NCI Protocol #: *n/a*

Local Protocol #: *14-508*

TITLE: A Phase II Study of the Efficacy and Safety of Lenalidomide, Subcutaneous Bortezomib and Dexamethasone Combination Therapy for patients with Newly Diagnosed Multiple Myeloma

Coordinating Center: Dana-Farber Cancer Institute (DFCI)
[redacted]

***Principal Investigator (PI):** Jacob Laubach, MD
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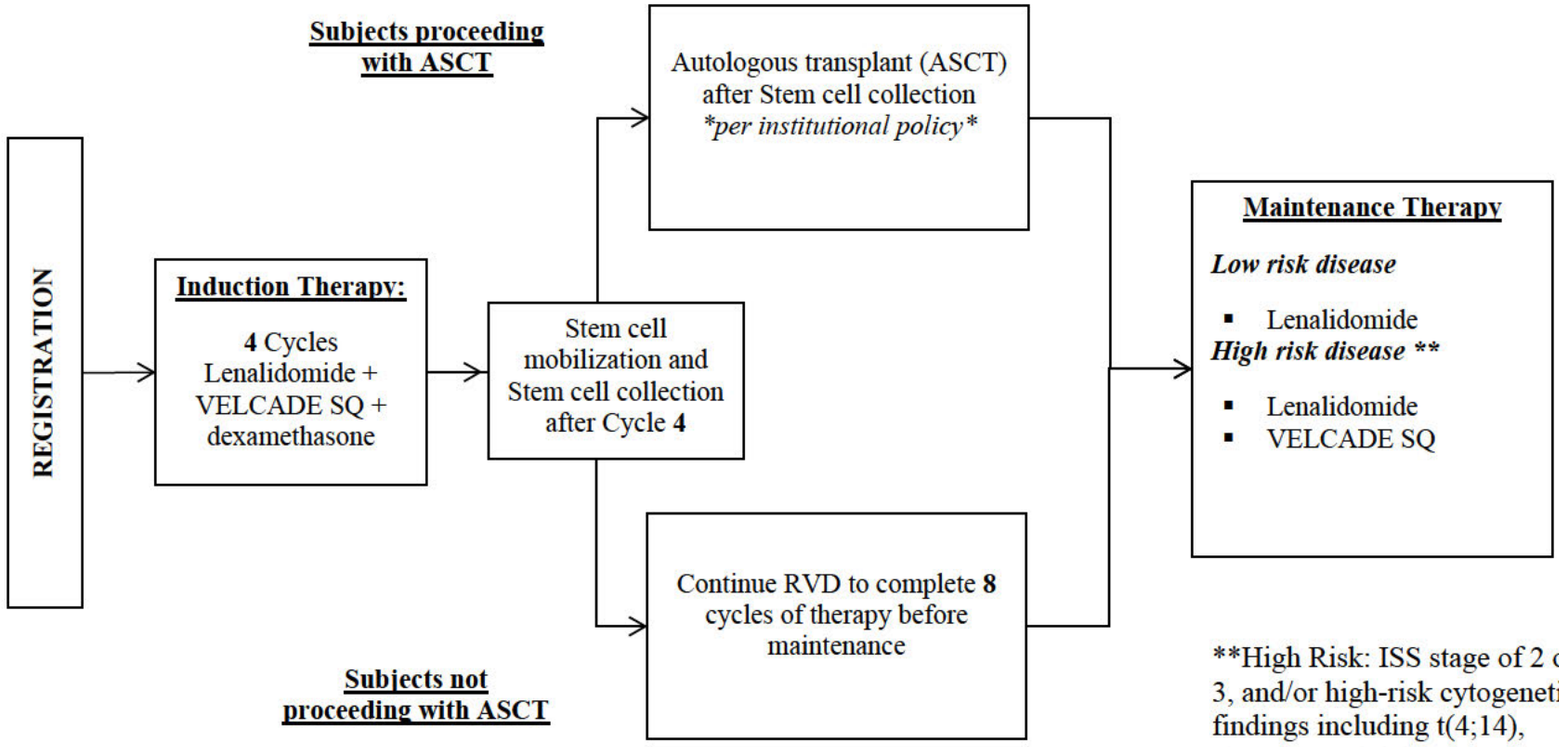
Research Project Manager
[redacted]

Agent(s):
Lenalidomide - supplied by Celgene Corporation -
Bortezomib– supplied by Millennium Pharmaceuticals, Inc.
Dexamethasone – commercial supply

IND #: N/A
IND Sponsor: N/A

Amendment / Version 9.0/ Version Date: April 18, 2022

SCHEMA



Cycle Length
Induction: 21 days
Maintenance: 28 days

SYNOPSIS

Title	A phase II Study of the Efficacy and Safety of lenalidomide, subcutaneous bortezomib, and dexamethasone combination therapy for patients with newly diagnosed multiple myeloma
Study Objectives	**Primary objectives** Evaluate the overall response rate after 4 cycles among all patients and the best response to induction therapy with the combination of lenalidomide, subcutaneous (SQ) bortezomib, and dexamethasone (RSQVD) in patients with newly diagnosed multiple myeloma. Evaluate the rate and severity of PN of SQ bortezomib in combination with lenalidomide, and dexamethasone after the 4th cycle among all patients, and after the final cycle of induction therapy for subjects who do not proceed with immediate autologous transplant and elect instead to complete 8 cycles of induction chemotherapy. **Secondary Objectives** Secondary objectives include safety, time to progression, progression-free survival, duration of response, and overall survival associated with the combination. For patients who elect to go on to stem cell transplant, exploratory endpoints will also be stem cell yield (number of CD34+ cells and days of harvesting) and engraftment parameters.
Study Design	This is an open-label, phase II study which will enroll up to 45 eligible patients with newly diagnosed multiple myeloma. All patients will receive lenalidomide, SQ bortezomib, and dexamethasone with doses and schedule established in a phase I study of RVD, wherein bortezomib will be given as a subcutaneous injection, in newly diagnosed multiple myeloma. The dose and schedule are as follows: • Oral lenalidomide 25 mg days 1-14 of 21 day schedule • Subcutaneous bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 • Oral Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 Patients will receive treatment in 21 day cycles. All patients who are able or willing to pursue stem cell transplantation will proceed to stem cell mobilization after 4 cycles. Patients may undergo additional cycles of induction therapy prior to mobilization or transplant if deemed clinically appropriate and after approval from the overall PI. Stem cell mobilization will be performed with cyclophosphamide and filgrastim or other acceptable agent(s). Those who undergo mobilization will have up to 4 weeks for collection, and recovery (if cyclophosphamide is used, patients may have and an additional 3 weeks for recovery for a total 7 weeks from Day 1 of

	collection) to resume treatment (Cycle 5). After stem cell mobilization, patients will have the option to proceed with transplant per institutional guidelines, or store stem cells and defer transplant to a later time point after first relapse and completion of clinical trial participation. The particular transplantation regimen is determined by the treating physician and participating institutions. Patients who do not proceed to SCT will receive 8 cycles of the induction therapy. Patients who undergo transplantation will receive post-transplant maintenance therapy with lenalidomide 10 mg administered on days 1-21 of each 28 day cycle. The dose of lenalidomide will be increased to 15 mg after three 28-day cycles if the 10 mg dose is tolerated well. Patients with high risk disease as defined by ISS stage of 2 or 3 and/or high-risk cytogenetic findings including t(4;14), t(14;16), and del17p will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28 day maintenance cycle. Patients who do not undergo transplantation will receive lenalidomide maintenance after completion of 8 induction cycles, with the dose of lenalidomide received in the final cycle of induction provided this dose was tolerated well, administered days 1 – 21 of each 28 day cycle. Patients with high risk disease as defined by ISS stage of 2 or 3 and/or high-risk cytogenetic findings including t(4;14), t(14;1 6), and del17p will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle.
Study Procedures	Participants are to be registered by faxing or emailing a completed eligibility checklist to the Research Project Manager between the hours of 8 am and 5 pm ET. The Research Project Manager should also be contacted by phone. The checklist will be verified and a participant number will be assigned. A confirmation of registration form and group assignment will be emailed to the site to complete the registration process. Participants will be seen 28 days following treatment discontinuation (whether scheduled or unscheduled). Study assessments to be performed at each visit are described in Section10.
Participant Sample	Participants in this trial will be 45 subjects with newly diagnosed multiple myeloma and no prior treatment for their disease.

