression free survival (PFS) was not reached (10 mg/kg) and was 18.6 mo (20 mg/kg).

1.2.2.4 Infusion Reactions

First-dose elotuzumab infusion reactions and other peri-infusional AEs have been observed in approximately 50% of subjects in clinical trials. Serious infusion reactions have been observed with elotuzumab; these have occurred on the first day of elotuzumab dosing or with subsequent elotuzumab infusions.

The most frequent elotuzumab peri-infusional AEs that occurred in ≥ 10% of subjects across all Phase 1 or Phase 1/2 studies, regardless of causality, include nausea, vomiting, chills, infusion-related reaction, flushing, dyspnea, cough, headache, dizziness, and rash.

The majority of peri-infusional AEs were Grade 1 or 2 and resolved with little or no treatment. There was no apparent dose-relationship for infusion reactions or peri-infusional AEs.

Seven (7) subjects across all 3 studies experienced ≥ Grade 3 elotuzumab related peri-infusional AEs (see Table 1.2.2.4A).

In Study 1701, 1 subject developed Grade 3 hypersensitivity (20 mg/kg, first infusion).

In Study 1702, 1 subject developed Grade 3 hypersensitivity (10 mg/kg, following a third dose.

In Phase 1 of Study 1703, 3 subjects developed ≥ Grade 3 events; stridor (20 mg/kg, following the third and fourth infusions), anaphylaxis (20 mg/kg, following a fourth infusion) and influenza-like illness (20 mg/kg).

In Phase 2 of Study 1703, 2 subjects developed ≥ Grade 3 events; 1 subject developed Grade 3 rash, during elotuzumab infusion (10 mg/kg); and 1 subject developed Grade 3 nausea (20 mg/kg, assessed by the investigator as unrelated to elotuzumab).

Table 1.2.2.4A: Elotuzumab-related Peri-Infusional AEs: SAEs and Severe AEs Grade Greater than or Equal to 3 Across 3 Studies

Study Subject	Cohort	Verbatim Term	Severity (CTCAE)	Comments
1701 Subject 3	20 mg/kg	Hypersensitivity	3	Grade 3 fever. Resolved same day. Discontinued from study
1702 Subject 4	10 mg/kg	Hypersensitivity	3	Event resolved the same day
1703 Ph 1 Subject 6	20 mg/kg	Anaphylaxis	4	Cycle 1 Day 22 Subject was withdrawn

Table 1.2.2.4A: Elotuzumab-related Peri-Infusional AEs: SAEs and Severe AEs Grade Greater than or Equal to 3 Across 3 Studies

Study Subject	Cohort	Verbatim Term	Severity (CTCAE)	Comments
1703 Ph 1 Subject 7	20 mg/kg	Stridor	3	Cycle 1 Days 15 and 22 Subject re-challenged and experienced infusion reaction again. Subject was withdrawn
1703 Ph 1 Subject	20 mg/kg	Influenza Like Illness	3	
1703 Ph 2 Subject 8	10 mg/kg	Rash	3	Began Cycle 2 Day 8 Subject rechallenged and recurred each treatment. Subject discontinued Cycle 3 Day 15
1703 Ph 2 Subject 9	20 mg/kg	Nausea	3	Investigator assessed as unrelated to elotuzumab infusion

To mitigate infusion reactions, all ongoing elotuzumab studies were amended for all subjects to receive premedication with IV corticosteroids, antihistamines (diphenhydramine or hydroxyzine) and acetaminophen prior to each elotuzumab infusion. In the study 1703 protocol, H2 antihistamines were also added as a premedication.

In the Phase 2 portion of the Study 1703, investigator-designated infusion reactions occurred in a total of 9 out of 73 subjects (12%). Only a single subject experienced a Grade 3 rash despite the premedication regimen (See Table 1.2.2.4B).

Table 1.2.2.4B: Study HuLuc63-1703 Phase 2 Investigator-Designated Infusion Reactions

Parameter	Treatment Group (mg/kg)		Total No. Subjects (N = 73)
	10 (N = 36)	20 (N = 37)	
	n (%)		
Any AE	5 (14)	4 (11)	9 (12)
Grade 1	3 (8)	2 (5)	5 (7)
Grade 2	1 (3)	2 (5)	3 (4)
Grade 3[a]	1 (3)	0	1 (1)

[a] Subject experienced a Grade 3 rash despite premedication regimen.

Since the implementation of a more stringent premedication regimen, elotuzumab infusions have been associated with predominantly Grade 1 or 2 peri-infusional AEs. All infusion reactions have been managed by infusion rate changes, and/or medications and resolved the same day or within

24 hours, and in most cases, subjects have continued with the study. Subjects premedicated with H1 and H2 antihistamines (such as diphenhydramine), ranitidine, acetaminophen, and IV corticosteroids prior to all doses of elotuzumab have not experienced serious infusion reactions. Using the updated premedication regimen across all ongoing elotuzumab studies has reduced the incidence of any-grade peri-infusion AE. Treatment with therapeutic monoclonal antibodies is associated with infusion reactions with variable time of onset and varying levels of incidence and severity. There was no apparent dose relationship for infusion reaction.

In summary, elotuzumab infusions have been associated with predominantly Grade 1 or 2 infusion reactions. All infusion reactions were managed by infusion rate changes and/or medications and resolved the same day or within 24 hours. In most cases, subjects have been able to continue on study. Only 1 subject premedicated with diphenhydramine, acetaminophen, and IV corticosteroids prior to all doses of elotuzumab developed a Grade 3 infusion reaction related to elotuzumab and discontinued study treatment.

1.2.3 Overall Risk/Benefit Assessment

Multiple myeloma accounts for 1% of all neoplasms and 10% of hematologic malignancies in the United States with an estimated annual incidence of 20,520 and estimated annual disease-specific mortality of almost 11,000. In spite of recent improvement in treatment options it remains largely incurable and is associated with very significant morbidity.

The majority of patients with newly diagnosed MM will require systemic therapy and many will be referred for ASCT as well. A combination of dexamethasone with bortezomib, an IMiD or both has become one of the most commonly recommended therapies in the first line setting. The choice of a specific regimen often depends on patient or physician preference, eligibility for ASCT or clinical trial and perceived risk based on established prognostic factors, such as stage and cytogenetics. The combination of BLD has been shown to be highly active and is now recommended as a standard of care by widely accepted treatment guidelines (NCCN Guidelines).

Elotuzumab as monotherapy or in combination with bortezomib or lenalidomide/dexamethasone is well tolerated. To date, the key elotuzumab safety signal has been infusion reaction AEs which have been successfully managed by appropriate clinical intervention resulting in event resolution in less than 24 hours. The majority of infusion reactions occur in the first cycle with decreasing incidence through Cycle 4. Following the implementation of an updated premedication scheme with H1 blocker, H2 blocker, acetaminophen, and IV corticosteroids, the incidence of any grade, and severe (Grade 3 and 4) elotuzumab infusion reaction AEs have decreased. For example, in the Phase 2 portion of Study 1703 (n = 73), there was only 1 Grade 3 infusion associated reaction: rash (10 mg/kg).

The elotuzumab dose of 10 mg/kg was selected based on accumulated safety, pharmacokinetic and pharmacodynamic data. The safety profile of elotuzumab does not appear to be dose dependent, with rates and severity of general AEs/SAEs and infusion related AEs/SAEs being similar at 10 and 20 mg/kg doses. Pharmacokinetic analysis suggests that trough serum antibody concentrations of elotuzumab are above the target levels determined from non-clinical models in almost all subjects treated at 20 mg/kg as well as 10 mg/kg. Moreover, elotuzumab administration at doses

≥ 10 mg/kg resulted in near-complete saturation of target sites on bone marrow plasma cells in studies 1702 and 1703.

Based on prior clinical experience, the dose and schedule of elotuzumab in this study is anticipated to be well tolerated. The risk of infusion reaction or other elotuzumab-related toxicity is not dose dependent. A 20 mg/kg dose of elotuzumab was tolerated in all studies to date and without dose limiting toxicity.

Although elotuzumab as a monotherapy did not have significant activity in relapsed/refractory myeloma, the combinations of elotuzumab with either bortezomib or lenalidomide/dexamethasone appear to be active and well tolerated. Given the previously demonstrated efficacy of the BLD regimen, it is expected that the combination of BLD and elotuzumab will be highly active.

2 OBJECTIVES

2.1 Research Hypothesis

The research hypothesis is that the combination of elotuzumab plus lenalidomide, bortezomib, and dexamethasone will result in a high level of anti-MM activity and will be well tolerated.

2.2 Original Primary Objectives

To estimate the response rate after 4 cycles of induction therapy in subjects treated with E-RVD.

2.3 Original Secondary Objectives

- To estimate the proportion of subjects with a successful stem cell mobilization after receiving four cycles of treatment with E-RVD
- To estimate the proportion of subjects requiring dose modification of any study drug during the first four cycles of E-RVD
- To characterize safety in subjects who receive E-RVD
- To provide preliminary information on the activity of E-RVD including best response, objective response rate (ORR), including ORR at end of 8 cycles for patients that complete 8 cycles of induction therapy, duration of response, time to response, progression free survival (PFS) and time to next treatment

2.4 Original Exploratory Objectives

- To provide preliminary information on the evaluation of minimal residual disease (MRD)
  For subjects who elect to undergo stem cell transplant (SCT), to characterize engraftment parameters

The original objectives for this study have been met as of October 2020. The new objective of the study is safety.

The following information will be collected:

- All SAEs.
- All ≥Grade 2 AEs.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event

3 PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 **Patients must meet the following criteria on screening examination to be eligible to participate in the study. All laboratory assessments should be performed within 21 days of initiation of protocol therapy unless otherwise specified. *Bone marrow biopsy should be performed within 30 days of initiation of protocol therapy.*** Subject is, in the investigator's opinion, willing and able to comply with the protocol requirements.

3.1.2 Subject has given voluntary signed written informed consent before performance of any study-related procedure that is not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

3.1.3 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Appendix 1).

3.1.4 Subject is a candidate for high-dose therapy and autologous SCT based on standard criteria at the institution where this treatment will be administered.

3.1.5

Participants must have a diagnosis of MM according Revised International Myeloma Working Group diagnostic criteria (Rajkumar 2014), which require the following findings,

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

- End organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - • Hypercalcemia: 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)
  - • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  - • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
- 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

3.1.6 Participants must also have measurable disease according to the Standard Diagnostic Criteria (Rajkumar 2009):

- Serum IgG, IgA, or IgM M-protein ≥ 0.5 g/dL, or
- Serum IgD M-protein ≥ 0.05 g/dL, or
- Urinary M-protein excretion of more than 200 mg/24 hours, or
- Serum free light chains of at least 100 mg/L with an abnormal FLC ratio

3.1.7 Subject agrees to refrain from blood donations during therapy on study and for 8 weeks after therapy is completed.

3.1.8 Men and women, age ≥ 18 years or legal age of consent per local regulations (whichever is greater).

3.1.9 Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting Lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking Lenalidomide through 90 days after the last dose of study drug. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 90 days after the last dose of study drug. All patients must be registered in and must comply with all requirements of the Revlimid REMS™ program.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Diagnosed with smoldering MM, monoclonal gammopathy of undetermined significance, Waldenstrom's macroglobulinemia, Plasma cell leukemia, POEMS syndrome or amyloidosis.

3.2.2 Participant has ≥ Grade 2 peripheral neuropathy on clinical examination within 21 days before initiation of protocol therapy.

3.2.3 Renal insufficiency, defined as creatinine clearance < 30 mL/min (either actual or calculated value), within 21 days of initiation of protocol therapy. The Cockgroft-Gault formula should be used for calculating creatinine clearance values:

(140-age) x Body mass (kg) x 0.85 (female) or 1.0 (male)
serum creat (mg/dL) x 72

** Ideal body weight (IBW) should be used if actual body weight is > 20% above IBW*

3.2.4 Platelet count <75,000 cells/mm³ at time of screening evaluation. Transfusion may not be used to meet platelet eligibility criteria within 7 days of obtaining screening evaluation.

3.2.5 Participants with an absolute neutrophil count (ANC) < 1000 cells/mm³ at time of screening evaluation. **Growth factor *may not* be used to meet ANC eligibility criteria within 14 days of obtaining screening evaluation.**

3.2.6 Participants with hemoglobin level < 8.0 g/dL, at time of screening. Transfusion may not be used to meet eligibility criteria within 7 days of obtaining screening evaluation.

3.2.7 Participants with hepatic impairment, defined as bilirubin > 1.5 x institutional upper limit of normal (ULN) or AST (SGOT), ALT (SGPT), or alkaline phosphatase > 3x institutional ULN, within 21 days of initiation of protocol therapy

3.2.8 Other ongoing or prior anti-myeloma therapy. Patients may be receiving concomitant therapy with bisphosphonates and low dose corticosteroids (e.g., prednisone up to but no more than 10 mg p.o. q.d. or its equivalent) for symptom management and comorbid conditions. Doses of corticosteroid should be stable for at least 7 days prior to study treatment.) The dose of corticosteroids for the treatment of their myeloma received by the participant should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol therapy

3.2.9 Known significant cardiac abnormalities including:

- Congestive heart failure, NYHA class III or IV
- Uncontrolled angina, arrhythmia or hypertension
- Myocardial infarction within the past six months
- Any other uncontrolled or severe cardiovascular condition
- Prior cerebrovascular event with residual neurologic deficit

3.2.10 Serious, intercurrent illness including, but not limited to, clinically relevant active infection, known active hepatitis B or C viral infection, known HIV infection, uncontrolled diabetes mellitus, or serious co-morbid medical conditions such as chronic restrictive pulmonary disease, and cirrhosis.