Treatment and Dosage	Each participant will receive lenalidomide as a single daily oral dose on Days 1-14 followed by 7-day rest period. Bortezomib will be administered as a subcutaneous injection on Days 1, 4, 8, and 11 followed by a 10-day rest period. At least 72 hours should elapse between bortezomib doses, but if needed an interval of 70 hours is permitted. Dexamethasone will be given as a single oral dose on Days 1, 2, 4, 5, 8, 9, 11 and 12 followed by a 9-day rest period. Each cycle of treatment will consist of 21 days. Doses of lenalidomide, bortezomib or dexamethasone may be interrupted or reduced in an attempt to manage toxicity according to the guidelines outlined in Section 6.
Duration of the Study	Patients will remain on protocol therapy until time of disease progression.
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 and end of study. 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 using either Mosteller or DuBois formula.
Efficacy Parameters	Starting with Cycle 2, response to treatment will be determined during each cycle using the criteria as outlined in Section 10. Initially response will be assessed by serum protein electrophoresis and quantification of M-protein and immunofixation and urine protein electrophoresis and quantification of M-protein and immunofixation from a 24-hour urine collection. Bone marrow biopsy will be done to confirm a complete response. For patients with M component/light chain paraprotein in the urine, a serum sample for FreeLite™ testing will be obtained. If a patient has no measurable serum or urine M-spike, patients can be followed by FreeLite™ testing (See Section 10.2.4.3 for FreeLite™ Response Criteria).

Abbreviation	Definition
°C	Degrees Celsius
°F	Degrees Fahrenheit
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
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
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
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
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
OS	Overall survival
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
QACT	Quality Assurance for Clinical Trials
QOW	Every other week
QW	Every week
RNA	Ribonucleic acid
RR	Response rate
RSQVD	Combination of Lenalidomide, Bortezomib (subcutaneous) and Dexamethasone
RSQV	Combination of Lenalidomide and Bortezomib (subcutaneous)
SAE	serious adverse event
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

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1. OBJECTIVES

1.1 Study Design

This is an open-label, phase II study which will enroll up to 45 eligible patients with newly diagnosed multiple myeloma.

All patients will receive lenalidomide, SQ bortezomib, and dexamethasone with doses and schedule established in a phase I study of RVD, with bortezomib injection given as a subcutaneous, in newly diagnosed multiple myeloma (DFCI study # 06-150).

The dose and schedule are as follows:

- Oral lenalidomide 25 mg days 1-14 of 21 day schedule
- Subcutaneous bortezomib 1.3 mg/m2 days 1, 4, 8, 11
- Oral Dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12

Patients will receive treatment in 21 day cycles. All patients who elect to, or are appropriate candidates will proceed to stem cell mobilization after 4 cycles. Patients may undergo additional cycles of induction therapy prior to mobilization or transplant if deemed clinically appropriate and after approval from the overall PI. Those who are not transplant candidates, or decline transplant may forgo stem cell mobilization and collection. Stem cell mobilization will be performed with cyclophosphamide and filgrastim or other acceptable agent(s) at the investigator's discretion. After stem cell mobilization, patient will have the option to proceed with transplant per institutional guidelines, or store stem cells and defer transplant to a later time point after first relapse and completion of clinical trial participation. Patients will have up to 4 weeks to collect, and recover (unless mobilized with cyclophosphamide, in which case, patients may have an 3 additional weeks to recover for a total of 7 weeks from Day 1 of collection) and must resume treatment (cycle 5) if they do not directly proceed with transplant. Patients who proceed with stem cell transplantation will receive melphalan conditioning chemotherapy followed by autologous stem cell rescue per institutional standard of care. Patients who do not proceed to SCT will receive 8 cycles of the combination therapy.

Patients who undergo transplantation will receive post-transplant maintenance therapy with lenalidomide 10 mg administered days 1-21 of each 28 day cycle, 60-110 days post-transplant, until disease progression. The dose of lenalidomide will be increased to 15 mg after three 28-day cycles if the 10 mg dose is tolerated well. Patients with high risk disease as defined by ISS stage of 2 or 3, and/ or high-risk cytogenetic findings including t(4;14), t(14;16), and del17p will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28 day maintenance cycle.

Patients who do not undergo transplantation will receive lenalidomide maintenance after completion of 8 induction cycles, with the dose of lenalidomide received in the final cycle of induction provided this dose was tolerated well, administered days 1 – 21 of each 28 day cycle, until disease progression. Patients with high risk disease as defined by ISS stage of 2 or 3, and/or high-risk cytogenetic findings including t(4;14), t(14;16), and del17p will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle.

1.2 Primary Objectives

- Evaluate among all patients the overall response rate after 4 cycles and the best response to induction therapy with the combination of lenalidomide, subcutaneous (SQ) bortezomib, and dexamethasone (RSQVD) in patients with newly diagnosed multiple myeloma.

- Evaluate the rate and severity of PN of SQ bortezomib in combination with lenalidomide and dexamethasone after the 4th cycle among all patients, and after the final cycle of induction therapy for subjects who do not undergo transplant and receive 8 cycles of induction chemotherapy

1.3 Secondary Objectives

- Assess safety
- Assess time to progression
- Assess progression-free survival
- Assess duration of response
- Assess overall survival
- Assess stem cell yield (number of CD34+ cells and days of harvesting) and engraftment parameters for patients who elect to go on to stem cell transplant

2. BACKGROUND

2.1 Multiple Myeloma

2.1.1 Epidemiology and Pathogenesis

Multiple Myeloma (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).

2.1.2 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. See Appendix F for more details.

2.1.3 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 enhancement 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 NFκB, 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).

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 1mg/m2 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.

A phase 1/2 evaluation of lenalidomide-bortezomib-dexamethasone in front-line myeloma was also conducted (Richardson 2010). Patients (N = 66) received 3-week cycles (n = 8) of bortezomib 1or 1.3 mg/m2 (days 1, 4, 8, 11), lenalidomide 15 to 25 mg (days 1-14), and dexamethasone 40 or 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12). Responding patients proceeded to maintenance or transplantation. Phase 2 dosing was determined to be bortezomib 1.3 mg/m2, lenalidomide 25 mg, and dexamethasone 20 mg. Most common toxicities included sensory neuropathy (80%) and fatigue (64%), with only 27%/2% and 32%/3% grade 2/3, respectively. In addition, 32% reported neuropathic pain (11%/3%, grade 2/3). Grade 3/4 hematologic toxicities included lymphopenia (14%), neutropenia (9%), and thrombocytopenia (6%). Thrombosis was rare (6% overall), and no treatment-related mortality was observed. Rate of partial response was 100% in both the phase 2 population and overall, with 74% and 67% each achieving very good partial response or better. Twenty-eight patients (42%) proceeded to undergo transplantation. With median follow-up of 21 months, estimated 18-month progression-free and overall survival for the combination treatment with/without transplantation were 75% and 97%, respectively. Lenalidomide-bortezomib-dexamethasone demonstrates favorable tolerability and is highly effective in the treatment of newly diagnosed myeloma.

2.1.3.1 Bortezomib

Clinical Experience

To date, more than 436,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski RZ, 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, antitumor activity was reported in subjects with Non-Hodgkin Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer (Orlowski RZ, 2002; Aghajanian C, 2002; Papandreou CN, 2004; Dimopoulos MA, 2005).

The safety and efficacy of bortezomib in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (Jagannath S, 2004) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy) (Richardson PG, 2003). In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous

treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (1998) were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039) (Richardson PG, 2005), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 treatment cycles as induction therapy, followed by 1.3-mg/m^2 bortezomib weekly on Days 1, 8, 15, and 22 of a 5-week cycle for 3 cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to 4 treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with bortezomib versus 18% with dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus < 1% with dexamethasone ($p < 0.0001$). The CR + nCR (near CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow-up, overall survival was significantly longer ($p = 0.0013$) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the bortezomib arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib ($p = 0.0005$). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib ($p = 0.0098$). Updated response rates and survival data were reported for M34101-039 (Richardson P, 2005). The updated CR + PR rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, $p = 0.0272$). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm ($p = 0.0002$).

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study (Fisher R, 2006). The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study (Goy A, 2007) was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients

with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of bortezomib, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant (San Miguel JF, 2008). The study was designed to determine the benefit of adding bortezomib to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were randomized to receive nine 6-week cycles of melphalan 9mg/m^2 and prednisone 60 mg/m^2 on Days 1 to 4, alone or in combination with bortezomib 1.3 mg/m^2 by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the bortezomib (VMP) group compared to 34% in the MP group ($p = 0.001$). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group ($p = 0.000001$) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

The VISTA study update after extended follow-up of 25.9 months, (San Miguel JF, 2008) confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% ($p = 0.0032$). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive bortezomib.
Based on investigator-reported best responses to subsequent therapies, patients relapsing after therapy with a novel agent were not intrinsically more resistant than after receiving a traditional agent.

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months) (Mateos MV, 2009). In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for VMP was 56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85) (San Miguel JF, 2011).

Subcutaneous Administration
A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and SQ routes of bortezomib administration have similar systemic drug exposure and proteasome inhibition. Importantly, SQ and IV administration of bortezomib appeared to result in similar efficacy profiles (ie, response rate) and similar safety profiles. The pilot study also provided preliminary evidence of good local tolerance for SQ injection of bortezomib, when administered at 1 mg/mL concentration (Moreau P, 2008).

The data from the Phase 1 pilot study formed the basis of the design of a randomized, Phase 3 study that compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m^2 dose and twice per week schedule in patients with relapsed multiple myeloma (Moreau P, 2011). 222 patients were randomly assigned in a 2:1 ratio to receive either subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups.

The ORR (CR+PR) after 4 cycles of treatment, assessed by computer algorithm implementation of EBMT response criteria, was 42 % in both the SQ and IV treatment groups for the response-evaluable population. The ORR after 4 cycles in the IV arm was consistent with what was observed in historical single-agent bortezomib trials with relapsed multiple myeloma subjects. The stratified Mantel-Haenszel estimate of the relative risk of achieving response for SQ treatment group versus IV treatment group was 0.99 with 95% CI (0.71, 1.37). The 95% CI for ORR_SQ - 0.6 ORR_IV was (6.1, 27.1), which excludes 0. Thus the study met the noninferiority objective (p-value for the noninferiority hypothesis was 0.00201). Results in the ITT population were similar; noninferiority of SQ versus IV was also demonstrated.

The CR rate after 4 cycles of treatment was 6% in the SQ treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SQ treatment group and 5% in the IV treatment group; the VGPR rate after 4 cycles of treatment was 4% in the SQ treatment group and 3% in the IV treatment group. Therefore, 17% subjects in the SQ treatment group and 16% subjects in the IV treatment group had obtained at least VGPR after the first 4 cycles.

The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SQ and IV treatment groups for the response-evaluable population. The stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SQ versus IV was 1with 95% CI (0.77, 1.31). Twenty-five percent of subjects in the SQ treatment group and 25% of subjects in the IV treatment group had obtained at least VGPR during the first 8 cycles.

The median TTP (Kaplan-Meier estimate) was 10.4 months in the SQ treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI (0.564, 1.249), and the p=0.3866 (stratified log-rank test), indicating similar results between the SQ and IV arm.
The median PFS (Kaplan-Meier estimate) was 10.2 months in the SQ treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI (0.574, 1.183), and the p=0.2945 (stratified log-rank test), indicating comparable results between the SQ and IV arm.
After a median follow-up of 11.8 months, the 1-year survival rate was 72.6% in the SQ arm and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5037, indicating similar results between the SQ and IV arm.

The median time to first response (Kaplan-Meier estimate) was 3.5 months for both the SQ and IV treatment groups. The hazard ratio was 1.059 with 95% CI (0.716, 1. 567), and the p=0.7725 (stratified log-rank test), indicating similar results between the SQ and IV arm. Among the responders, the median time to first response was 1.4 months (44 days) in the SQ arm and 1.4 months (43 days) in the IV arm. Among the responders, the median duration of response (Kaplan-Meier estimate) was 9.7 months in the SQ treatment group, compared with 8.7 months in the IV treatment group.

Overall, similar efficacy results were observed in the SQ and IV treatment groups, and the study demonstrated that bortezomib SC administration is not inferior to bortezomib IV administration (Moreau P, 2011).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

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.

3.1.1 Participants must have a diagnosis of MM according Revised International Myeloma Working Group diagnostic

criteria (Rajkumar 2014):

- 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- Anything over institutional normal limits for creatinine that is also clinically documented
    - 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
      OR
  - 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

***Note**: Laboratory assessments used to support the CRAB criteria in the IMWG 2014 Diagnostic Criteria of MM are performed at the time of diagnosis. These assessments are not required to be performed within the 21 days of initiation of protocol therapy.*

3.1.2 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

3.1.3 Patient has received no prior treatment with any systemic therapy for the treatment of multiple myeloma

- Prior treatment of hypercalcemia or spinal cord compression with corticosteroids does not disqualify the patient (the dose should not exceed the equivalent of 160 mg of dexamethasone in a 2 week period).
- Patients may receive corticosteroids for the management of their multiple myeloma that should not exceed the equivalent of 160mg of dexamethasone in a 2 week period and should be stable for at least 7 days prior to the initiation of therapy
- Bisphosphonates are permitted.
- Patients treated with local radiotherapy with or without concomitant exposure to steroids, for pain control or management of cord/nerve root compression, are eligible. Two weeks must have lapsed since last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry to the protocol deferred until the radiotherapy is completed.

3.1.4 Age ≥ 18 years at the time of signing Informed Consent

3.1.5 ECOG performance status ≤2 (Karnofsky ≥ 50%, see Appendix A)

3.1.6 Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with

the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.1.7 Subject must be able to adhere to the study visit schedule and other protocol requirements.

3.1.8 All necessary baseline studies for determining eligibility must be obtained within 21 days prior to enrollment.

3.1.9 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 50 μL/mL 10 to14 days prior to therapy and repeated again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS® program) and must either commit to complete abstinence from heterosexual contact or begin TWO acceptable methods of birth control, one highly effective method and one additional effective (barrier) method, AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must practice complete abstinence or agree to use a condom during sexual contact with a FCBP even if they have had a successful vasectomy. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.*A female of childbearing potential is a sexually mature female who:

- has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries)
- has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

3.1.10 Ability to understand and the willingness to sign a written informed consent document

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 Renal insufficiency (serum creatinine levels > 2.5 mg/dL, calculated Crcl with Cockcroft-Gault formula, see Appendix B, < 45 ml/min)

3.2.2 Subjects with evidence of mucosal or internal bleeding and/or platelet refractory (i.e., unable to maintain a platelet count ≥ 50,000 cells/mm^3)

3.2.3 Subjects with an absolute neutrophil count (ANC) < 1000 cells/mm^3. Growth factors may not be used to meet ANC eligibility criteria

3.2.4 Subjects with a hemoglobin < 8.0 g/dL

3.2.5 AST (SGOT) and ALT (SGPT) > 2 x institutional ULN, bilirubin levels ≥ 1.5 institutional ULN

3.2.6 Concomitant therapy medications that include corticosteroids (except as indicated in inclusion criteria).

3.2.7 Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (Appendix C), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

3.2.8 Clinically relevant active infection requiring treatment (antibiotics, antivirals, antifungals).

3.2.9 Any serious co-morbid 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.

3.2.10 Female subject is pregnant or breast-feeding.

3.2.11 Serious psychiatric illness or addiction likely to interfere with participation in this clinical study.

3.2.12 Uncontrolled diabetes mellitus.

3.2.13 Contraindication to any required concomitant drugs or supportive therapies including hypersensitivity to all anticoagulation and antiplatelet options or hypersensitivity to acyclovir or similar anti-viral drug.

3.2.14 History of allergic reaction/hypersensitivity attributed to compounds containing boron, mannitol, polysorbate 80 or sodium citrate dehydrate.

3.2.15 POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes).

3.2.16 Known seropositive for or active HIV infection or hepatitis B or C viral infection. Patients who are seropositive because of hepatitis B virus vaccine are eligible.

3.2.17 Known intolerance to steroid therapy.

3.2.18 Patient has hypersensitivity to bortezomib, boron, or mannitol.

3.2.19 Diagnosed or treated for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

3.2.20 Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.

3.2.21 Radiation therapy within 7 days of enrollment. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 7 days have elapsed since the last date of therapy.

3.2.22 Participant must be able to swallow pills.

3.3 Inclusion of Women and Minorities

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.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy 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 protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. 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 must be canceled. Registration cancellations must be made in OnCore as soon as possible

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the lead site by the Study Coordinator or Research Project Manager. Following registration, participants should begin protocol therapy as soon as possible after registration. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Research Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed to [redacted] e-mailed to the Research Project Manager:

- Copy of labs and clinical information that satisfy inclusion criteria
- Signed participant consent form
- HIPAA authorization form, if applicable
- Completed eligibility checklist

The research nurse or data manager at the participating site will then call [redacted] or e-mail the Research Project Manager to verify eligibility. To complete the registration process, the Research Project Manager will follow DF/HCC Standard Operating Procedure for Human Subject Research titled *Subject Protocol Registration* (SOP# REGIST-101) and register the participant on the protocol. The lead site will then fax or email the participant study number to confirm registration.

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

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

Drug administration guidelines, pretreatment recommendations and concomitant medications are outlined throughout Section 5.