3.2.11 Any condition, including laboratory abnormalities, that in the opinion of the investigator places the subject at unacceptable risk if he/she were to participate in the study.

3.2.12 Prior malignancy (within the last 5 years) except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer

3.2.13 Known hypersensitivity to acyclovir or similar anti-viral drug

3.2.14 Known intolerance to steroid therapy

3.2.15 Contraindication or prior intolerance to thromboembolic prophylaxis with aspirin, warfarin or low-molecular weight heparin

3.2.16 Participants with known brain metastases.

3.2.17 Poor tolerability or known allergy to any of the study drugs or compounds of similar chemical or biologic composition to dexamethasone, boron or mannitol.

3.2.18 Female participants pregnant or breast-feeding.

3.2.19 Participants who have undergone major surgery $\leq$ 4 weeks prior to starting study drug or who have not recovered from side effects of the surgery.

3.2.20 Participants with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Women, minorities and members of other underrepresented populations will have equal consideration for participation in this trial. Please note, however, that the prevalence of MM is more common among men than women, occurs more frequently with increasing age, and develops twice as often among black individuals than among white individuals. Inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of these underrepresented populations.

3.4 Screening Procedures

The Investigator is responsible for keeping a record of all participants screened for entry into the study and subsequently excluded. The reason(s) for exclusion must also be recorded. The following screening procedures must be performed within 21 days of initiation of protocol therapy, unless otherwise stipulated in the Study Calendar (Section 9):

- Participants who are potentially eligible for study participation must sign an informed consent form prior to the undertaking of screening procedures for this study that are not a part of standard medical care.
- Inclusion and exclusion criteria reviewed.
- MM diagnosis will be confirmed
- Complete medical history will be obtained to include documentation of all concomitant medications used in the prior 3 weeks.
- Baseline Symptom Assessment

- Physical examination to include measurement of vital signs, height, weight and calculation of body surface area (BSA).
- ECOG performance status will be evaluated (Appendix I)
- 12-lead ECG (see Study Calendar for details)
- 2D Echocardiogram or MUGA
- A neurologic assessment will be performed including **(FACT/GOG Ntx)**.
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorous, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, lactate dehydrogenase (LDH), uric acid, beta 2-microglobulin.
- Thyroid function to include TSH and T4
- Coagulation tests
- Urinalysis, including microscopic analysis and color
- B2 microglobulin
- M component quantification by immunoelectrophoresis (IEP) from serum and urine and 24 hour urine collection for paraprotein measurement
- Serum sample for FreeLite™ testing
- Serum or urine pregnancy test (sensitivity of at least 50 mIU/mL), for FCBP must be completed. The first test should be performed within 10-14 days, and the second test within 24 hours prior to initiation of lenalidomide. All patients must register into the Revlimid REMS program.
- Skeletal survey (including chest X-ray) for quantification of bone lesions, with magnetic resonance imaging (MRI) and CT scans as clinically indicated.
- Imaging of extramedullary plasmacytomas if present
- Bone marrow aspiration and biopsy to be evaluated for morphology and for cytogenetics by standard banding and FISH, including marrow karyotype if possible. Suggested probes include, at a minimum del 13q14, t(4:14), t(11;14), t(14:16), and del 17p.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for All Institutions

Eligible participants from all institutions will be registered with the DF/HCC Quality Assurance Office for Clinical Trials (ODQ). Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied. An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist. Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. Notify the project manager at the coordinating site, who will inform the ODQ Registrar of registration cancellations, as soon as possible.

4.2 Registration Process

4.2.1 Registration Process for DF/HCC participating sites and All Institutions

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.

3. E-mail all the following documents to ACT Oncology at EloRVD@actoncology.com
   a. Copy of all screening tests and procedures
   b. Signed informed consent form
   c. HIPAA authorization form (if separate from the informed consent document)
   d. Eligibility Checklist

4. ACT Oncology will review the registration documents for completeness and follow up with the site if any clarification is required or if any additional source documents are needed. Once all documents are verified to be in order, ACT Oncology will provide confirmation by e-mail to the study coordinator at the site, the overall study PI, and a designee of DFCI team. Once the study PI, or his designee, approves the subject for enrollment, he/she will send an approval e-mail back to ACT and the site team. A designee at DFCI (or DF/HCC study coordinator for DF/HCC sites) will proceed to register the participant with the ODQ Registrar.

5. Following the registration, an email confirming the subject is on study will be sent to the Overall PI, site PI and study coordinator(s), from the Lead Site.

The registration process is summarized as follows:

Site (DFCI or Other Investigative Site) → ACT Oncology → DFCI Coordinating Center PI → Approval to ACT Oncology and site→ DFCI Coordinating Center (or DF/HCC coordinator for DF/HCC centers) will enroll participants and will confirm subject registration on study

Note: Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

A participant cannot initiate study treatment until the Participating Institution receives an e-mail Confirmation of ODQ Registration and Confirmation of Registration with ACT Oncology.

5 TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for lenalidomide, bortezomib, dexamethasone and elotuzumab are

described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Treatment Dose and Schedule				
Treatment Cycle	**1 and 2**	**3 and 4**	**5 through 8**	**Maintenance**
Elotuzumab IV	10 mg/kg IV Days 1, 8, & 15	10 mg/kg IV Days 1 & 11	10mg/kg IV Days 1, & 11	20mg/kg IV Day 1
Bortezomib Sq	1.3 mg/m^2 Days 1, 4, 8, 11 SQ	1.3 mg/m^2 Days 1, 4, 8, 11 SQ	1.3 mg/m^2 Days 1, 4, 8, 11 SQ	1.3 mg/m^2 Days 1 & 15 SQ
Lenalidomide PO	25mg po Days 1 - 14	25 mg po Days 1 - 14	25 mg po Days 1 -1 4	10 mg po Days 1 – 21* OR dose tolerated during induction Days 1 – 21**
Dexamethasone PO	20 mg po D 2, 4, 5, 9, 11 & 12 28 mg po (3 -24h) pre Elo***	20 mg po D 2, 4, 5, 8, 9 & 12 28 mg po (3 - 24h) pre Elo***	10 mg po D 2, 4, 5, 8, 9, & 12 28 mg po (3 -24h) pre Elo***	-
Dexamethasone IV	8 mg IV (45 – 90min pre Elo) D 1, 8 and 15	8 mg IV (45-90min pre Elo) D 1, and 11	8 mg IV (45 – 90 min pre Elo) D 1 & 11	8 mg IV (45-90 mins pre Elo) D 1

[a] Risk based see section 5.4.4.2

* For patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics and for for patients undergoing ASCT who are ISS I or II without high-risk cytogenetics

** For patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage I without high-risk cytogenetics and for patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage II or III and/or have high-risk cytogenetics

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

Drug administration guidelines, pretreatment recommendations and concomitant medications are outlined throughout this section.

5.1 Pre-treatment Criteria

Patients must meet all the eligibility criteria including pre-treatment assessments prior to initiation of therapy. Refer to Section 9 study calendar for all pre-treatment study procedures.

Pre-treatment concomitant medications and procedures that are required and or recommended and those to be avoided are detailed in Section 5.5: General Concomitant medications and Supportive Care Guidelines.

All patients should be evaluated for adverse events prior to continuation of therapy beyond Cycle 1, day 1 including intra-cycle dosing and initiation of subsequent cycles. Dose modifications and guidelines for initiation of a new cycle of therapy are outlined in Section 6.

5.2 Treatment

5.2.1 Induction (Cycles 1 - 8): Induction regimen will consist of a treatment cycle every 21 days with:

- Elotuzumab at 10 mg/kg on Days 1, 8, and 15 during Induction Cycles 1 and 2 and 10 mg/kg on Days 1 and 11 during Induction Cycles 3 through 8.
- Bortezomib at 1.3 mg/m^2 SQ on Days 1, 4, 8, and 11 of Cycles 1 - 8, followed by a 10-day rest period.
- Lenalidomide as a single daily oral dose of 25 mg on Days 1 - 14 of Cycles 1 - 8, followed by 7-day rest period. (Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline).
- Dexamethasone as a single daily oral dose of 20 mg/day on Days 2, 4, 5, 9, 11, and 12 during Cycles 1 and 2.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1, 8, and 15 in during Induction Cycles 1 and 2.
- Dexamethasone as a single oral dose of 20 mg/day on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 3 and 4.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of Induction Cycles 3 and 4.
- Dexamethasone 10 mg as a single oral dose of 10 mg on Days 2, 4, 5, 8, 9, and 12 during induction Cycles 5 through 8.
- Dexamethasone 28 mg po (3 – 24 hours before elotuzumab) and 8 mg IV (45-90 minutes before elotuzumab) on Days 1 and 11 of induction Cycles 5 through 8.

5.2.2 Stem cell mobilization:

Stem cell mobilization will be performed for **all** subjects at the end of Induction Cycle 4. Stem cell mobilization will be performed with either cyclophosphamide 2500 mg/m^2 and filgrastim or filgrastim with or without plerixafor. If stem cell mobilization using this approach is unsuccessful, a second attempt at collection can be undertaken within one month of the first attempt at mobilization. Subjects who attain at least a PR may elect to stop E-RVD at the end of Induction Cycle 4 and proceed to autologous SCT as per the institutional guidelines. The decision whether subjects will proceed to SCT will be made on the basis of treating physician recommendations and patient preference. Physician recommendations are typically based on disease response and on how well subjects are tolerating treatment. The kind of decision making process related to SCT is considered nowadays standard of care in the multiple myeloma field. Subjects who do not proceed to SCT may receive a full 8 cycles of the induction therapy. However, prior to continuing to

Induction Cycle 5, all stem cell harvest-related toxicities must have resolved or improved to CTCAE Grade ≤ 1 and subjects must meet the following stem cell harvest recovery criteria:

a) ECOG ≤ 2;
b) Absolute neutrophil count >1000 cells/mm^3;
c) Platelet count ≥ 75,000 cell/mm^3 (75 x 10^9/L);
d) Hemoglobin ≥ 8 g/dL at most recent measurement;
e) Total bilirubin < 1.5 x upper limit of normal (ULN);
f) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 3 x ULN;
g) Able to undergo further treatment in the judgment of the investigator.

In the event that therapy is delayed due to stem cell mobilization, collection, or transplant, the treating physician will determine optimal timing of treatment re-initiation. In the event that during this period off treatment myeloma-related parameters (i.e. serum monoclonal protein, urine monoclonal protein and/or involved free light chain) increase and meet criteria for progression, patients may continue on therapy if the increase in these parameters is felt to be related to delay in therapy and there could be clinical benefit associated with further therapy. This determination will be made by the treating physician in consultation with the overall study PI.

5.2.3 Maintenance:

Subjects who receive 8 cycles of the induction regimen will be allowed to continue treatment on a maintenance schedule, if they have at least stable disease and are eligible to receive maintenance treatment. Additionally, subjects who received SCT at the end of Induction Cycle 4 will forego Cycles 5 to 8 of therapy and will be allowed to continue treatment directly on a maintenance schedule after recovery from SCT provided that all SCT-related toxicities have resolved or improved to CTCAE Grade ≤ 1 and they meet the stem cell harvest recovery criteria defined in Section 5.2.2.

Maintenance therapy will continue until disease relapse, unacceptable toxicity, withdrawal of consent or no further clinical benefit is experienced. Subjects unable to tolerate any of the individual drugs (eg, elotuzumab, lenalidomide or bortezomib) during the maintenance phase may stop those individual drugs and continue on the remaining drugs, with or without dexamethasone, at the investigator's discretion.

Maintenance therapy will be administered to all patients, with the specific maintenance regimen determined by risk category. Each cycle of maintenance therapy is 28 days.

Patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance with:

- Elotuzumab 20 mg/kg on Day 1 of each 28 day cycle;
- Lenalidomide 10 mg Days 1 – 21;
- Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ;

- IV dexamethasone 8 mg on Day 1 (45-90 minutes before elotuzumab).

Patients undergoing ASCT who are ISS I or II without high-risk cytogenetics will receive maintenance with:

- Elotuzumab 20 mg/kg Day 1 of each 28 day cycle;
- Lenalidomide 10 mg Days 1 – 21; and
- IV dexamethasone 8 mg on Day 1 (45-90 minutes before elotuzumab).

Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage II or III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance with:

- Elotuzumab 20 mg/kg on Day 1 of each 28 day cycle;
- Lenalidomide at the dose tolerated during induction Days 1 – 21;
- Bortezomib 1.3 mg/m^2 Days 1 and 15 SQ; and
- IV dexamethasone 8 mg on Day 1 (45-90 minutes before elotuzumab).

Patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage I without high-risk cytogenetics will receive maintenance with:

- Elotuzumab 20 mg/kg Day 1 of each 28 day cycle;
- Lenalidomide at the dose tolerated during induction Days 1 – 21; and
- IV dexamethasone 8 mg on Day 1 (45-90 minutes before elotuzumab).

5.2.4 Tumor assessments:

It is recommended that disease assessments are performed per standard of care.

5.3 Agent Administration

5.3.1 Elotuzumab

Note: administer elotuzumab 30 to 90 minutes following bortezomib when both drugs are given on the same day. Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the instructions provided in Section 7.4.4 and Appendix VII.