Patients will receive induction treatment in 21 day cycles. All patients will proceed to stem cell mobilization after 4 cycles except those who are not transplant candidates, or those who do not plan to go on to transplant. Patients may undergo additional cycles of induction therapy prior to mobilization or transplant if deemed clinically appropriate and after approval from the overall PI. Stem cell mobilization will be performed with cyclophosphamide and filgrastim or other agent(s) at the investigator's discretion. After stem cell mobilization, patient will have the option to proceed with transplant per institutional guidelines, or store stem cells and defer transplant to a later time point after first relapse and completion of clinical trial participation. Patients who do not undergo transplantation will have 4 weeks to complete collection, and recovery, unless cyclophosphamide is used, in which case, patients will have a total of 7 weeks (3 additional weeks for recovery) from Day 1 of collection to resume Cycle 5 of therapy.. Patients who do not proceed to SCT will receive 8 cycles of the combination therapy.

Patients who undergo transplantation will receive post-transplant maintenance therapy with lenalidomide 10 mg administered days 1-21 of each 28 day cycle starting at approximately 3 months post-transplant, until disease progression. The dose of lenalidomide will be increased to 15 mg after three 28 day cycles if the 10 mg dose is tolerated well. Patients with high risk disease as defined by ISS stage of 2 or 3, and/or high -risk cytogenetic findings including t(4;14), t(14;16), and del17p will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m^2 days 1 and 15 of each 28 day maintenance cycle.

Patients who do not undergo transplantation will receive lenalidomide maintenance after completion of 8 induction cycles, with the dose of lenalidomide received in the final cycle of induction provided this dose was tolerated well, administered days 1 – 21 of each 28 day cycle, until disease progression. Patients with high risk disease as defined by ISS stage of 2 or 3, and/or high-risk cytogenetic findings including t(4;14), t(14;16), and del17p will, in addition to lenalidomide, receive VELCADE maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle.

5.1 Treatment Regimen

Lenalidomide, Bortezomib and Dexamethasone Cycles 1 - 8 (Induction)				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Lenalidomide	25 mg	Oral	Days 1-14	(21 days)
Bortezomib	1.3 mg/m2	SQ injection	Days 1, 4 , 8, and 11	
Dexamethasone	20 mg	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12	

For patients who undergo transplantation

	Lenalidomide and Bortezomib Cycles 5+ (Maintenance)				
Risk	**Agent**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Low	Lenalidomide	10 mg Cycles 9-11, if well tolerated,15 mg Cycles 12+ (see section 5)	Oral	Days 1-21	(28 days)
High	Lenalidomide	10 mg Cycles 9-11, if well tolerated,15 mg Cycles 12+ (see section 5)	Oral	Days 1-21	
	Bortezomib	1.3 mg/m2	SQ injection	Days 1 and 15	

For patients who do not undergo transplantation

	Lenalidomide and Bortezomib Cycles 9+ (Maintenance)				
Risk	**Agent**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Low	Lenalidomide	Same dose as received in final Cycle of induction	Oral	Days 1-21	(28 days)
High	Lenalidomide	Same dose as received in final Cycle of induction	Oral	Days 1-21	
	Bortezomib	1.3 mg/m2	SQ injection	Days 1 and 15	

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle. On days when all three drugs are administered, dexamethasone should be taken in the morning before bortezomib administration. Lenalidomide can be taken later during the day, as long as both dexamethasone and lenalidomide

will be taken at the same time each day.

5.2 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 10):

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 21 days
- Baseline Symptom Assessment
- Physical examination to include measurement of vital signs, height, weight and calculation of body surface area (BSA). Height required at baseline only.
- ECOG performance status will be evaluated
- 12-lead ECG
- A neurologic assessment will be performed including **(FACT/GOG Ntx See Appendix E)**.
- Hematology
- Clinical laboratory tests
- Thyroid function
- Urinalysis
- 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 prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS® program). All patients must be registered into the Revlimid REMS ® program.
- Skeletal survey for quantification of bone lesions with magnetic resonance imaging (MRI) and CT scans as clinically indicated. 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.
- Chest X-ray is required to provide a baseline reference in the event that the patient develops cardiac or pulmonary symptoms during the study. If results of a chest X-ray 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 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.
- Soft tissue plasmacytoma assessment
- Collection of correlative samples

5.3 Pre-Treatment Criteria

Patients must meet all the eligibility criteria including pre- treatment assessments prior to initiation of therapy in Cycle 1 Day 1 except that they must only meet one of the two renal insufficiency eligibility criteria: Either they must have a creatinine clearance >40 mL per min or serum creatinine <177 μmol/L (<2 mg/dL) .

Pre-treatment concomitant medications and procedures that are required and or recommended and those to be avoided are detailed in Section 5.6.

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.

5.4 Assessments

Assessments required at screening visit and on cycle 1 day 1 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.

- The 7 days window does not apply for sampling of Serum M-protein (S-PEP) and Urine M-protein (U-PEP) on cycle 1 day 1.
- Results of biochemistry assessments need to be available prior to dosing on day 1 of each cycle.
- 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.
- If soft tissue plasmacytoma is present, this must be assessed by clinical examination at screening, at day 1 cycle 1 and day 1 for each subsequent cycle and at end of treatment. Assessment of the lesion(s) by MRI or CT is required at screening, and thereafter every 6 cycles (or as clinically indicated) during treatment phase and follow-up or PD. If the soft tissue plasmacytoma is not able to be assessed by clinical examination then only imaging is required.
- Following cycle 2, a 7 day +/- window is permitted *between* cycles.
- Bone X-rays need to be performed on study only if clinically indicated (e.g. bone pain) or to assess disease response (please refer to study table).
- Patients must be instructed to notify the Investigator of any undesirable symptoms or side effects while on study. AE monitoring should be continued at least 28 days following the last dose of study treatment.

5.4.1 Hematology:

- Complete blood count consisting of a total white blood cell count with differential (total neutrophil [including bands, if available], lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin; 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 results are required prior to bortezomib dosing on cycle 1-8 days 1, 4, 8, and 11 for total neutrophils [including bands, if available] and platelet counts. Only high risk myeloma patients are required to have Day 15 hematology labs drawn during maintenance prior to bortezomib.
    - If a patient discontinues bortezomib on days 4, 8, or 11 during induction or day 15 during maintenance, the patient is not required to have hematology labs drawn for those days.

5.4.2 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.

5.4.3 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), cholesterol, GGT, LDL, HDL, uric acid and triglycerides.
    - GGT, uric acid, LDL, HDL, and triglycerides and total cholesterol are only required at baseline, and as clinically indicated during the trial
- If total bilirubin > institutional ULN, direct and indirect bilirubin should be performed.
- Results of biochemistry assessments need to be available prior to dosing on day 1 of each cycle (both in induction and in maintenance)
- Biochemistry assessment is also required at end of treatment
- 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 as clinically indicated during the trial

5.4.4 Urinalysis

- 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.

5.4.5 Thyroid

- Includes Thyroid Stimulating Hormone (TSH) and free T4 (thyroxine).

5.4.6 M component quantification

- immunoelectrophoresis (IEP) from serum and urine and 24 hour urine collection for paraprotein measurement- Those who

do not present in their urine will have UPEP and IEP (urine) done at baseline, and then every third cycle thereafter.

- Serum M-protein (S-PEP), urine M-protein (U-PEP), Serum IF and Urine IF: assessments will be performed by the local laboratory.
- IEP from serum and urine, UPEP and SPEP will be performed on day 1 of every cycle (both in induction and maintenance cycle) and at end of treatment
- The assessments will be performed at screening and on day 1 of every. After C1D1 patients may stop UPEP measurement if they meet the following criteria: 1) the subject is not followed by their UPEP (that is, the subject does not have light chain myeloma with a urine M-spike of >200 mg/24 hours at baseline or C1D1), 2) there has been no measurable disease by UPEP for 2 consecutive cycles, and 3) the subject is in a complete response. A urine sample to measure UPEP should be obtained at suspected disease progression and to confirm PD.
- Exception: sIF and uIF are not required on day 1 of cycle 1.

5.5 Agent Administration

5.5.1 Lenalidomide

Lenalidomide will be given as a single daily oral dose on days 1-14 followed by a 7-day rest period during inductions. Following Cycle 2, a window of +/- 7 days is allowed between RVD treatment cycles for scheduling purposes. Dose modification guidelines are described in Section 6 (Dose Modifications/Delays).

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

Patients who undergo transplantation will receive lenalidomide maintenance at 10 mg on days 1-21 of each 28 day cycle starting at approximately 3 months post-transplant. If the 10 mg dose is tolerated well, the dose of lenalidomide will be increased to 15 mg after three 28 day cycles of maintenance, until disease progression

Patients who do not undergo transplantation will receive lenalidomide at the same dose taken in the final cycle of induction provided this dose was tolerated well, administered days 1 – 21 of each 28 day cycle, until disease progression.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Administration of lenalidomide should be at approximately the same time each day. Drug may be taken with or without food. If a dose is missed, it should be taken as soon as possible on the same day. 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. If a dose of lenalidomide is vomited, the participant should continue with the regular schedule of the drug at the next dose.

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 Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program 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. Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. **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.

5.5.2 Bortezomib

Bortezomib will be administered subcutaneously on days 1, 4, 8, and 11 followed by a 10-day rest period in Cycles 1-8. Following Cycle 2, a window of +/- 7 days is allowed between RVD treatment cycles for scheduling purposes. Dose modification guidelines are described in Section 6 (Dose Modifications/Delays).

Patients with high-risk disease will receive bortezomib during the maintenance period, with subcutaneous bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle.

Drug will be administered 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 drug to be administered will be determined based on Body Surface Area (BSA). BSA is to be calculated based on body weight using the DuBois or Mosteller formula (Appendix B). The dose should be calculated on Day 1 of the cycle or as per institutional practice, and should be recalculated at the start of the next cycle; the dose administered should remain the same throughout the cycle. If a participant experiences a notable change in weight (i.e., loss or gain of 5% body weight) within the cycle, as determined by an unscheduled weight assessment, then the participant's dose should be recalculated at that time.

Vials are for single use administration. At least 72 hours must elapse between bortezomib doses. Dosing at an interval of 70 hours may be considered for scheduling, patient convenience or hardship. If the patient develops toxicity including neuropathy, this approach, less than 72 hours between doses, is not recommended. Bortezomib should not be administered in participants who have a known allergy to bortezomib, boron or mannitol.
Different volumes of 0.9% sodium chloride are used to reconstitute the drug for the different routes of administration. Caution should be used when calculating the reconstituting volume and the final concentration for administration. Refer to the Package Insert for complete details.

5.5.2.1 Subcutaneous Administration

When administering SQ, sites for 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 bortezomib Package Insert for complete drug preparation and administration guidelines for subcutaneous administration.

5.5.3 Dexamethasone

Dexamethasone will be given as a single daily oral dose on days 1, 2, 4, 5, 8, 9, 11 and 12, followed by a 9-day rest period in Cycle 1-8. All participants will receive a dexamethasone dose of 20 mg. Following cycle 2, a window of +/- 7 days is allowed between RVD treatment cycles for scheduling purposes. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

Dexamethasone should be taken at approximately the same time each day. It is recommended that dexamethasone be taken in the morning to reduce insomnia. Each dose should be taken with food. If a dose of dexamethasone is missed or vomited, 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.

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Required Concomitant Medication

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.

All subjects are required to enroll in to the Revlimid REMS program and follow the appropriate recommendations for prevention of pregnancy.

5.6.2 Recommended Concomitant Medication

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 recommended 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.

It is recommended that participants receive pneumocystis jiroveci pneumonia (PJP) 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.

Use of growth factors is allowed according to institutional guidelines. Subjects may receive RBC transfusions and platelet transfusions if clinically indicated.

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.

5.6.3 Prohibited Concomitant Medication

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.

5.7 Duration of Therapy

All patients will receive RSQVD. Patients will receive treatment in 21 day cycles during induction, and 28 day cycles during maintenance. All patients who plan to pursue transplant will proceed to stem cell mobilization after 4 cycles. Stem cell mobilization will be performed with cyclophosphamide and filgrastim or other acceptable agent(s) per the investigator's discretion. After stem cell mobilization, patients will have the option to proceed with transplant per institutional guidelines, or store stem cells and defer transplant to a later time point after first relapse and completion of clinical trial participation. Those who defer transplantation will have 4 weeks for stem cell collection and recovery before resuming treatment (Cycle 5). Those who are mobilized with cyclophosphamide will have an additional 3 weeks (for a total of 7 weeks from Day 1 of collection) to recover and resume. Patients who proceed with stem cell transplantation will receive melphalan conditioning chemotherapy followed by autologous stem cell rescue per institutional standard of care. Patients who do not proceed to SCT may receive 8 cycles of the combination therapy.

Patients who undergo transplantation will receive post-transplant maintenance therapy with lenalidomide administered days 1-21 of each 28 day cycle, 60-110 days post-transplant, until disease progression. Patients with high risk disease will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28 day maintenance cycle.

Patients who do not undergo transplantation will receive lenalidomide maintenance after completion of 8 induction cycles, with the dose of lenalidomide received in the final cycle of induction provided this dose was tolerated well, administered days 1 – 21 of each 28 day cycle, until disease progression. Patients with high risk disease will, in addition to lenalidomide, receive bortezomib maintenance with SQ bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle.

5.8 Criteria for Taking a Participant Off Protocol Therapy

Patients may be removed from study should they withdrawal consent, have no further clinical benefit from therapy or until one of the

following criteria applies:

- Disease progression
- Significant (>21 day) treatment delay
- Intercurrent illness that prevents further administration of treatment
- Non-compliance/failure to return for follow-up
- Administrative reasons
- Significant protocol violation (one that compromises the integrity of the study or safety of the participant)
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- Suspected pregnancy or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the Clinical Research Support - DF/HCC website or obtained from the lead site study staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Jacob Laubach at [redacted]

5.9 Duration of Follow Up

During therapy patients are followed every treatment cycle.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Stopped taking study medication
- Withdrawal of consent for data submission
- Death

The primary reason for study removal and the date the participant was removed must be documented in the source documents and in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website, (DF/HCC ODQ forms, policies and manuals), or obtained from the ODQ registration staff.

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. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications should be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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 4.0 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.

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 guidelines.

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. If 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. In the event one of the study drug is discontinued due to toxicity, the subject is allowed to continue receiving the other agents in the regimen.

6.1 Lenalidomide

6.1.1 Dose Reduction

Starting dose of lenalidomide (Days 1 – 14 every 21 days)	1ST Dose Reduction	2ND Dose Reduction	3rd Dose Reduction	4th Dose Reduction
25 mg	15 mg	10 mg	5 mg	Discontinue lenalidomide
10 mg (starting dose in maintenance)	5 mg	Discontinue lenalidomide		

6.1.2 Suggested Dose Modification Guidelines for both Induction and Maintenance

* These dose reduction rules may be waived after prior discussion with the overall PI.

CTCAE Category	Lenalidomide toxicity and Dose Modification

Absolute neutrophil count < 500/mm^3 **and/or** Platelet count < 30,000/mm^3	Lenalidomide will be held and resumed with one dose level reduction when ANC ≥ 500/mm^3 and/or platelet count is ≥ 30,000/mm^3 If with 5 mg/day, lenalidomide will be discontinued definitively.
Neurologic Toxicity ≥ Grade 3	Lenalidomide will be held. If toxicity resolves to ≤ grade 1, lenalidomide will be resumed at at one dose level reduction If with 5 mg/day, lenalidomide will be held. If toxicity resolves to ≤ grade 1, lenalidomide may be resumed at a dose of 5 mg/day for the remainder of the cycle or be discontinued definitively at the investigator's discretion
Cardiac Toxicity ≥ Grade 2	Lenalidomide will be held. If toxicity resolves to ≤ grade 1, lenalidomide may be resumed with one dose level reduction .If with 5 mg/day, lenalidomide will be held. If toxicity resolves to ≤ grade 1, lenalidomide may be resumed at a dose of 5 mg/day for the remainder of the cycle or be discontinued definitively at the investigator's discretion .
Renal Failure: Creat Clear < 30 ml/min	Lenalidomide will be discontinued. Alternate etiology for severe renal impairment should be evaluated.
Other Non-Hematologic Toxicity: Grade 3 Other Non-Hematologic Toxicity: Grade 4	Lenalidomide will be held until toxicity resolves to ≤ grade 2 and contact study PI. After consultation with the study PI, drug may be resumed at one dose level reduction Lenalidome will be discontinued

6.2 Bortezomib

6.2.1 Dose Reduction

For dose reduction guidelines due to neuropathy, please refer to the neuropathy management algorithm further down in this section.

Bortezomib may be discontinued at the discretion of the treating physician in consultation with the overall principal investigator if bortezomib-related toxicity has progressed to the point that further treatment with the agent is not felt to be safe. In these

circumstances, patients may continue with lenalidomide and dexamethasone at the discretion of the treating physician and the overall principal investigator.

The following sequence of reductions are standard and recommended, but an alternative sequence to dosing and or schedule modifications in response to bortezomib related toxicity can be pursued based on investigator discretion following discussion with overall principal investigator.

Starting Dose of Bortezomib (SQ)	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
1.3 mg/m^2	1mg/m^2	0.7 mg/m^2	0.7 mg/m^2 on days 1 and 8[a]

[a] 3rd A third dose reduction for participants with high risk disease in maintenance is discontinuation of bortezomib

Once bortezomib is reduced for any toxicity, the dose may not be re-escalated.

If after bortezomib has been held and the toxicity does not resolve, then bortezomib must be discontinued.