5.3.2 Induction Cycles 1 and 2

Elotuzumab will be administered at a dose of 10 mg/kg IV on Days 1, 8, and 15 in 21-day cycles in Induction Cycles 1 and 2. The dosing window for elotuzumab is -1/+3 days for Induction Cycles 1 and 2.

5.3.3 Induction Cycles 3 – 8

Elotuzumab will be administered at a dose of 10 mg/kg IV on Days 1 and 11 in 21-day cycles in Induction Cycles 3 – 8. The dosing window for elotuzumab is -3/+7 for Induction Cycles 3 through 8.

5.3.4 Maintenance Cycles

Elotuzumab will be administered at a dose of 20 mg/kg IV on Day 1 in 28-day cycles. The dosing window for elotuzumab is -3/+7 days beginning with Maintenance Cycle 1.

See Appendix VII for instructions regarding preparation and administration of elotuzumab. The first infusion is expected to require approximately 3 hours.

5.3.5 Vital Signs, Physical Measurements, and Physical Examination

Vital signs (body temperature, respiratory rate, seated blood pressure and heart rate) will be recorded as outlined in Section 9, Table 9.1. Blood pressure, respiratory rate and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to dosing. Subjects will have vital signs measured as follows:

- Prior to pre-medication administration
- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of infusion
- At the end of the infusion
- Thirty and 120 minutes post completion of the elotuzumab infusion for Induction Cycles 1 and 2
- Induction Cycle 3 and beyond post infusion vital signs will be measured at 30 minutes
- Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes during and for 2 hours after the end of the elotuzumab infusion

Height will be recorded at screening. Weight will be measured at study visits as indicated in Tables 9.

A full physical examination will be performed at the screening visit, whereas a targeted exam will occur as indicated in Section 9, Table 9.1. Targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms, or concerns. Targeted physical examination includes assessment of heart, lung, and abdomen.

5.3.6 Performance Status

Performance assessment will be performed according to Section 9, Table 9.1 as described in Appendix 1. The assessment should be completed prior to any study-related procedures, treatment or clinician assessment.

5.3.7 Elotuzumab Premedication

5.3.7.1 Elotuzumab Premedication Regimen in Subjects without a Prior Infusion Reaction

On days of elotuzumab infusion, the dexamethasone dose will be split into a po and IV administration (described in Section 5.4.5 which will also serve as premedication for elotuzumab).

Intravenous and po dexamethasone doses are calculated to provide a total dose that is bioequivalent to the 20 mg oral dose during Induction Cycles 1 - 4 and 10 mg oral dose during Induction Cycles 5 - 8 and during maintenance (dexamethasone 8 mg IV is approximately bioequivalent to 11 mg po).

In addition, the following must also be administered 45 to 90 minutes before initiating the elotuzumab:

H1 blocker: diphenhydramine (25 - 50 mg po or IV) or equivalent (45-90 mins prior to the start of infusion)

H2 blocker: ranitidine (50 mg IV) or equivalent

Acetaminophen (650 - 1000 mg po).

Consult the PI for further guidance regarding alternative pre-medications for subjects allergic or intolerant to any premedication or to determine if locally used equivalent medications are acceptable.

5.3.7.2 Elotuzumab Premedication Regimen in Subjects with a Prior Infusion Reaction

To be re-treated with elotuzumab, subjects with prior infusion reaction must receive H1 and H2 blockers and acetaminophen at no more than the maximum doses specified (eg:50 mg diphenhydramine, 50 mg ranitidine [or equivalent], and 1000 mg acetaminophen) 45 to 90 minutes before initiating the elotuzumab.

Doses of IV dexamethasone above 10 mg require a decrease in the po dexamethasone. Recommended dexamethasone dosing is summarized in Table 5.3. Decisions to use more

aggressive premedication schemes in subjects with only prior Grade 1 or only one prior Grade 2 infusion reaction must be approved by the Principal Investigator.

Table 5.3: Corticosteroid Premedication[a]

Prior Infusion Reaction	Corticosteroid Premedication[b] Before Elotuzumab
None or Only Grade 1 infusion reaction[c]	**Induction Cycles 1 – 8**: 28 mg po dexamethasone (3 - 24 hrs. before elotuzumab)[e] AND 8 mg IV dexamethasone at least 45- 90 min before elotuzumab **Maintenance:** 8 mg IV dexamethasone at least 45- 90 min before elotuzumab
Prior Grade 2 infusion reaction[d]	**Induction cycles and Maintenance:** 28 mg po dexamethasone (3 - 24 hrs. before elotuzumab[e] AND 10 mg IV dexamethasone at least 45 - 90 min before elotuzumab
Prior Grade 3 or recurrent Grade 2 infusion reaction	**Induction cycles and Maintenance:** 8 mg po dexamethasone (12 - 24 hrs. before elotuzumab) AND 8 mg po dexamethasone (at least 3 hrs. before elotuzumab, on the same day as the infusion) AND 18 mg IV dexamethasone at least 45 – 90 min before elotuzumab

[a] For prior infusion reactions, use maximum doses H1, H2 blockers and acetaminophen as described in Section 5.3.6.2

[b] At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 - 24 and 3 hours before elotuzumab for prior Grade 1 and 2 infusion reactions.

[c] Subjects with prior Grade 1 infusion reaction may be premedicated as per Grade 2 infusion reactions if approved by the medical monitor.

[d] Subjects with prior Grade 2 infusion reaction may be premedicated as per Grade 3 infusion reactions if approved by the medical monitor.

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

If a subject with a prior Grade 2 to 3 infusion reaction also requires dose reduction of dexamethasone, the dexamethasone dose on the days of elotuzumab infusion should be no lower than 8 mg IV (on the day of elotuzumab infusion at least 45 – 90 minutes before elotuzumab).

Subjects with Grade 4 infusion reaction are not eligible to receive additional elotuzumab. These subjects may continue to receive lenalidomide, bortezomib, and dexamethasone.

If a subject is unable to tolerate premedications, the study PI should be made aware.

For patients who have not experienced an infusion reaction, the 28 mg dose of dexamethasone can be reduced first to 20 mg and secondly to 12 mg. The 8 mg IV dose can be reducted to one level,

to 4 mg. Study participants who have experienced a prior infusion reaction will not be able to reduce the dexamethasone pre-medication dose.

5.3.8 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

5.3.8.1 Grade 1 Infusion Reaction

For Grade 1 elotuzumab infusion-related reactions, consider temporary interruption of infusion or slowing of infusion rate and treatment with supportive measures, as clinically indicated. Unless symptoms worsen, the infusion can resume or continue as planned.

5.3.8.2 Grade 2-3 Infusion Reaction

Infusion reactions during the elotuzumab infusion: 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: anti-emetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures.

For Grade 2 infusion reactions, once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at the same rate of infusion at which the infusion reaction occurred. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (according to Table 2, Appendix VII). For Grade 3 infusion reactions, once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at one level lower than the rate of infusion at which the infusion reaction occurred (refer to Table 2, Appendix VII). If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (Table 2, Appendix VII). However, final determination about the rate of infusion will be determined by the treating physician and may be considered on a case-by-case basis. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes during and 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 5.3.

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

Subsequent elotuzumab infusion after a prior Grade 2 or 3 infusion reaction: Subjects with prior Grade 2 infusion reactions should have the subsequent infusion started at the same rate of infusion at which the infusion reaction occurred and the infusion rate may be escalated in a stepwise fashion (Table 2, Appendix VII) to a maximum of 5 mL per minute. Subjects with prior Grade 3 infusion reactions should have the subsequent infusion started at one level lower

than the rate of infusion at which the infusion reaction occurred. See Appendix VII for guidelines regarding escalation of the infusion rate.

5.3.8.3 Grade 4 Infusion Reaction

Elotuzumab must be permanently discontinued. Subjects may continue with lenalidomide, bortezomib, and dexamethasone per protocol.

5.4 Lenalidomide

5.4.1 Induction Cycles

Lenalidomide **25 mg po will be administered on Days 1 through 14 followed by 7 days rest in 21 day cycles. On the days of elotuzumab administration, **the dose of lenalidomide is to be administered at least 2 hours after completion of elotuzumab dosing.**
****(Lenalidomide starting dose to be adjusted according to baseline renal function according to Package Insert guideline).**

5.4.2 Maintenance Cycles

Maintenance therapy will be administered to all patients, with the specific maintenance regimen determined by risk category. Each maintenance cycles is 28 days.

Patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance with:

- Lenalidomide 10 mg days 1 – 21 of each 28 day cycle;

Patients undergoing ASCT who are ISS I or II without high-risk cytogenetics will receive maintenance with:

- Lenalidomide 10 mg Days 1 – 21 of each 28 day Cycle 1 – 21; and

Patients opting not to proceed with ASCT who are ISS stage II or III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance following 8 cycles of induction with:

- Lenalidomide at the dose tolerated during induction Days 1 – 21 of each 28 day cycle;

Patients opting not to proceed with ASCT who are ISS stage I without high-risk cytogenetics will receive maintenance following 8 cycles of induction with:

- Lenalidomide at the dose tolerated during induction days 1 – 21 of each 28 day cycle

5.4.3 ALL Cycles

Only enough lenalidomide for 1 cycle of therapy may be provided to the participant each cycle.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Administration of lenalidomide will be at approximately the same time each day. **However, the dose of lenalidomide is to be administered at least 2 hours after completion of elotuzumab dosing.** Drug may be taken with or without food. If a dose of lenalidomide is missed and it has

been less than 12 hours since the intended scheduled dose time, the subject should take the missed dose as soon as he/she remembers. If it has been more than 12 hours, this lenalidomide dose should not be taken. Do not take 2 doses at the same time. If it is missed for the entire day or vomited, the dose should not be made up and the participant should continue with the regular schedule of the drug at the next dose. A drug diary will be provided to participants to record oral administration of doses.

Participants who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Participants experiencing adverse events may need study treatment modifications (see Section 6).

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

All study participants are required to register in and comply with the Revlimid REMS® program.

5.4.4 Bortezomib

Bortezomib will be administered SQ under the supervision of the investigator or identified sub-investigator(s). Participants may be treated on an out-patient basis, if possible. The amount (in mg) of bortezomib to be administered will be determined based on BSA. BSA is to be calculated based on body weight using the DuBois formula (Appendix II) and in accordance with institutional standards. At a minimum, the dose will be calculated on Day 1 of each cycle. At least 70-72 hours must elapse between bortezomib doses. If the patient develops toxicity including neuropathy, less than 72 hours between doses is not recommended, but not prohibited. Bortezomib should not be administered in participants who have a known allergy to bortezomib, boron or mannitol.

5.4.4.1 Induction Cycles 1 to 8

Bortezomib (1.3 mg/m^2) SQ injection will be administered on Days 1, 4, 8, and 11 in 21-day cycles. The dosing window for bortezomib is ± 1 day when bortezomib is administered twice per week; at least 72 hours must elapse between consecutive doses of bortezomib. However, dosing at an interval of 70 hours is permitted for scheduling reasons, subject convenience, or hardship.

5.4.4.2 Maintenance Cycles

Maintenance therapy will be administered to all patients, with the specific maintenance regimen determined by risk category. Each maintenance cycle is 28 days.

Patients undergoing ASCT who are ISS stage III and/or have high-risk cytogenetics and patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage II or III and/or have high-risk cytogenetics including t(4;14), t(14;16); or del17p will receive maintenance with:

- Bortezomib 1.3 mg/m2 days 1 and 15 SQ

Patients undergoing ASCT who are ISS I or II without high-risk and **patients opting not to proceed with ASCT following 8 cycles of induction who are ISS stage I without high-risk cytogenetics** will

- Bortezomib will not be administered in the maintenance cycles

5.4.5 Dexamethasone

5.4.5.1 Induction Cycles 1 and 2

Dexamethasone 20 mg po will be administered on Days 2, 4, 5, 9, 11 and 12 in 21-day cycles.

On days of elotuzumab infusion (Days 1, 8, and 15), dexamethasone will be administered as a split dose of:

- 28 mg po (between 3 - 24 hours before the start of elotuzumab infusion) AND
- 8 mg IV (on the day of elotuzumab infusion at least 90 - 45 minutes before the start of elotuzumab infusion).

If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally.

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

Refer to table 5.3 for clarification on dexamethasone administration in the event of infusion reactions or in absence of reactions.

5.4.5.2 Induction Cycles 3 and 4

Dexamethasone 20 mg po will be administered on Days 2, 4, 5, 8, 9, and 12 in 21-day cycles.

On days of elotuzumab infusion (Days 1 and 11), dexamethasone will be administered as a split dose of:

- 28 mg po (between 3 - 24 hours before the start of elotuzumab infusion) AND
- 8 mg IV (on the day of elotuzumab infusion at least 90 - 45 minutes before the start of elotuzumab infusion).

If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally.

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

Refer to table 5.3 for clarification on dexamethasone administration in the event of infusion reactions or in absence of reactions.

5.4.5.3 Induction Cycles 5 - 8

Dexamethasone 10 mg po will be administered on Days 2, 4, 5, 8, 9, and 12 in 21-day cycles.

On days of elotuzumab infusion (Days 1 and 11), dexamethasone will be administered as a split dose of:

- 28 mg po (between 3 - 24 hours before the start of elotuzumab infusion) AND
- 8 mg IV (on the day of elotuzumab infusion at least 90 - 45 minutes before the start of infusion).