If the toxicity resolves, bortezomib may be restarted at the same schedule the patient was on prior to holding therapy with specified dose reduction.

If the patient was receiving 0.7 mg/m^2, discontinue drug unless patient is responding, in which case, this should be discussed with the principal investigator.

6.2.2 Suggested Dose Modification Guidelines

* These dose reduction rules may be waived after prior discussion with the overall PI.

Drug Related Adverse Event Dose Modification Guidelines for Lenalidomide and Bortezomib During a Cycle of combined therapy		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. Resume dosing if resolved to ≥ 25,000/mm3 with: One level dose reduction of lenalidomide and 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 platelet transfusion is permitted on the day of dosing.
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L) Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue therapy. Monitor CBC on days 4, 8 and 11.Use of G-CSF is allowed and recommended on the day of dosing, except in cycle 1. Resume dosing if resolved to ≥ 750/mm^3 with: One level dose reduction of lenalidomide and 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 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 below in 6.2.2 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.
All dose modifications should be based on the worst preceding toxicity.		
* It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing		

Drug Related Adverse Event Dose Modification Guidelines for Bortezomib only:

- For non hematologic toxicities bortezomib is to be held for up to 3 weeks until the toxicity returns to Grade 1 or better.
- Patients with mild hepatic impairment (bilirubin ≤ 1.5 × institutional ULN) do not require a starting dose adjustment. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (**>** 1.5 -3.0 X institutional ULN) while on study, the investigator should hold bortezomib until the toxicity returns to < Grade 2. Restarting bortezomib at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of bortezomib -induced liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection and multiple myeloma-related liver disease.

The following sequence of reductions are standard and recommended, but an alternative sequence to dosing and or schedule modifications in response to bortezomib related neuropathy can be pursued based on investigator discretion following discussion with overall principal investigator.

Management of Patients With Bortezomib -Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms [a]	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities or Daily Living [ADL][b])	Reduce bortezomib to 1mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue bortezomib
Source: Bortezomib USPI issued January 2012. Abbreviations: ADL = activities of daily living [a] Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. [b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc [c] Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

The neurotoxicity-directed questionnaire (Appendix E) 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.

6.3 Dexamethasone

6.3.1 Dose Reduction

Starting Dose of dexamethasone (Days 1, 2, 4, 5, 8, 9, 11 and 12)	**1ST Dose Reduction**	**2nd Dose Reduction**
20 mg	12 mg	Discontinue dexamethasone

*If bortezomib has been reduced to a weekly schedule, dexamethasone need only be given on days of and after bortezomib or at the investigator's discretion.

6.3.2 Suggested Dose Modification Guidelines for both Induction and Maintenance

* These dose reduction rules may be waived after prior discussion with the overall PI.

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. 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 first reduction.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. 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. 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.

6.4 Initiation of New Cycle of RSQVD or RSQV Maintenance Therapy

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

- ANC ≥ 1,000/ mm^3
- Platelet count ≥ 70,000/ mm^3
- Any other lenalidomide or bortezomib, related adverse event that may have occurred has resolved to ≤ grade 2 severity (or according to the dose modification table).
- Herpes Zoster lesions are dry
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity

If these conditions are not met on Day 1 of a new cycle, the participant will be evaluated weekly and a new cycle of therapy will not be initiated until the toxicity has resolved as described above. 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 3 weeks. If study drug is held for more than 3 weeks due to drug related toxicity, the subject will either discontinue therapy altogether, or, if toxicity may be specifically attributed to one agent, this agent will be discontinued and the subject can continue receiving therapy with the remaining agents.. 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.

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.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events Lists

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.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of informed consent signature, through the study and until 30 days following the completion of therapy. Participants continuing to experience toxicity beyond 30 days following completion of therapy may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

7.1.1 Adverse Event List(s) for Lenalidomide

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

Incidence of events in individuals treated with lenalidomide	≥10%	≥1%	<1%
	• neutropenia • fatigue • thrombocytopenia • anemia • rash • diarrhea • constipation • nausea • loss of appetite itching • dry skin • muscle cramps • lack or loss of strength • dizziness • insomnia • swelling of the extremities • headache • back and joint pain • fever • cough • upper respiratory infection • dyspnea	• DVT • PE • blood clots that could lead to stroke, heart attack or organ failure • febrile neutropenia • atrial fibrillation • pneumonia or lung infection • sepsis • dehydration • renal failure	• angioedema • serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) • allergic skin reaction similar to that seen with thalidomide • tumor lysis syndrome (TLS) tumor flare reaction (TFR) • rhabdomyolysis

7.1.2 Adverse Event List(s) Bortezomib

Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection

Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ϕ
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*

Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*
Source: Bortezomib (VELCADE®) Investigator's Brochure Edition 16. Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%. * Fatal outcomes have been reported. ± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included. ϕ Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.	

Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Pr eferred Term	Observed Incidence [a]
Blood and lymphatic system disorders	
Di *sseminated intravascular coagulation*	Rare
Cardiac Disorders	
At *rioventricular block complete*	Rare
Ca *rdiac tamponade*	Rare
Ear and labyrinth disorders	
De *afness bilateral*	Rare
Eye Disorders	
O *phthalmic herpes*	Rare
Optic neuropathy	Rare
Blindness	Rare
Gastrointestinal Disorders	
Ac *ute pancreatitis*	Rare

Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Pr eferred Term	Observed Incidence [a]
Isc *hemic colitis*	Rare
Hepatobiliary disorders	
He *patitis*	Uncommon
Li *ver failure*	Unknown
Infections and infestations	
He *rpes meningoencephalitis*	Rare
Se *ptic shock*	Rare
Progressive multifocal leukoencephalopathy	Very rare
Immune System Disorders	
An *gioedema*	Rare
Nervous System Disorders	
Au *tonomic neuropathy*	Rare
Dy *sautonomia*	Unknown
En *cephalopathy*	Rare
Respiratory, thoracic and mediastinal disorders:	
Ac *ute diffuse infiltrative pulmonary disease*[b]	Rare
Ac *ute respiratory distress syndrome (ARDS)*	Rare
Int *erstitial pneumonia*	Rare
Lu *ng infiltration*	Rare
Pn *eumonitis*	Rare
Pu *lmonary hypertension*	Rare

Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Pr eferred Term	Observed Incidence [a]
Skin and subcutaneous system disorders	
Ac *ute febrile neutrophilic dermatosis*	Unknown
To *xic epidermal necrolysis*	Unknown
Source: Bortezomib (VELCADE®) Investigator's Brochure Edition 16. A Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000, including isolated reports). B Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.	

7.1.3 Adverse Event List(s) Dexamethasone

Incidence of events in individuals treated with dexamethasone	10-15%	1-9%	<1%	Rare
	● 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	● loss of appetite ● muscle twitching ● increased thirst ● frequent urination ● increased perspiration ● diarrhea ● nausea ● headache ● bone thinning ● spinal fracture or fracture of bones ● tachycardia ● fungal infections	● blurred vision ● personality changes ● stomach ulcers with bleeding that may cause hematemesis ● blood in the stool ● abdominal pain	● bowel perforation ● irritation and bleeding of the esophagus ● heart failure ● shortness of breath ● abdominal cramps ●hypotension ● convulsions ● dizziness ● cataracts ● glaucoma ● pancreatic inflammation ●hypokalemia ● DVT or PE ● malaise ● itching ● hirsutism ● muscle weakness or loss of muscle mass ● rupture of tendons ● menstrual cycle disturbances ● hiccups

7.2 Adverse Event Characteristics

7.2.1 Adverse Event (AE)

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or medical condition temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency 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.

7.2.2 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.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Secondary malignancies must be reported as serious adverse events regardless of their relationship to the study treatments/procedures.

7.2.3 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide and/or bortezomib, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events upon investigator's knowledge.

7.2.3.1 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, the study drug is to be discontinued immediately and permanently, and the participant is to be instructed to return any unused portion of the study drug to the Investigator. The sponsor- investigator must report about pregnancy, suspected pregnancy, or positive pregnancy test to Celgene Drug Safety (as required by the Revlimid REMS® program) by facsimile or email using the Pregnancy Initial Report Form and Millennium Department of Pharmacovigilance faxing the completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee immediately after the Investigator's knowledge of the pregnancy. The patient should be referred to an obstetrician/gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be followed for the final pregnancy outcome. The Investigator will follow the participant until completion of the pregnancy, and must notify Celgene Drug Safety and Millennium of the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The investigator will then provide the information to Dana-Farber Cancer Institute for follow-up as necessary. The sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee, and Celgene as required by the Revlimid REMS® program. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

If the abnormal outcome of the pregnancy meets any of the serious criteria (i.e., , stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form. 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 Millennium 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.

See sections 7.2.7 and 7.2.8.2 for SAE and Pregnancy reporting contact information of Celgene and Millennium.

7.2.4 Expectedness

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

7.2.4.1 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, the package insert, IND Safety letters and should be included in the informed consent document as a potential risk.

Refer to Section 7.1 for a listing of expected adverse events associated with the study agents.

7.2.4.2 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.

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 not study-related 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 study-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.

7.2.5 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 and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. 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.

The investigator must evaluate all abnormal laboratory results to determine the clinical significance. If an abnormal result appears to

be clinically significant, it must be considered to be an adverse event.

The descriptions and grading scales found in the CTEP Version 4.0 of the NCI CTCAE will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

7.2.6 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the study PI.

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.

7.2.7 Serious Adverse Event Reporting

All serious adverse events that occur after the date of informed consent signature, during treatment, or within 30 days of the last dose of treatment must be reported to the study PI on the MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm. **When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.**

Since this is an investigator-initiated study, the principal investigator Jacob P. Laubach, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) from all sites participating in the study to any regulatory agency and to the sponsor- investigator's EC or IRB. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations

This includes events meeting the criteria outlined in Section 7.2.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- 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.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event, regardless of relationship with any study drug or expectedness within 24 hours of learning of the occurrence. 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 hours after learning of it and document the time of his or her first awareness of the adverse event.

Report serious adverse events by telephone, email or facsimile to:

Dana-Farber Cancer Institute
Jacob Laubach, MD
[redacted] and to the Research Project Manager at [redacted]

The initial report must be as complete as possible, including the event term (s), seriousness criteria, intensity of the event (sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.), an assessment of the sponsor-investigator's or sub-investigator's determination of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH Form 3500A. A final report to document resolution of the SAE is required.

Within the following 24-48 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 Millennium, Celgene and Dana-Farber Cancer Institute and IRB, on file.

7.2.8 Expedited Reporting by Investigator to Celgene and Millennium

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance and Celgene in writing. The investigator must use a MEDWATCH 3500A form of any SAE within 24 hours and no later than 4 calendar days (for fatal and life-threatening SAE) or within 4 calendar days (for all other serious SAE) of the sponsor-investigator's observation or awareness of the event. **The sponsor-investigator must fax the MEDWATCH Form per the timelines above.**

The Celgene tracking number (RV-MM-PI-003788 and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene and/or Millennium should be attached to the SAE and retained with the patient records.

Follow-up information on the SAE may be requested by Millennium and Celgene.

7.2.8.1 Celgene Drug Safety Contact Information

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: [redacted]
E-mail: [redacted]

7.2.8.2 Millennium Pharmacovigilance Contact Information

SAE and Pregnancy Reporting Contact Information:
Toll-Free Fax #: [redacted]
E-mail: [redacted]

7.2.9 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported on the study-specific Case Report Form, 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 and the adverse event.

7.2.10 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 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 the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.2.11 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.

7.2.12 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 on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

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.

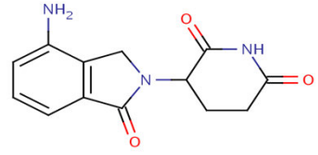
8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and other agents administered in this study can be found in Section 7.1.

8.1 Lenalidomide (REVLIMID®)

8.1.1 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 C13H13N3O3, and the gram molecular weight is 259.3.

8.1.2 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.

8.1.3 Storage and Stability

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

8.1.4 Handling

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

8.1.5 Availability

.Lenalidomide will be provided free of charge from commercial supply via a study specific order form provided by lead study team during start up. Lenalidomide will be dispensed by Biologics, a pharmacy registered in the Revlimid REMS program and will be shipped either to the patient's home directly, or to the site's pharmacy for dispensation to the patient each study cycle.

8.1.6 Preparation

Lenalidomide is an oral drug, and does not require specific preparation details.

8.1.7 Administration

Lenalidomide will be given days 1-14 in a 21 day cycle during the induction phase and days 1-21 in a 28 day cycle for the maintenance phase.

At all times when dispensing lenalidomide protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants.

8.1.8 Ordering

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, 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.

8.1.9 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.

8.1.10 Destruction and Return

Participants will be instructed to return empty bottles or unused capsules to their research pharmacy where the drug will be disposed of per the site's institutional policy.

8.2 Bortezomib (VELCADE®)

Bortezomib (VELCADE®) for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), bortezomib in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. Bortezomib is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic 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. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (Adams J, 1999). In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Adams J, 1999; Teicher BA, 1999; Cusack JC, Jr., 2001; Le Blanc R, 2002; Williams S, 2003; Nawrocki ST, 2002; Satou Y, 2004; Boccadoro M, 2005; Goel A, 2006, Mitsiades N, 2003; Sayers TJ, 2003; Yu C, 2003; O'Connor OA, 2006; Davd E, 2005). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey DJ, 1999).

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-α, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects (HideshimaT, 2001; Obeng EA, 2006; Ling YH, 2002; Yang Y, 2004; Kaluz S, 2006; An WG, 2000, Roccaro AM, 2006; Mitsiades N, 2002).

8.2.1 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 will be supplied by Millennium Pharmaceuticals.

8.2.2 Storage and Stability

At the study site, all study drug*s* will be stored in a locked, safe area to prevent unauthorized access.

Vials containing lyophilized bortezomib for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

8.2.3 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.

8.2.4 Availability

Bortezomib will be supplied free of charge by Millennium Pharmaceuticals. A study specific drug order form will be provided by the lead site to the site study team during the start up and activation process.

8.2.5 Preparation

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area.

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. Different volumes of 0.9% sodium chloride are used to reconstitute the drug for the different routes of administration. Caution should be used when calculating the reconstituting volume and the final concentration for administration. Refer to the Package Insert for complete details.

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL for subcutaneous administration.

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.

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. Reconstituted bortezomib 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. A log must be kept of all disposed materials.

Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

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

8.2.6 Ordering

To order drug, a clinical trial material distribution request and verification form will need to be submitted to Millennium (protocol X05419). The form, with contact information, will be provided during the study start-up period. An MPI representative will review, approve and forward your order onto the distributor for drug shipment.

8.2.7 Accountability

A drug accountability log will be maintained by the investigate site to include drug receipt, dispensing and disposal or return of bortezomib supplies.

8.2.8 Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.

For Product Complaints or Medication Errors, call MedComm Solutions at 1-866-835-2233

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance.

8.2.9 Destruction

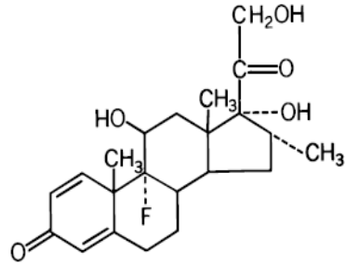
For commercially-labeled bortezomib and for IND-exempt studies, a bortezomib drug return form will be provided to each site's research pharmacy. Any unused or expired bortezomib must be returned to Millennium. Be sure to document drug return on your drug accountability logs. Bortezomib will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations. All drug will be administered to eligible patients under the supervision of the investigator or identified subinvestigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see Appendix B), total drug administered in milliliters and milligrams, and date and time of administration. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

8.3 Dexamethasone

8.3.1 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:



8.3.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 4 mg tablets for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

8.3.3 Storage and Stability

Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

8.3.4 Handling

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

8.3.5 Availability

Dexamethasone supply will be obtained through commercial supply.

8.3.6 Preparation

Dexamethasone is an oral drug, and does not require specific preparation details.

8.3.7 Ordering

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

8.3.8 Destruction and Return

Dexamethasone is a commercial drug and does not require any specific destruction or return details.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

No further correlative samples will be collected

9.0 STUDY CALENDAR

Screening evaluations are to be conducted within 21 days prior to initiation of protocol therapy, unless otherwise stipulated. If a bone marrow biopsy was performed within 6 weeks of the patient's Cycle 1 Day 1 visit, the biopsy need not be repeated. For those who need not have their marrow repeated, the missing bone marrow aspirate correlative samples will not be considered a violation. All assessments must be performed prior to administration of any study medication. Assessments required at screening visit and on Cycle 1 Day 1 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.