If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally.

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

Refer to table 5.3 for clarification on dexamethasone administration in the event of infusion reactions or in absence of reactions.

For all cycles, each dexamethasone dose should be taken with food and at the same time each day. If a dose is missed or vomited, the dose should not be made up and the participant should continue with regular schedule of the drug.

5.4.5.4 Maintenance Cycles

On the day of the elotuzumab infusion, dexamethasone will be administered as a dose of:

- 8 mg IV (on the day of elotuzumab infusion at least 90 - 45 minutes before the start of infusion).

If elotuzumab dosing is skipped or discontinued, dexamethasone will be administered orally.

Refer to table 5.3 for clarification on dexamethasone administration in the event of infusion reactions or in absence of reactions.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Required Concomitant Therapy

It is required that participants receive prophylaxis against herpes zoster using oral acyclovir (400 mgs twice daily) or valacyclovir (500 mgs twice daily) or equivalent antiviral therapy per institutional guidelines and at the discretion of the site investigator, unless the participant develops a hypersensitivity to the agents. The dose will be adjusted based upon serum creatinine levels according to package insert.

Subjects must complete stem cell mobilization. Treatments and procedures necessary for stem cell mobilization and SCT (if applicable) are permitted at the discretion of the investigator and according to the standards of participating institutions.

Pre-treatment with dexamethasone IV (at least 90 - 45 minutes prior to elotuzumab on the day of infusion), and diphenhydramine (or equivalent H1 blocker [eg, hydroxyzine] if allergic to diphenhydramine), an H2 blocker (ranitidine or equivalent), and acetaminophen 30 to 90 minutes prior to elotuzumab infusions is required in all subjects (See Sections 5.3.7). If persistent intolerance develops with one or more of these medications, consult with the Principal Investigator.

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

Therapy to reduce the risk of thrombotic events associated with lenalidomide, is required for all participants. Participants should receive daily aspirin administration (81 or 325 mg) to decrease the risk of thromboembolic complications, however, caution should be used in participants who develop thrombocytopenia. Patients at high-risk for thromboembolic disease, such as those with prior h/o DVT, should receive anticoagulation with low molecular weight heparin or warfarin. It is recommended that if the platelet count falls below 50,000/mm^3, thromboprophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or above this level.

5.5.2 Recommended Concomitant Therapy

It is recommended that participants receive pneumocystis carinii pneumonia (PCP) prophylaxis using appropriate therapy according to institutional guidelines and at the discretion of the investigator.

It is also recommended that the following adjunctive approaches be considered to prevent neuropathy at the discretion of the site investigator:

- Multi-B Complex Vitamins, once daily: with B1, B12, B6 at RDA. B6 dose should not exceed 100 mg.
- Folic acid 1 mg/daily
- Vitamin E and Vitamin D: Up to 400 IU daily
- Acetyl L-Carnitine: 500 mg twice a day with food AND
- Alpha-Lipoic Acid: 500 mg a day with food OR
- A combination pill of: Alpha lipoic acid 200 mg + Acetyl-L-Carnitine 500 mg: take ONE twice a day with food.

Please note that all above supplements should not be taken on days of bortezomib administration.

At the discretion of the site investigator, cocoa butter, which is rich in Vitamin E, xanthines and natural serotonins, can also be used. It is generally applied to extremities twice a day with gentle massage. Menthol-based creams can also be used for areas of numbness as needed.

Other recommended therapy:

- Concomitant bisphosphonate therapy, according to individual institution guidelines.
- Diligent dental/mouth care is recommended.
- All supportive measures consistent with optimal participant care will be given throughout the study.

5.5.3 Prohibited Concomitant Therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Concomitant systemic corticosteroids, other than as part of the protocol-specified therapeutic regimen, or topical corticosteroid without systemic absorption, are prohibited. Low dose steroids (prednisone 10mg or equivalent) for treatment of co-morbid conditions or study related toxicities, particularly rash, is allowed. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study. Guidelines for selection and use of other concomitant medications should be derived from the lenalidomide, bortezomib, and dexamethasone prescribing information.

5.5.4 Permitted at Investigator's Discretion

- Additional glucocorticoids, antihistamines, and analgesics, for the management of infusion reactions. Additional supportive measures should be provided as indicated including oxygen inhalation, epinephrine, and bronchodilators
- Antimicrobial (including anti-fungal) or antiviral prophylaxis
- Prophylactic anticoagulation (aspirin, warfarin or low molecular weight heparin) to prevent thromboembolic events)
- Anti-emetics
- Erythropoietin (EPO) or darbepoetin (according to the package insert and institutional guidelines). Note: Erythropoietin cannot be used within 7 days of screening evaluations to meet eligibility criteria
- Red blood cell or platelet transfusion
- Prophylactic administration of G-CSF in a subject who is experiencing recurrent difficulties with neutropenia, or therapeutic use in subjects with serious neutropenic complications (such as tissue infection, sepsis syndrome or fungal infection) may be considered at the

investigator's discretion, consistent with American Society of Clinical Oncology guidelines (ASCO 2006). NOTE: GCSF cannot be used within 14 days of screening evaluations to meet eligibility criteria.

- Bisphosphonates according to the ASCO 2007 Clinical Practice Guidelines. (Kyle 2007)
- General supportive interventions, including but not limited to intravenous fluids and oral or parenteral electrolyte supplementation.
- A bowel regimen to prevent constipation, according to local practice, is highly recommended.

5.6 Duration of Therapy

Duration of therapy will depend on response to therapy, evidence of disease progression, and tolerance. Participants who have stable or responding disease to treatment and have an acceptable toxicity profile will be allowed to continue maintenance treatment until disease relapse, unacceptable toxicity or until one of the following criteria applies:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (must discontinue all study drugs under this protocol)
- Termination of the study by the Sponsor/Investigator
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Progressive Disease (see Table 10.2.4.1 for definition of progressive disease).
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy (other than stem cell mobilization and SCT) before documented progression will be discontinued from all study treatment (including elotuzumab, bortezomib, lenalidomide, and dexamethasone), however, tumor assessments must continue until progression
- Subjects experiencing a Grade 4 infusion reaction to elotuzumab must discontinue the elotuzumab. Subjects may continue bortezomib, lenalidomide, and dexamethasone.
- Subjects who experience Grade 2 neuropathy with pain or ≥ Grade 3 neuropathy related to bortezomib following dose delay and dose reduction must discontinue the bortezomib. Subjects may continue the elotuzumab, lenalidomide, and dexamethasone.
- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to lenalidomide must discontinue lenalidomide. Subjects may continue bortezomib, dexamethasone, and elotuzumab.
- Subjects experiencing a treatment delay of more than 21 days in all study drugs (bortezomib, lenalidomide, dexamethasone and elotuzumab) due to an AE related to study drug must be discontinued from study drugs. Subjects experiencing delays unrelated to study drug, for example due to radiation therapy, may delay study drug up to 42 days. Delays more than 21 days must be discussed with the PI with the exceptions detailed in Section 6.2.1 and related to stem cell mobilization, harvest, and/or transplant.

5.7 Surgery and Radiation

-
- Localized radiotherapy can be given pre-study with a 2 week break prior to the start of systemic treatment, as long as this radiation therapy is to a site of pre-existing disease and there is resolution of hematologic or gastrointestinal toxicity that may be related to radiation.
- If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for disease progression, treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated. Kyphoplasty, vertebroplasty or emergency orthopedic surgery is permitted.

5.8 Duration of Follow Up

During therapy patients are followed every treatment cycle.

5.9 Criteria for Removal from Study

Participants will be removed from studyif the patient withdraws consent for follow-up or in the event of death. Please see Section 5.6 for complete list of reasons for removal from study..

In the event of unusual or life-threatening complications, participating investigators must immediately notify the study Principal Investigator (PI): Jacob Laubach at [redacted] (telephone) or [redacted].

Participants will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

6 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

The following adverse events will be collected:

- All SAEs.
- All ≥Grade 2 AEs.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

6.1.1 CAEPRs for CTEP-Supplied Investigational Agent(s)

This section is not applicable to the study.

6.1.2 Adverse Events List for Lenalidomide

The following is a list of adverse events that are associated with the use of lenalidomide.

Events that have occurred in >10% of individuals treated with lenalidomide		
Neutropenia	Loss of appetite	Headache
Anemia	Itching	Back and joint pain
Thrombocytopenia	Dry skin	Fever
Fatigue	Muscle cramps	Cough
Rash	Lack or loss of strength	Upper respiratory infection
Diarrhea	Dizziness	Dyspnea
Constipation	Insomnia	
Nausea	Swelling of the extremities	
Events that have occurred in <10% of individuals treated with lenalidomide		
Risk of DVT	Febrile neutropenia	Sepsis
PE and blood clots that could lead to stroke	Atrial fibrillation	Dehydration
Heart attack, or organ failure	Pneumonia or lung infections	Renal failure
Other rare events that have occurred in individuals treated with lenalidomide		
Angioedema, serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or an allergic skin reaction similar to that seen with thalidomide. Tumor lysis syndrome (TLS), tumor flare reaction (TFR), and rhabdomyolysis. In addition, lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Participants will be instructed to inform their doctor if taking digoxin. There may be an increased risk of second cancers in participants who are on lenalidomide maintenance therapy after a bone marrow transplant.		

6.1.3 Adverse Events List for Bortezomib

The following is a list of adverse events that are associated with the use of bortezomib.

Events that have occurred in >10% of individuals treated with bortezomib		
Fatigue	Nerve injury	Cough
Loss of strength	Vomiting	Headache
Nausea	Decreased blood counts	Rash
Diarrhea	Edema	Hypotension
Constipation	Muscle or joint pain	Shingles
Loss of appetite	Shortness of breath	
Events that have occurred in <10% of individuals treated with bortezomib		

Congestive heart failure Dizziness.		
Rare or less frequent events that have occurred in individuals treated with bortezomib		
Tumor lysis syndrome (TLS), Hypertension, Interstitial lung disease, Pericarditis	Arrhythmia, Angioedema, Hyponatremia, Hypomagnesemia,	Hypophosphatemia, Hypoglycemia Herpes meningogenphalitis

6.1.4 Adverse Events List for Dexamethasone

Events that have occurred in >10% of individuals treated with dexamethasone		
Increased appetite Weight gain Sleep disturbance Hypertension Fluid retention	Ankle swelling Bruising Infection Mood changes Slow wound healing	Depression Hyperglycemia, which may lead to fatigue, weight loss, excessive thirst, and frequent urination
Events that have occurred in <10% of individuals treated with dexamethasone include		
Loss of appetite Muscle twitching Increased thirst Frequent urination	Increased perspiration Diarrhea Nausea Headache	Spinal fracture or fracture of bones Tachycardia Fungal infections.
Events that have occurred in <1% of individuals treated with dexamethasone		
Blurred vision Personality changes	Stomach ulcers with bleeding that may cause hematemesis	Blood in the stool Abdominal pain.
Other, less frequent, events that may occur in individuals treated with dexamethasone		
Bowel perforation Irritation and bleeding of the esophagus Heart failure Allergic reaction that may lead to facial redness Shortness of breath Abdominal cramps Hypotension Convulsions Brain swelling	Dizziness Cataracts Glaucoma and increased blood pressure in the eye Development of diabetes Pancreatic inflammation Abdominal swelling Hypokalemia DVT or PE Malaise	Swelling and/or redness of skin Allergic skin reactions Itching Hirsutism Muscle weakness or loss of muscle mass Rupture of tendons Menstrual cycle disturbances Hiccups.

6.1.5 Adverse Events List for Elotuzumab

Refer to the current Investigational drug brochure for Elotuzumab for listings of treatment emergent adverse events.

6.2 Toxicity Management

Before each drug dose, the participant will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology CTEP Version 4.03 of the NCI CTCAE. Dose modifications or delays will be performed based on the toxicity experienced during a cycle of therapy or newly encountered on day 1 of each cycle. Reduction and/or temporary suspension of one agent and not the other is appropriate if toxicity is related primarily to one of the agents. The participant may continue on therapy if the toxicity can be managed according to the dose modification guidelines as outlined below.

Once a treatment dose is reduced for toxicity, no re-escalation of that treatment will be allowed. Drug may be held for no more than 21 days to allow resolution of toxicity from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from therapy, the patient may be able to continue treatment with a dose reduction at the Investigator discretion and in consultation with the Principal Investigator, after resolution of the adverse event. The dose reduction steps are detailed below.

If the dose of one drug in the regimen (ie, lenalidomide, bortezomib, dexamethasone, or elotuzumab) is delayed, interrupted, or discontinued, the treatment with the other drugs should continue as scheduled. However, if either po or IV dexamethasone is delayed or discontinued, discuss ongoing elotuzumab administration with the Principal Investigator.

Subjects experiencing a 21 day delay in all study drugs (lenalidomide, bortezomib, dexamethasone, and elotuzumab) due to an AE(s) related to study drug must be discontinued from study drug. Subjects experiencing delays unrelated to study drug, for example due to radiation therapy may delay study drug up to 42 days. Delays greater than 21days must be discussed with the Principal Investigator with the exceptions detailed below.

The effect of elotuzumab has been studied extensively in combination with Lenalidomide and Bortezomib, and dosages of 10 mg/kg IV are used in all phase III and randomized phase II studies to date. Nonetheless, the four drug combination proposed in this study has not yet being evaluated in humans. Therefore, after the enrollment of 10 subjects in the study, further subject enrollment will be placed on hold to evaluate safety/toxicity data pertaining to the 4 drug combination, and specifically regarding Elotuzumab will be reviewed in order to make trial conduct recommendations based on an analysis of risk vs. benefit.

6.2.1 Permitted treatment delays

1) Up to 4 weeks for stem cell mobilization and recovery (if cyclophosphamide is used, an additional 3 weeks for recovery [total 7 weeks] is allowed); subjects experiencing delays greater than 4 weeks (7 weeks for subjects receiving cyclophosphamide) must be discontinued from study treatment but are followed for progression.

2) Subjects undergoing SCT are allowed a 12 week period of recovery from day 0 before initiation of post transplant maintenance therapy; subjects experiencing delays greater than 12 weeks must be discontinued from study treatment.

6.2.1.1 Elotuzumab

In Induction Cycles 1 and 2, elotuzumab doses that fall outside of the prespecified window of -1/+3 days must be skipped.

Beginning with Induction Cycle 3 and during maintenance cycles, the elotuzumab dosing window is -3/+7 days, and doses that fall outside of this window must be skipped.

6.2.1.2 Lenalidomide

If a dose of lenalidomide is missed and it has been less than 12 hours since the intended scheduled dose time, the subject should take the missed dose as soon as he/she remembers. If it has been more than 12 hours, this lenalidomide dose should not be taken. Do not take 2 doses at the same time.

6.2.1.3 Dexamethasone

Dexamethasone delay should be performed as clinically indicated at the discretion of the investigator. On the weeks of treatment with elotuzumab, the dexamethasone dose must be administered as part of the premedication for elotuzumab per the guidance in Section 5.4.5

6.2.1.4 Bortezomib

Treatment with bortezomib may be delayed for recovery from any AE/SAEs as described in Section 4.3.5. The treatment window for bortezomib during Induction Cycles 1 - 8 is ± 1 day, but the interval between consecutive doses of bortezomib must be at least 72 hours. Beginning with Maintenance Cycle 1, the window for bortezomib is ± 3 days.

6.2.2 Dose Reduction Steps

6.2.2.1 Dose Reduction Steps for Lenalidomide

Starting dose of lenalidomide Days 1 – 14 every 21 days Cycles 1 - 8 *Maintenance therapy Days 1 - 21	**1ST Dose Reduction**	**2ND Dose Reduction**	**3RD Dose Reduction**	**4TH Dose Reduction**
25 mg	15mg	10 mg	5 mg	Discontinue lenalidomide

6.2.2.2 Dose Reduction Steps for Bortezomib

Starting Dose of bortezomib SQ) Days 1, 4, 8 and 11 in Cycles 1-8 *Maintenance therapy Days 1 and 8	**1ST Dose Reduction**	**2ND Dose Reduction**	**3RD Dose Reduction**	**4TH Dose Reduction**
1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.7 mg/m^2 days 1 and 8	Discontinue bortezomib

*Dose reductions during the maintenance therapy should follow the same steps of 1.3 mg/m^2 to 1.0 mg/m^2 to 0.7 mg/m^2 without further change in schedule (Days 1 and 15). Dose reductions below 0.7 mg/m^2 days 1 and 8, during induction and or 1 and 15 during maintenance, will require prior study PI permission and documentation.

6.2.2.3 Dose Reductions Steps for Dexamethasone

Dexamethasone Dose Reductions

Starting Dose of Dexamethasone	1ST Dose Reduction	2ND Dose Reduction
20 mg PO	12 mg PO	0 mg PO

6.2.2.4 Dose Reduction Steps for Elotuzumab

No dose reductions are permitted for elotuzumab

6.3 Dose Modification/Delays

Each Adverse Event should be attributed to a specific study drug if possible so that dose modifications can be made accordingly. Further clarification can be obtained in consultation with the study PI. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity. Drug may be held for no more than 21 days to allow resolution of toxicity. The same dose modification guidelines will apply to maintenance cycles unless otherwise noted.

Participants who discontinue one study drug for toxicity may continue to be treated on protocol with the remaining study drugs.

6.3.1 Drug Related Adverse Event Dose Modification Guidelines for Lenalidomide and Bortezomib During a Cycle.

Worst Toxicity		Dose Modification Guidelines At any time **during a cycle of therapy** (including intended day of dosing)
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia	Platelet count < 10,000 or Grade 4 (< 25 x 10^9/L) with bleeding.	Temporarily discontinue therapy including antiembolic prophylaxis. Monitor CBC on Days 4, 8 and 11 during induction Cycles 1 – 8 and Days 1 and 15 during maintenance. Resume dosing if resolved to ≥ 25,000/mm^3 with: One level dose reduction of lenalidomide and /or One level dose reduction of bortezomib Dose reduction of one drug and not the others is permitted at the investigators discretion. If no other toxicity requires a dose reduction and thrombocytopenia can be managed with the use of platelet transfusions, no dose reductions are required. Use of plt transfusion is permitted on the day of dosing.
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L) or Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue therapy. Monitor CBC on Days 4, 8 and 11 during induction Cycles 1 – 8 and Days 1 and 15 during maintenance. Use of G-CSF is allowed and recommended and is allowed on day of dosing. Resume dosing if resolved to ≥ 750/mm^3 with: One level dose reduction of lenalidomide and /or One level dose reduction of bortezomib Dose reduction of one drug and not the other is permitted at the investigators discretion. If no other toxicity requires a dose reduction and neutropenia can be managed with the use of G-CSF, no dose reductions are required.
NON-HEMATOLOGICAL TOXICITIES		

Herpes Zoster reactivation	Any Grade	Hold bortezomib until lesions are dry. Increase antiviral prophylaxis to therapeutic dose until lesions are healing and dry.
Peripheral neuropathy	≥ Grade 3 or Grade 2 with pain	See Section 6.3.1.1 for bortezomib dose reductions. Consideration for dose reduction of lenalidomide may be given after reduction of bortezomib.
Other drug related non hematologic toxicity	≥ Grade 3	Determine attribution of toxicity if possible and hold appropriate therapy. Follow at least weekly. If toxicity resolves to ≤ Grade 2 resume therapy with one level dose reduction of appropriate drug.

6.3.1.1 Dose modifications for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy

The neurotoxicity-directed questionnaire (Appendix VI) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the participant's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the participant completes the Neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

Recommended Dose Modification for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness, and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce by one dose level. If a second dose reduction is necessary, bortezomib will be given once weekly during induction on Days 1 and 8 at 0.7 mg/m^2 or Days 1 and 15 during maintenance
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to < grade 2. When toxicity resolves, reinitiate at one level dose reduction. If a second dose reduction is necessary, bortezomib will be given once weekly during induction on Days 1 and 8 at 0.7 mg/m^2 or Days 1 and 15 during maintenance
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue bortezomib

Grading based on CTEP Version 4.03of the NCI Common Terminology Criteria for Adverse Events (CTCAE): http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

ADL = activities of daily living

6.3.2 Dexamethasone Dose Modifications

Dexamethasone dose modifications		
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. When the event grade is ≤ 2, restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole,. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve to grade <2. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory (grade <3).

Dose reduction for persistent Grade 2 or Grade ≥ 3 AEs believed to be related to dexamethasone and not listed above are permitted. The AE must be documented in the CRF.

More aggressive dose reductions for lower grade toxicity than those listed above must first be discussed with the Principal Investigator

6.4 Initiation of New Cycle of E-RVD Therapy (Day 1)

Additional criteria for initiation of Cycle 5 following stem cell mobilization are detailed in section 6.5

A new course of treatment may begin on the scheduled Day 1 of a new cycle of E-RVD if the following criteria are met:

- ANC $\geq$ 1,000/ mm^3 (growth factor support is permitted; it is allowed on the same day as treatment administration) platelet count $\geq$ 50,000/ mm^3 (platelet support is permitted; it is allowed on the same day as treatment administration).
- Any other lenalidomide, bortezomib, dexamethasone or elotuzumab related adverse event that may have occurred has resolved to $\leq$ grade 2 severity (or according to the dose modification table).
- Herpes Zoster lesions are dry

If there are dose modifications or delays in the previous cycle, these guidelines should be followed for the initiation of a new cycle.

If there are no other toxicities that require a dose reduction and thrombocytopenia and/or neutropenia can be managed by the use of platelet transfusions or G-CSF, no dose reductions are required but may be made at the investigators discretion. Consultation with the PI is recommended.

- If lenalidomide was held during the previous cycle and restarted at a reduced dose level, without interruption for the remainder of the cycle, then the reduced dose level will be initiated on Day 1 of the new cycle.
- If lenalidomide dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to lenalidomide-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with one-level dose reduction.
- If any two or more doses of bortezomib were held during the cycle (either consecutively or two or more in one cycle), then the new cycle will be started with one level dose reduction.
- If the new cycle is delayed due to bortezomib-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

Dose modifications for toxicity are permitted according to section 6. The maximum amount of time for which a drug may be held due to toxicity is 21 days. If study drug is held for more than 21 days due to toxicity the participant will be removed from the study. If however the patient was clearly benefiting from therapy, the patient may be able to continue treatment with a dose reduction at the Investigator discretion and in consultation with the Principal Investigator, after resolution of the adverse event.

6.5 Initiation of Induction Cycle 5 post Stem Cell Mobilization

Prior to continuing to Induction Cycle 5, all stem cell harvest-related toxicities must have resolved or improved to CTCAE Grade $\leq$ 1 and subjects must meet the following stem cell harvest recovery criteria:

a) ECOG $\leq$ 2;
b) Absolute neutrophil count >1000 cells/mm3;
c) Platelet count $\geq$ 75,000 cell/mm3 (75 x 109/L);
d) Hemoglobin $\geq$ 8 g/dL at most recent measurement;
e) Total bilirubin < 1.5 x upper limit of normal (ULN);

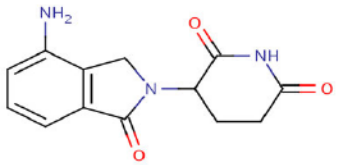
f) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN;
g) Able to undergo further treatment in the judgment of the investigator.

7 DRUG FORMULATION AND ADMINISTRATION

7.1 Lenalidomide (REVLIMID®)

7.1.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

7.1.2 Form

Lenalidomide is off-white to pale-yellow solid powder. Lenalidomide is soluble in organic solvent/water mixtures, and buffered aqueous solvents. It is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

7.1.3 Storage and Stability

Lenalidomide is commercially available and will be dispensed by a pharmacist registered in the Revlimid REMS® program. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

7.1.4 Handling

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

7.1.5 Availability

Lenalidomide is commercially available and will be dispensed by a pharmacist registered in the Revlimid REMS® program.

7.1.6 Ordering

Lenalidomide will be provided as commercial supply in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

7.1.7 Accountability

Lenalidomide is commercially available therefore, no drug accountability records are required. The investigator is responsible for monitoring patient compliance by monitoring patient diary and or pill count.

7.1.8 Destruction and Return

Participants will be instructed to return empty bottles or unused capsules via the Revlimid REMS® program.

7.2 Bortezomib (VELCADE®)

7.2.1 Description

Bortezomib for Injection is a small molecule proteasome inhibitor developed by Millennium as a novel agent to treat human malignancies. By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of NF-κB activation, its attenuation of IL-6-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.

7.2.2 Form

Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in sterile, single use vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol. Bortezomib is commercially available and will not be supplied as part of this clinical trial.

7.2.3 Storage and Stability

Vials containing lyophilized bortezomib for Injection should be stored according to label requirements. Store at USP Controlled Room Temperature which is 25◦C (77◦F); excursions permitted from 15 to 30◦C (59 to 86◦F).

7.2.4 Handling

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices.

7.2.5 Availability

Commercial supplies of bortezomib will be used for this study.

7.2.6 Preparation

Each vial of bortezomib should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with normal (0.9%) saline, Sodium Chloride Injection USP. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. The reconstituted solution should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. Caution should be used when calculating the reconstituting volume and the final concentration for administration.

Reconstitution Volumes and Final Concentration for SubcutaneousAdministration

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

Refer to the Package Insert for complete details.

7.2.7 Ordering

Commercial supplies of bortezomib will be used for this trial.

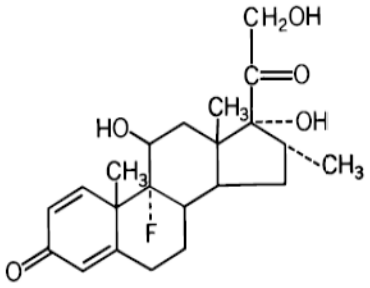
7.2.8 Accountability

Commercial supplies of bortezomib will be used for this trial, therefore no drug accountability records are required.

7.3 Dexamethasone

7.3.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs. The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



7.3.2 Availability

Dexamethasone supply will be obtained through commercial supply.

7.3.3 Ordering

The investigator or designee will order drug supply from commercial supply.

7.4 Elotuzumab

7.4.1 Description

Elotuzumab for injection has been developed to be used as an intravenous (IV) infusion for the clinical studies. Drug product is a non-pyrogenic lyophilized powder which is white to off-white contained in 20-cc Type I glass vials, closed with 20-mm stoppers and sealed with aluminum seals. Each vial of drug product contains the labeled amount of BMS-901608 drug substance, sucrose, sodium citrate dihydrate, citric acid, and polysorbate 80. A 10% overfill is included in each vial to account for vial, needle, syringe (VNS) holdup. The drug product will be reconstituted prior to administration.

Prior to administration the drug product must be reconstituted with Sterile Water for Injection, USP, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Appendix VII

7.4.2 Storage and Stability

Elotuzumab for injection should be stored refrigerated at 2° to 8°C (36° - 46°F) with protection from light. Do not freeze or shake.
Reconstituted and diluted solution of elotuzumab for injection is stable for up to 24 hours, under refrigerated conditions, 2° to 8°C (36° - 46°F). The drug solution should be equilibrated to room temperature and the container must be gently inverted to mix well before administration. Do not use the accelerated warming method. After the dose is diluted in normal saline, it must be fully administered within 8 hours if stored at room temperature.

7.4.3 Availability

Elotuzumab for injection will be supplied by BMS.

7.4.4 Preparation and Administration

The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg for Induction Cycles and 20mg/kg for Maintenance Cycles. Dose calculations and re-calculations will be based on the site's institutional standard.

Prior to administration the drug product must be reconstituted with Sterile Water for Injection, USP, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Appendix VII. After the dose is diluted in normal saline, the infusion must be completed within 8 hours if stored at room temperature. If a delay is anticipated, the prepared dose may be refrigerated at 2° to 8°C for up to 24 hours. If stored under refrigerated conditions, the prepared study drug solution should be equilibrated to room temperature (process takes 2 - 2.5 hours) and the container must be gently inverted to mix well before administration. Do not use the accelerated warming method. If administration is delayed beyond the specified time, the prepared dose solution must be discarded, and the reason documented by the pharmacist in study drug accountability records.

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

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

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

If no infusion reactions were observed during the first cycle of elotuzumab, the second cycle can commence at a rate of 5 mL per minute (see Table 2 Appendix VII).

Further instructions on the escalation of the infusion rate and in case of infusion reactions, are provided in Appendix VII.

7.4.5 Ordering

Each participating institution will order Elotuzumab directly from the supplier Bristol Myers Squibb Pharmaceuticals (BMS). A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center to BMS.

7.4.6 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.4.7 Destruction and Return

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible DFCI Study Monitor or designee unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification (ID) of the person disposing the containers. The method of disposal, (eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

8 CORRELATIVE/SPECIAL STUDIES

Not applicable.

9 STUDY ASSESSMENTS AND PROCEDURES

Table 9.1 Flow Chart/Time and Events Schedule

Procedure	Screening[1] (within 21 days prior to C1D1)	Induction Cycle 1[1] to 4 Each cycle is 21 days					Post Cycle 4 and pre- stem cell collection	Induction Cycle 5 – 8 Each cycle is 21 days				Maintenance Cycles 9+ Each cycle is 28 days		End of Study [30]
		Day 1	Day 4	Day 8	Day 11	Day 15		Day 1	Day 4	Day 8	Day 11	Day 1	Day 15	
Informed consent	X													
Inclusion/Exclusion criteria	X													
Complete Medical History	X													
Diagnosis & history of MM	X													
Vital signs, height, weight/BSA[2]	X	X[1,2]	X[2]	X[2]	X[2]	X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X
Physical examination	X	X[1]					X	X				X		X
ECOG performance status	X	X[1]					X	X				X		X
12-Lead ECG[3]	X													
Chest X-ray[4]	X													
Echocardiogram or MUGA	X													
Hematology[5, 6, 7]	X	X	X	X	X	X[7]	X	X	X	X	X	X	X	X
Coagulation[8]	X													
Biochemistry[9,10]	X	X[1,9]					X	X[9]				X[9]		X
Urinalysis[11]	X						X							
Calculated Creatinine Clearance	X						X	X						X

Serum/Urine Pregnancy test[12,13]	X	X		X[12]		X[12]	X	X			X Day 15[12]	X	X[12]	X[12]
Thyroid function[14]	X													
Patient Reported Outcomes (FACT GOG-NTX)/Sensory [28] Neuropathy grading[28]	X	X[28]						X[28]				X[28]		X
Disease Assessment	X						X[32]	X[32]				X[32]		X
Serum M-protein (S-PEP)[15, 17]	X	X[15,16]					X	X[15]				X		X
Urine M-protein (U-PEP)[15,17,18]	X	X[15,16]					X	X[15]				X		X
Serum Free light chain (FLC)[15]	X	X[21]					X	X				X		X
Serum Immunofixation (sIF)[15]	X						X	X				X		X
Urine Immunofixation (uIF)[15,18]	X						X	X				X		X
Skeletal survey [19]	X													
Evaluation of soft tissue plasmacytomas[20]	X	X[20]					X	X[20]				X[20]		
Bone Marrow for plasma cell count[22]	X[21]						X[22]							
Stem Cell Mobilization							X[33]							
Autologous Stem Cell transplant							X[34]							
Bortezomib[31]		X	X	X	X			X	X	X	X	X	X	
Lenalidomide oral dosing[31]		Daily days 1-14						Daily days 1-14				Daily days 1-21		

Dexamethasone dosing[31]		Refer to section 5.4.5						Refer to section 5.4.5				X		
Elotuzumab-Premedication[31]		X		X Cycles 1 and 2	X Cycles 3 and 4	X Cycles 1		X			X	X		
Elotuzumab dosing[31]		X		X Cycles 1 and 2	X Cycles 3 and 4	X Cycles 1		X			X	X		
Adverse Events[23]		Continuous												

1. Assessments required at screening visit, except for hematology, do not have to be repeated if performed ≤ 7 days prior to Cycle 1 Day 1 unless otherwise specified. To take into account scheduling conflicts (e.g., over public holidays), a 3 day +/- window will be allowed for all assessments, unless otherwise specified. Following Cycle 2, a 7 day + window is permitted *between* cycles. However every effort must be made to follow the schedule outlined in the above table.
2. Height required at baseline only. BSA is to be calculated based on body weight using the DuBois formula (Appendix II) and in accordance with institutional standards. At a minimum, the dose will be calculated on Day 1 of each cycle. Vital signs to be measured prior to elotuzumab pre-medication, pre-elotuzumab infusion, 30 minutes after the start of the infusion, at the end of the infusion and 30 and 120 minutes after completion of the infusion (120 min for C 1 and 2 only). Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes during and for 2 hours after the end of the elotuzumab infusion. Vital signs to be measured prior to bortezomib on days not administered with elotuzumab.
3. ECG 12 lead at baseline and as clinically indicated.
4. A Chest X-ray is required to provide a baseline reference in the event that the patient develops cardiac or pulmonary symptoms during the study. The chest X-ray may be included in the skeletal survey assessment.
5. Hematology includes the following parameters: complete blood count consisting of a total white blood cell count with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin; hematocrit and platelet count. Hematology assessments should be performed on the scheduled day or up to three days prior, even if study medication is being held. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. Hematology assessment on day 15 is only required before C1 and 2, and in maintenance when bortezomib will be administered on day 15.
6. Baseline hematology and biochemistry labs may be repeated once, if needed, to obtain acceptable values before the patient would screen fail, however no G-CSF or platelet transfusions are allowed to correct values.
7. Hematology results are required prior to BTZ dosing on Induction Cycle 1-8 days 1, 4, 8, and 11 and maintenance cycles Days 1 and 15 for total neutrophils [including bands] and platelet counts. Hematology results are also required prior to Elotuzumab administration on day 15 of Cycle 1 and 2.
8. Coagulation profile includes prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen. Evaluation should be performed at screening visit and may be repeated at the Investigator's discretion, if medically indicated. If patient is receiving coumadin or other anticoagulant therapy, then coagulation parameters should be monitored more frequently, per investigator's discretion
9. Results of biochemistry assessments need to be available prior to dosing on Day 1 of each cycle.
10. Biochemistry includes the following parameters: Urea or BUN, creatinine, sodium, potassium, glucose, total calcium (corrected for serum albumin) or ionized calcium, albumin, total protein, total bilirubin, lactate dehydrogenase, alkaline phosphatase, AST/SGOT, ALT/SGPT, phosphorous, magnesium, chloride, CO2(HCO3), , and uric acid. If total bilirubin > ULN, direct and indirect bilirubin should be performed. Biochemistry assessments should be

performed on the scheduled day even if study medication is being held. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. β-2 Microglobulin to be included at screening and day 1 of each cycle.

11. Urinalysis includes dipstick and microscopic exams. Dipstick examination includes: protein, glucose, blood, and specific gravity. Microscopic examination (only required if macro is abnormal) includes: WBC/HPF, RBC/HPF, and any additional findings. Baseline labs may be repeated, if needed, to obtain acceptable values before the patient would screen fail. Evaluation may be repeated while the patient is on study, where clinically indicated.
12 Pregnancy tests (sensitivity of at least 50 mIU/mL), must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. Females of childbearing potential with regular or no menstruation must have a pregnancy test weekly for the first 28 days, then every 28 days (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide.
13. All patients must enroll in the Revlimid REMS® program.
14. Thyroid Function includes Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine).
15. Disease assessments are recommended to be done per standard of care.
16. The "7 days" time window (footnote 1 above) does not apply for sampling of Serum M-protein (S-PEP) and Urine M-protein (U-PEP) on Cycle 1 Day 1.
17. IMWG criteria will be used to assess response. Disease assessments are recommended to be done per standard of care.
18. Disease assessments are recommended to be done per standard of care.
19. Skeletal survey should be performed at screening. If results of a skeletal survey performed within 8 weeks prior to screening visit are available, and if there is no clinical indication to repeat, then skeletal survey needs not to be repeated at screening visit. Bone X-rays need to be performed on study only if clinically indicated (e.g. bone pain).
20. Soft tissue plasmacytoma: If present must be assessed by clinical examination and MRI or CT at screening. Assessment of the lesion(s) by MRI or CT is also required at the end of Induction Cycle 4, at time of complete response (CR) if it is achieved, and when medically indicated during treatment
21. Screening bone marrow biopsy should be performed within 30 days of C1D1.
22. Bone marrow aspiration and biopsy to be evaluated for morphology and for cytogenetics by standard banding and FISH, including marrow karyotype if possible. Suggested probes include, at a minimum del 13q14, t(4:14), t(11;14), t(14:16), and del 17p. After Baseline, bone marrow sampling for plasma cell count is required to qualify CR and at the end of cycle 4 for all patients.
23. Patients must be instructed to notify the Investigator of any undesirable symptoms or side effects while on study.

28 FACT GOG-NTX questionnaire should be administered at screening and on day 1 of each odd cycle and at the study completion visit. Sensory neuropathy grading scores will also be evaluated at these visits.
30. End of study visit should occur within 28 days of discontinuation of treatment.
31 Refer to Section 5 for drug administration, dosing and schedule and section 6 for dose modification guidelines.
32 Disease assessments are recommended to be done as per standard of care.
33 Required for all patients at the end of Induction Cycle 4. To be performed per institutional guidelines.
34 ASCT is optional and per institutional; guidelines after Induction Cycle 4.

10 MEASUREMENT OF EFFECT

In this study, patients must have measurable disease (see Section 10.2.2). The disease response will be assessed using criteria based on the modified International Working Group Uniform Response Criteria (Rajkumar 2011) in Section 10.2.4.1. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by FreeLite™ Disease Response Criteria provided in Section 10.2.4.2.

The same method of assessment and technique should be used for disease measurement at baseline, during the study and follow-up.

10.1 Antitumor Effect– Solid Tumors

This section is not applicable to this study.

10.2 Antitumor Effect – Hematologic Tumors

10.2.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for response: All patients who receive study therapy and at least one follow-up assessment will be included in a response evaluation. Responses will be classified according to the definitions stated below. (Note: Participants who exhibit disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

10.2.2 Disease Parameters

Measurable disease: Measurable disease is disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of FLC and is defined by at least one of the following three measurements:

- Serum IgG, IgA, or IgM M-protein $\geq$ 0.5 g/dL, or
- Serum IgD M-protein $\geq$ 0.05 g/dL
- Urine M-protein $\geq$ 200 mg/24 h
- Serum FLC assay: Involved FLC level $\geq$ 10 mg/dl ($\geq$ 100 mg/l) provided serum FLC ratio is abnormal.

10.2.3 Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of therapy. Response will be assessed by M-protein quantification, protein electrophoresis and immunofixation from serum and a 24-hour urine collection. A serum sample for FreeLite™ testing will be obtained. In addition,

bone marrow aspiration will be performed to confirm response and to differentiate between CR and stringent CR.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up.

10.2.4 Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (Rajkumar 2011). A six-week confirmation measurement for disease response assessments is required in this protocol.

10.2.4.1 International Myeloma Working Group Response Criteria

Response	*IMWG criteria*
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following:

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

All response categories (sCR, CR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is 5 g/dL.

10.2.4.1 Additional response criteria for specific disease states

Minor response in patients with relapsed and refractory myeloma adapted from the EMBT criteria[3]	≥ 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)

10.2.4.2 Duration of Response and Endpoint Definitions

Duration of overall response: The duration of overall response is measured as the time from initiation of first response to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Duration of overall complete response: The duration of overall CR is measured as the time from initiation of CR to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

10.2.4.3 Progression-Free Survival

Progression-Free Survival (PFS): PFS is defined as the time from randomization to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

10.2.5 Response Review

Central review of disease response assessments is not planned for this trial. Disease response assessments will be performed locally on the following disease response measures: M-protein quantification and immunofixation from serum and a 24-hour urine collection, and serum FreeLite™ testing.

10.3 Other Response Parameters

This section is not applicable to this study.

11 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after the date of informed consent signature or any procedure specified in the protocol, even if the event is not considered to be related to the study.
Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.
- 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 (eg, pathogenic or non-pathogenic) via the study drug is an SAE.
- Overdose
- Secondary malignancy

Potential drug-induced liver injury (DILI)

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

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

Overdose

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

11.1.3 Pregnancy

Pregnancies and suspected pregnancies occurring while the participant is on study drug or within 28 days of the participant's last dose of study drug should be reported immediately upon investigator's knowledge. If the participant is on study drug, the study drug is to be discontinued immediately and the participant is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be

reported immediately of the Investigator's knowledge of the pregnancy by phone and e-mail / facsimile to Dana-Farber Cancer Institute using the Pregnancy Reporting Form. Immediately upon receipt of this report, Dana-Farber will inform BMS Safety Department, and Celgene as required by the Revlimid REMS ® program. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the participant until completion of the pregnancy, and must notify Dana-Farber Cancer Institute of the outcome of the pregnancy (including notification of false-positive tests) within 24 business hours of having knowledge of the event by email / facsimile using the Follow-Up Pregnancy Reporting Form. Immediately upon receipt of this report, Dana-Farber will inform BMS and Celgene as required by the Revlimid REMS® program using the Follow-Up Pregnancy Reporting Form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Dana-Farber Cancer Institute with 24 business hours of the Investigator's knowledge of the event by e-mail or facsimile. Immediately upon receipt of this report, Dana-Farber will inform BMS and Celgene as required by the Revlimid REMS® program).

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to Dana-Farber within 24 business hours of the Investigator's knowledge of the event by e-mail or facsimile. Immediately upon receipt of this report, Dana-Farber will inform BMS and Celgene as required by the Revlimid REMS® program. In the case of a live "normal" birth, Dana-Farber Cancer Institute should be advised as soon as the information is available. Dana-Farber will inform BMS, and Celgene as required by the Revlimid REMS® program.

If the patient is found not to be pregnant, any determination regarding the participant's continued participation in the study will be determined by the Investigator.

A female partner of a male taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male participant should notify the investigator of his partner's pregnancy and her healthcare provider information. The investigator will then provide the information to Dana-Farber Cancer Institute for follow-up as necessary. Dana-Farber will inform BMS, and Celgene as required by the Revlimid REMS® program.

11.1.4 Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

- Respite care

11.2 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.2.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list of the Investigator's Brochure or the package insert, and should be included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agents.

11.2.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or ongoing IND safety letters.

11.2.3 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

An event will be considered unrelated in a situation where, for chronological reasons, the causal relationship between the AE and administration of the study drug is unlikely, or concomitant use of other drugs or therapeutic interventions or preexisting conditions provide sufficient explanations for the observed event.

An event will be considered possibly related in a situation where, for chronological reasons, the causal relationship between the AE and administration of the study drug is possible, and concomitant use of other drugs or therapeutic interventions or preexisting conditions do not provide sufficient explanations for the observed event.

11.3 Procedures for AE and SAE Recording and Reporting

Reporting Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

. All AEs must be recorded in the participant's medical record, stating the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study drug(s) and the adverse event as defined in section 11.2.3.

Whenever possible, a diagnosis or a single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, seriousness, intensity (severity), action taken with respect to study treatment, corrective treatment/therapy given, diagnostic investigations results, outcome, and the Investigator's opinion as to whether there is a reasonable possibility that the AE was caused by the study treatment or by the study procedure(s).

The investigator must evaluate all abnormal laboratory results to determine the clinical significance. All abnormal laboratory or test results that induce clinical signs or symptoms, or require therapy, are considered clinically significant and are recorded as adverse events. The investigator will be the final determinant of clinical significance.

The descriptions and grading scales found in the CTEP Version 4.03 of the NCI CTCAE will be utilized for AE reporting. The CTEP Version 4 of the CTCAE is identified and located on the CTEP website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

11.3.1 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the study PI. All Serious Adverse Events (SAEs) that occur following the date of informed consent signature, during treatment, must be reported.

The following must be reported to the coordinating center:

- All SAEs.
- All ≥Grade 2 AEs.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.

Any other AE that in the opinion of the investigator is a clinically significant event.Each adverse event will be assessed to determine if it meets the criteria for SAE reporting. Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study PI, the participating site's IRB, and others as described below.

All SAEs must also be reported to the Coordinating Center in order to comply with the responsibility for oversight of the project and reporting to the FDA.

11.3.1.1 Serious Adverse Event Reporting

When the Investigator or his/her designee becomes aware that an SAE has occurred they will complete the MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents) for all SAEs. The completed form will be e-mailed to the DFCI project manager at [redacted] All SAE reports that have the minimum data set for reporting should be submitted to the coordinating center, , even if only limited information is available. This must occur within 24 business hours of learning of the occurrence, regardless of the relationship of the SAE to 'Study Drug.' In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. Each investigative site will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI (within 5 calendar days if the event is grade 4, and within 24 hours for grade 5), who will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected. DFCI will submit to the FDA after the Lead Investigator review, if the event meets reporting requirements.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented by e-mailing a follow up MEDWATCH form to the coordinating center. .

Within the following 24 business hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. The investigator must keep copies of all AE information, including correspondence with BMS and Dana-Farber Cancer Institute and IRB, on file.

11.3.1.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will state the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study and the adverse event.

Non serious adverse events will be reported to the coordinating center. All applicable events, including event term, grade, attribution, expectedness, and start and stop dates must be reported. This will be

reported via a spreadsheet. The completed spreadsheet will be emailed to the DFCI project manager, [redacted]. Adverse events will be reported within 14 days after a participant's day 1 maintenance visit.

11.3.2 Reporting to Bristol Myers Squibb

DFCI, the Coordinating Center, is responsible for reporting SAEs to BMS. The Lead Principal Investigator or Project Manager may request additional source documentation pertaining to the SAE. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form.

DFCI should report the SAEs, as defined in Section 11.1.2, to BMS within 24 hrs of becoming aware of the event. The MedWatch form, or another form previously approved by BMS, can be used to report the event.

DFCI will submit the SAEs to: [redacted] or via fax at [redacted].

All serious adverse events that occur during treatment must be reported.

11.3.3 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in below.

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All unexpected Grade 4 (life-threatening or disabling) events.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention

The Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

11.3.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the investigational agent or product.

Unexpected fatal or life-threatening experiences associated with the use of the investigational product will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the investigational product will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

INDSRs will be reported to the FDA by telephone (1-800-FDA-1088) or by mail using MEDWATCH Form FDA 3500A.

11.3.5 Reporting to the NIH Office of Biotechnology Activities (OBA)

This section is not applicable to this study.

11.3.6 Reporting to the Institutional Biosafety Committee (IBC)

This section is not applicable to this study.

11.3.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.4 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from the date of informed consent signature, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the study PI and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12 DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

12.2 The DFCI CTO will monitor and manage the data on an ongoing basis, using a risk-based monitoring approach that incorporates remote data review as well as one onsite monitoring visit per year for sites with active patientsSafety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the study PI and study team.
The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of completion of therapy; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Specified data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. See Section 5.1 of DSMP for additional details.

During the course of the study, communication between the Coordinating Center and participating sites will occur via regular e-mail correspodence. Teleconferences will be scheduled as needed.

13 REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The study PI (or Protocol Chair) will disseminate protocol amendment information to all participating investigators. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

13.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix VIII

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13.7 Cooperative Research and Development Agreement/Clinical Trials Agreement (CTA)

This is not a CTEP-supported study, therefore, this section is not applicable.

14 STATISTICAL CONSIDERATIONS

14.1 Endpoints

14.1.1 Original Primary Endpoint

The primary endpoint is response rate at Week 12, which is defined as the proportion of subjects who achieved a response of PR or better (sCR, CR, or VGPR) at Week 12 after first dose of study drug. Response will be determined by modified IMWG criteria.

14.1.2 Original Secondary Endpoints

The proportion of subjects with successful stem cell mobilization after 12 weeks. A successful stem cell mobilization is defined as the ability to collect a total of at least 2 x 10^6 CD34+ cells/kg.

The proportion of subjects requiring at least one dose modification (ie, dose reduction, dose held, or dose not given) of any study drug during Induction Cycles 1 - 4.

The exploratory endpoints for this study are listed as the following:

14.1.2.1 Best Response On-Study and Objective Response Rate

Best response on-study refers to the best response prior to discontinuation of all study therapy. The Objective response rate (ORR) is defined as the proportion of treated subjects who achieve a best response of CR, sCR, VGPR, or PR using the IMWG criteria (see Section 10.2.4.1 for definitions of CR, sCR, VGPR and PR response). The proportion of subjects who complete 8 cycles of therapy that achieved a response of PR or better (sCR, CR, or VGPR) at Week 24 after first dose of study drug will also be reported.

14.1.2.2 Time to Response and Duration of Response

Time to response is defined as the time from first dose of study drug to the first documentation of response PR or better. This analysis will be restricted to subjects whose best response is PR or better.

Duration of response (DOR) is the time from first response (PR or better) until a progression event (documented progression or death). Only subjects who ever achieved a response of PR or better will be considered. Subjects who neither progress nor die will be censored on the date of their last tumor assessment.

14.1.2.3 Progression-Free Survival (PFS)

Progression-Free Survival (PFS) is defined as the time from first dose until documented progression or death. A subject who neither progresses nor dies will be censored on the date of his or her last tumor assessments.

14.1.2.4 Time to next treatment

The time to subsequent myeloma therapy is defined as the interval from randomization to earliest start date of subsequent myeloma therapy. Subjects who do not receive any subsequent myeloma therapy will be censored at the date of their last follow-up visit. Subjects with no follow-up visits will be censored at their last date of study medication.

14.1.2.5 Safety Endpoints

Safety endpoints are serious and non-serious AEs, clinical laboratory tests (hematology, chemistry, urinalysis, coagulation panel), vital sign measurements, and physical examination with assessment of ECOG PS

14.1.3 Exploratory Endpoints

Assessment of minimal residual disease
The achievement of minimal residual disease will be evaluated and reported on patients that achieve a complete response

14.1.3.1 Engraftment Parameters

Engraftment parameters will be collected and reported only among subjects who proceed to SCT. Neutrophil engraftment is defined as an absolute neutrophil count > 500/μL for two consecutive days and platelet engraftment is defined as platelets > 20,000/μL for two consecutive days without platelet infusion within the previous week.

14.2 Sample Size/Accrual Rate

This is a single arm, open-label study to estimate the response rate at Week 12. Approximately 40 subjects will be treated. With an observed response rate of 90% and 40 subjects, the lower bound of the 95% confidence interval (CI) would be in excess of 75%, which was the response rate at Week 12 in a recent Phase 2 study of subjects treated with BLD.[6] The table below gives two-sided, 95%, exact (Clopper and Pearson) CIs for a range of response rates, based on a sample size of 40.

Table 14.2 Upper bounds (%) of Clopper-Pearson interval for a range of observed event rates (Sample Size Equals 40)

Number of Responses	Response Rate	95% Confidence Interval
38	95%	(83.3%, 99.4%)
36	90%	(76.3%, 97.2%)
34	85%	(70.2%, 94.3%)
32	80%	(64.4%, 90.0%)
30	75%	(58.8%, 87.3))
28	70%	(53.5%, 83.4%)

Patients who are enrolled on study but do not receive any study treatment may be replaced.

As of October 2020, the original endpoints have been met.

14.3 Stratification Factors

There are no stratification factors planned in this trial. Patients will be enrolled into a given cohort based on sequence of entering the trial and cohort availability.

14.4 Analysis

The primary and secondary endpoints analysis will be based on all treated subjects. The analysis for subject disposition will be based on enrolled subjects. All other efficacy and safety analysis will be based on all treated subjects. Additional exploratory analyses will be included in the statistical analysis plan.

14.4.1 Demographics and Baseline Characteristics

Subject characteristics including demographic characteristics, disease characteristics, baseline ECOG performance status, and relevant genetic characteristics, will be summarized using descriptive statistics. Number of screening failures will also be summarized.

14.4.2 Efficacy Analyses

14.4.2.1 Week 12 Analyses:

A 95%, two-sided, exact CI for the response rate at Week 12, the primary endpoint, will be computed using the Clopper and Pearson method. Depth of response at Week 12 will be summarized by proportion of subjects who achieve sCR, CR, VGPR, PR, MR, SD and PD.
The proportion of and two-sided, 95% CI for the successful harvest rate at Week 12, the secondary endpoint, will be computed using the Clopper and Pearson method.

14.4.2.2 Efficacy Based on the Entire Study Duration

The efficacy analyses described below will be done on all treated subjects and also by the following subgroups: subjects who received SCT and subjects who did not receive SCT.

An estimate of best ORR during the study, along with its 95% CI using the Clopper-Pearson method, will be computed. The tumor response data will be listed by visits for each subject.
The distributions of duration response, PFS, and overall survival will be analyzed using the Kaplan-Meier product-limit method.

14.4.3 Safety Analyses

Safety will be assessed by the nature, frequency, and severity of AEs, and the results of clinical laboratory tests including hematology, blood chemistry, and urinalysis. Safety analyses will be done on all treated subjects and also by the following subgroups: subjects who received SCT and subjects who did not receive SCT. Medical history, physical examinations, vital signs, and ECG will be displayed.

Adverse events will be categorized using the latest version of MedDRA and the severity will be graded using CTCAE (Version 4.03). Any occurrence and severe (worst grade ≥ 3) AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT). All recorded AEs, SAEs and AEs leading to study drug discontinuation will be listed and tabulated by SOC and PT. The proportion of subjects with at least one dose modification of any study drug during the first 4

cycles will be computed. In addition, a 95% confidence interval for the rate of dose modification will be computed using the Clopper and Pearson method.

Laboratory values will be graded using NCI CTC. Shift from baseline to worst on-study value will be displayed for hematologic and blood chemistry laboratory examinations.

The effect of elotuzumab has been studied extensively in combination with Lenalidomide and Bortezomib, and dosages of 10 mg/kg IV are used in all phase III and randomized phase II studies to date. Nonetheless, the four drug combination proposed in this study has not yet being evaluated in humans. Therefore, after the enrollment of 10 subjects in the study, further subject enrollment will be placed on hold to evaluate safety/toxicity data pertaining to the 4 drug combination, and specifically regarding Elotuzumab.

14.4.4 Pharmacokinetic Analyses

Not applicable.

14.4.5 Biomarker Analyses

Not applicable

14.4.6 Outcomes Research Analyses

Not applicable.

14.4.7 Other Analyses

14.4.7.1 Immunogenicity Analyses

Not Applicable.

14.4.8 Interim Analyses

There is no interim analysis planned for this study.

15 PUBLICATION PLAN

Data from this trial will be reported once it is released from the DSMC for publication. The final results of this study will be published in manuscript form in a major peer-reviewed journal. The study PI will be responsible for submitting the final manuscript for publication. The final manuscript will be reviewed by all parties involved. Approval will be obtained from the primary responsible party before any information can be used or passed on to a third party or submitted for publication.

Co-authorship of this manuscript will be determined according to the level of participation in the study as measured by accrual from each participating site, thereby including individuals who have

been most involved in the design, conduct, and analysis of the study. Additional individuals may receive acknowledgement in the final manuscript for their support of the conduct of the study, as well as their review of the manuscript.

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17 APPENDICES

Appendix I: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II: DuBois Formula for Body Surface Area

Body surface area (BSA) should be calculated using the DuBois formula that yields the following result in meters squared (m^2):[1]

$$BSA\ (m^2) = Wt\ (kg)^{0.425} \times Ht\ (cm)^{0.725} \times 0.007184$$

[1]DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916; 17:863-71.

Appendix III: The New York Heart Association 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.

Appendix IV: International Myeloma Foundation 2003 Diagnostic Criteria:

17.1.1 A diagnosis of MM requires that all three of the following must be met:

- Monoclonal plasma cells in the bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma
- Monoclonal protein (M-protein) present in the serum and/or urine. If no monoclonal protein is detected (non-secretory) disease, then > 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma
- Myeloma-related organ dysfunction (1 or more) of the following. A variety of other types of end-organ dysfunction can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification of myeloma if proven to be myeloma related.

  [C] Calcium elevation in the blood, defined as serum calcium > 10.5 mg/dl or upper limit of normal

  [R] Renal insufficiency, defined as serum creatinine > 2 mg/dl

  [A] Anemia, defined as hemoglobin <10 g/dl or 2 g < normal

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

Appendix V: FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

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

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

Participant Signature: _____ **Date:** _____

Cycle:_____

Appendix VI Lines of Therapy

According to the IMWG Consensus panel 1 on uniform reporting criteria in clinical trials2, a line of therapy consists of at least 1 or more cycles of a planned treatment regimen. This may consist of single-agent or combination therapy or a sequence of treatments administered in a planned manner. For example, a planned induction, followed by ASCT followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course is modified as a result of progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease.

Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the "Response Criteria" section of this document.

Appendix VII Preparation and administration of elotuzumab

Dose Preparation Instructions

After dilution in normal saline, the infusion must be completed within 8 hours if kept at room temperature (25°C). If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2°C to 8°C for up to 24 hours. If stored under refrigerated conditions, the study drug solution should be equilibrated to room temperature (takes about 2 to 2.5 hours), and the container must be gently inverted to thoroughly mix the contents before administration. If the storage time limit is exceeded, the prepared dose solution must be discarded and the reason documented by the pharmacist in the study drug accountability records.

Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the dose administration section (see Administration Instruction section below) discussed below. The dose of elotuzumab will be calculated using the subject's predose weight on Day of treatment in each cycle, and then added to 0.9% saline for infusion. Do not round up or down.

Reconstitute elotuzumab lyophilized study drug, as described in Steps 1 to 5. Each 400 mg vial contains 10% overfill for a total of 440 mg of study drug but is intended to deliver 400 mg of elotuzumab. Standard aseptic technique should be utilized.

Step 1: Remove the flip-top from elotuzumab and Sterile Water for Injection (SWFI) vials.

Step 2: Withdraw 17 mL of SWFI using an 18-gauge or smaller needle. Place the elotuzumab vial upright on a flat surface and insert the syringe needle into the vial through the center of the rubber stopper. Slowly inject the SWFI along the side of the vial to help prevent bubbling or foaming. Slowly remove the syringe needle out of the vial.

Step 3: DO NOT SHAKE. Avoid prolonged or vigorous agitation. Hold the vial upright and gently swirl the solution by rotating the vial to dissolve the lyophilized cake. Then gently invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Finally, hold the vial upright again and gently swirl the solution a few more times to dissolve any remaining particles.

Step 4: After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. The final volume of the reconstituted solution is approximately 17.6 mL, for an approximate concentration of 25 mg/mL.

It is acceptable to have small bubbles and/or foam around the edge of the vial. The reconstituted preparation results in a colorless to slightly yellow, clear to slightly opalescent solution.

Step 5: Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with normal saline into an infusion bag (see Table 1). Final drug volume will be calculated based on dose level and subject weight: For example, a subject receiving 10 mg/kg elotuzumab who weighs 80 kg on Day 1 (predose) will require 800 mg of study drug for infusion. Withdraw 32 mL of elotuzumab (25 mg/mL) from 2 vials and add to an infusion bag already containing 230

mL saline, for a total of 262 mL to be infused. The same subject receiving 20 mg/kg elotuzumab will require 1600 mg of study drug for infusion. Withdraw 64 mL of elotuzumab (25 mg/mL) from 4 vials and add to an infusion bag already containing 340 mL saline, for a total of 404 mL to be infused. Use a new sterile needle for withdrawing solution from each vial.

Table 1 Appendix VII: Dose Level and Dilution

Dose Level	Volume 0.9% Normal Saline
10 mg/kg	230 mL
20 mg/kg	340 mL

Administration Instructions

During the first cycle, the elotuzumab infusion rate will be increased gradually to a maximum of 5mL/min as presented in Table 2 Appendix VII. The first dose of elotuzumab will be administered following premedications (described in Section 5.3.7) to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5 mL per minute (30 mL/hour). If the subject does not have an infusion reaction within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an infusion reaction within 30 minutes, escalate the infusion rate to a maximum of 2 mL per minute (120 mL/hour). If a subject experiences a Grade ≥ 2 infusion reaction, the infusion must be interrupted. Please refer to Section 5.3.8 for detailed information on the management of infusion reaction and re-initiation of infusion.

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

The third dose of elotuzumab should be initiated at an infusion rate of 5 mL per minute if no infusion reactions were reported with previous elotuzumab infusions. If no infusion reactions were observed during the first cycle of elotuzumab, the second cycle can commence at a rate of 5 mL per minute (see Table 2 Appendix VII). If a subject experiences a Grade ≥ 2 infusion reaction, the infusion must be interrupted. Please refer to Section 5.3.8 for detailed information on the management of infusion reaction and reinitiation of infusion. If a subject experiences a ≤ Grade 3 elotuzumab infusion reaction that has resolved to ≤ Grade 1, subsequent infusion rate of elotuzumab should be escalated in a stepwise fashion (see Table 2 Appendix VII).

Administer through a low-protein-binding 0.22-micrometer in-line filter (placed as proximal to the subject as is practical). Prime the infusion line with study drug before starting the infusion.

Set the IV pump to deliver the infusion at the rate of 0.5 mL per minute (including the drug in the line). The total time of infusion will vary depending upon the maximum tolerated mL/min infusion rate as discussed above.

Record every time the infusion is started and stopped and the reason why the start and stop occurred.

Monitor the IV setup and the subject's IV site frequently during infusion, checking for the correct infusion rate and IV site infiltration.

Ensure that the full volume of elotuzumab is infused. After elotuzumab has been infused from the line, discontinue the infusion, disconnect the IV tubing, and dispose of materials appropriately according to the facility's standard procedure.

Table 2 Appendix VII: Elotuzumab Infusion Rate

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	**Approximate Total Duration: 2hrs 50min**		**262 mL***
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	**Approximate Total Duration: 1hrs 13min**		**262 mL**
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3	**Approximate Total Duration: 53min**		
5mL/min	53 min	262mL	0mL
Cycle 2 +	**Approximate Total Duration: 53min**		**262 mL**
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level are permitted only if no infusion reactions are encountered.

APPENDIX VIII Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

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1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Children's Hospital Boston (CHB), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research

Organization (CRO), that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines . In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Jacob Laubach will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials).
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

2.2 Coordinating Center

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain FDA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

2.3 DF/HCC ODQ and Multiple Myeloma Research Consortium (MMRC)

In addition to the DF/HCC ODQ Sponsor assistance at the Coordinating Center, the following support services will be delegated to Multiple Myeloma Research Consortium (MMRC).

Lead Business Unit	Operational Tasks & Assumptions
Clin Ops	Review of final study materials including study protocol, IB, pharmacy instructions, EDC forms, and project plans by MMRC Clinical Operations staff.
Clin Ops	Kick Off Meeting: Includes time for meeting attendance and preparation. Assumes attendance by Clinical Operations, Legal.

Clin Ops	Review Draft Clinical Project Plans: Assumes time to review Project Plans by MMRC Clinical Operations.
Clin Ops	Template CRF Review by MMRC Clinical Operations.
Legal	Site Identification: MMRC will provide feasibility survey to potential MMRC sites and collate responses.
Legal	Clinical Trial Agreements: Assumes MMRF Legal preparation of draft CTA, negotiating and facilitating signatures.
Clin Ops	Review Informed Consent Forms: MMRC Clinical Operations and Legal, if required, review of template and modifications to ICF
Clin Ops	Teleconferences - Monthly meetings, one (1) hour in length with attendance by clinical Operations and Legal.
Clin Ops	Project Management: MMRC staff to provide overall PM support to ensure adherence to project plans, timelines, and study quality. MMRC staff serves as central point of contact for all MMRC participating centers; oversee performance and directly implements action plans/communications to ensure MMRC internal study start-up benchmarks are met and enrollment targets are achieved. Initiates action plans to overcome issues/delays at sites or with industry partner.
Clin Ops	On-Site Project Management and Support by MMPMs: On-site support of rapid completion of review committee submission packages; drives budget/CTA finalization, and essential document collection. Provides ongoing, day-to-day oversight to assigned study staff (CRC, DM etc.) and supports rapid study enrollment through chart reviews, patient DB searches, and patient appointment schedules. Conducts internal investigation and reports outcomes for issues/problems related to enrollment against accrual plan.
Finance	Financial Project Management: Includes activities associated with invoice processing, budget forecasting, and periodic study financial reconciliation.
Admin	Administrative Support: Assumes MMRF administrative staff provide support for all MMRF personnel involved with the study

2.4 Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations

and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each Participating Institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.

For protocols using investigational agents, the Participating Institution will order their own investigational agents.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee and must be submitted and approved by the DFCI IRB prior to participant registration:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- Participating IRB's approval for all amendments
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, which covered entities (DF/HCC Multi-Center Protocol Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC ODQ case number (as described below) and DF/HCC protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration

Participant registration is completed through ODQ by the Lead Institution. Please refer to Section 4.0 Registration Procedures in the protocol for information regarding participant registration.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.7.4 Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day of the registration.
Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

3.8 DF/HCC Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for ODQ CRF/eCRF completion and correspondence, and correspondence with the Coordinating Center.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe derivations from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.9.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions.
The Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in Section 7.4.5 of the protocol.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DFCI CTO provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

Site initiations will be conducted as either an on-site visit or via web teleconference. Following site initiation, DFCI CTO will implement on-site as well as virtual monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. The Participating Institutions will be required

to submit source documents to the Coordinating Center for DFCI CTO monitoring. Also Participating Institutions will be subject to on-site monitoring conducted by the DFCI CTO.

Virtual or remote monitoring will be performed on an ongoing basis as remote Clinical Data Review with on-site visits occurring once per year including a close-out visit. The DFCI CTO site monitor will request source documents for data that requires source document verification (SDV). These documents should be faxed or scanned/emailed to the CRA. Monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

Regulatory authorities may also request access to source documents, data capture records, and other study documentation for on-site audit or inspection. The investigator will notify DFCI in the event of an audit request.

During the course of the study, communication between the Coordinating Center and participating sites will occur via regular teleconference.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and

accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One audit on-site will be schedule by the ODQ assuming at least three subjects have been treated on protocol at the site. Approximately 3-4 subjects would be audited at the site over a 2 day period. If violations which impact subject safety or the integrity of the study are found, more subject records may be audited. Additional audits may occur if evidence of non-compliance is found during the routine monitoring.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.