Procedure		**Screening** (within 21 days prior to C1D1)	**Induction** Cycles 1-8[1, 2] (21 days)				**Maintenance** Cycles 9+ (28 days)		**Confirmation of CR**	**End of Treatment[20]**
			Day 1	Day 4	Day 8	Day 11	Day 1	Day 15		
Informed consent		X								
Complete Medical History, Height		X								
Physical exam Vital signs, weight/BSA, ECOG PS[4]		X	X				X			X
12-Lead ECG		X								
Chest X-ray[3]		X								
Hematology [5,6]		X	X	X	X	X	X	X		X
Coagulation[5]		X								
Biochemistry[5,7,8]		X	X				X			X
Urinalysis[5]		X								
Calculated Creatinine Clearance, [5]		X	X[21]				X			X
Serum/Urine Pregnancy test, [9]		X	X		X[9]		X			X
Thyroid function		X								
Patient Reported Outcomes (FACT GOG-NTX)/Sensory Neuropathy grading[10]		X	X[10]				X[10]			X
S-PEP, U-PEP[11]		X	X[11]				X			X
Serum Free light chain (FLC)[12]		X	X[12]				X[12]			X[12]
Serum Immunofixation (sIF) Urine Immunofixation		X	X[13]				X[13]			X

Skeletal survey (Bone X-ray) [14]		X								
Evaluation of soft tissue plasmacytomas[15]		X	X							X
Bortezomib SQ injection[16]			X	X	X	X	Days 1 and 15[16]			
Lenalidomide oral dosing			Daily days 1-14 of a 21 day cycle				Daily days 1-21 of a 28 day cycle			
Dexamethasone oral dosing			Days 1, 2, 4, 5, 8, 9, 11 and 12							

Adverse Events	Collect continuously until the end of treatment visit
Concomitant medications	Collect continuously until the end of treatment visit

1. C1D1 assessments, except for hematology, do not have to be repeated if screening assessments performed ≤ 7 days prior to cycle 1 day 1.Hematology results do not need to meet again eligibility criteria on C1D1, but need to be available and reviewed before doses of study drug can be given to meet criteria for treatment administration.
2. +/-3 day window will be allowed for all assessments
3. Chest X-ray 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 chest X-ray need not be repeated at screening visit.
4. Per investigator discretion, physical exam, ECOG, and vitals may be performed every other cycle. . On cycles that do not require a physical exam, a telehealth visit may be substituted instead.
5. Per treating investigator discretion, study required labs may be performed every other study cycle. Should be performed on the scheduled day or up to three days prior, even if study medication is being held, or more frequently when medically indicated- Day 15 hematology labs are not required for low risk patients during maintenance or for patients who are not receiving bortezomib on days 4, 8, or 11 during induction
6. Hematology results are required prior to bortezomib dosing on cycle 1-8, days 1, 4, 8, and 11
7. Results of biochemistry assessments need to be available prior to dosing on day 1 of each cycle- GGT, B2M, Triglycerides, HDL, LDL, Uric Acid, and Total Cholesterol need only be performed at baseline, and as indicated throughout the study
8. Should be performed on the scheduled day even if study medication is being held.
9. Must occur within 10–14 days **and** 24 hours prior to prescribing lenalidomide for Cycle 1. 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.
10. FACT GOG-NTX questionnaire should be administered at screening and on day 1 of each odd cycle and at the end of treatment visit.
11. The 7 days time window does not apply for Serum M-protein (S-PEP) and Urine M-protein (U-PEP) on C1D1- Assessments must be completed on C1D1 and every subsequent Day 1 thereafter of both induction and maintenance cycles- After C1D1 patients may stop UPEP measurement if they meet the following criteria: 1) the subject is not followed by their UPEP (that is, the subject does not have light chain myeloma with a urine M-spike of >200 mg/24 hours at baseline or C1D1), 2) there has been no measurable disease by UPEP for 2 consecutive cycles, and 3) the subject is in a complete response. A urine sample to measure UPEP should be obtained at suspected disease progression and to confirm PD.
12. Serum for free light chain analysis will be collected at baseline, day 1 of every cycle both in induction and maintenance and at the end of treatment
13. 24 h urine collection for Urine M-protein (U-PEP) +/- Urine Immunofixation (IF) is required on day 1 of every cycle, both in induction and maintenance. After C1D1 patients may stop UPEP measurement if they meet the following criteria: 1) the subject is not followed by their UPEP (that is, the subject does not have light chain myeloma with a urine M-spike of >200 mg/24 hours at baseline or C1D1), 2) there has been no measurable disease by UPEP for 2 consecutive cycles,

and 3) the subject is in a complete response. A urine sample to measure UPEP should be obtained at suspected disease progression and to confirm PD.

14. 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.
15. If soft tissue plasmacytoma is present must this must be assessed by clinical examination at screening, at day 1 cycle 1 and day 1 for each subsequent cycle and at end of treatment. Assessment of the lesion(s) by MRI or CT is required at screening, and thereafter every 6 cycles (or as clinically indicated) during treatment phase and follow-up or PD. If the soft tissue plasmacytoma is not able to be assessed by clinical examination then only imaging is required.
16. Patients with high-risk disease will receive bortezomib during the maintenance period, with subcutaneous bortezomib 1.3 mg/m2 days 1 and 15 of each 28-day maintenance cycle
17. End of treatment visit should occur within 28 days of discontinuation of treatment
18. Not required for C1D1 if completed at baseline- Required on Day 1 of each induction cycle through Cycle 8.
19. Macroscopic analysis only unless results are abnormal, in which case a microscopic examination is required.

9. MEASUREMENT OF EFFECT

The disease response will be assessed using criteria based on the International Working Group Response Criteria in Section 11.1.4 as primary exploratory end point, and using criteria based on the modified EBMT Response criteria in Section 11.1.5 as a secondary measure. 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 11.1.4.1.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up. Disease response should be confirmed by two consecutive assessments at a minimum of 6 weeks apart.

9.1 Antitumor Effect – Hematologic Tumors

9.1.1 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 participants who receive at least one dose of therapy, and have had their disease re-assessed with at least one follow-up visit, will be considered evaluable for response. These participants will have their response 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.)

9.1.2 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 M-protein $\geq$ (0.5 g/dl) 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.

9.1.3 Methods of Evaluation of Measureable Disease

All baseline evaluations should be performed according to the Study Calendar Section 9. 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 and biopsy 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.

9.1.4 Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (Rajkumar 2011) and the modified EBMT Response criteria as a secondary measure. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by FreeLite™ Disease Response Criteria.

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 relapse categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ 1 gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

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

9.1.4.1 FreeLite™ Disease Response Criteria

Complete Response: For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative at enrollment, normalization of serum free light chain ratio.

Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.

Partial Response: If only measurable parameter is serum immunoglobulins free light chain (FLC), EITHER of the following changes quality as partial response:

- A 50% decrease in the difference between involved and uninvolved FLC levels; OR

- A 50% decrease in the level of involved FLC AND a 50% decrease (or normalization) in the ratio of involved/uninvolved FLC

Progressive Disease: If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression:

- 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dL; OR

- 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

9.1.5 Modified EBMT Response Criteria

Response	Criteria for Response [a]
Complete response (CR)	Requires all of the following: Disappearance of the original monoclonal protein from the blood and urine on at least two determinations for a minimum of six weeks by immunofixation studies. <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks. [b] No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).[c] Disappearance of soft tissue plasmacytomas for at least six weeks.
Near Complete Response (nCR)	Requires the following: Same as CR, but immunofixation studies continue to show presence of the monoclonal protein
Very Good Partial Response (VGPR)	Requires the following: ≥ 90% reduction in serum M-protein plus urine M-protein level <100mg per 24 hours on at least two determinations for a minimum of six weeks.
Partial response (PR)	PR includes participants in whom some, but not all, criteria for CR are fulfilled providing the remaining criteria satisfy the requirements for PR. Required all of the following: ≥50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, reduction in 24-hour urinary light chain excretion by either ≥90% or to <200 mg for at least two determinations six weeks apart.

Response	Criteria for Response [a]
	≥50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).[c]
Minimal response (MR)	MR included participants in whom some, but not all, criteria for PR were fulfilled, providing the remaining criteria satisfied the requirements for MR. Required all of the following: ≥25% to ≤ 49% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, a 50 to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for at least two determinations six weeks apart. 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).[c]
No change (NC)	Not meeting the criteria for MR or PD.
Progressive disease (PD) (for participants not in CR)	Requires one or more of the following: >25% increase[d] in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation. >25% increase[d] in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation. >25% increase[d] in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%. Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).
Relapse from CR	Required at least one of the following: Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least one follow-up and excluding oligoclonal immune reconstitution. ≥5% plasma cells in the bone marrow aspirate or biopsy. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)[e].

a Based on the criteria reported by Blade et al., 1998.
b Per Blade *et al*., 1998, if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow except in participants with nonsecretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
c Per Blade *et al*., 1998, skeletal X-Rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).
d It is suggested that the reference point for calculating any increase should be the lowest value of the preceding confirmed response (MR, PR or CR) or the baseline value if there is no previous confirmed response.
e Other clinical data may be requested by the IRC, as necessary, to assess the cause of the hypercalcemia.

9.1.6 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 from any cause. 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 from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

Overall survival (OS): OS is defined as the time from registration to death from any cause. Alive patients are censored at the date last known alive.

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

9.1.7 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. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

10.1 Data Reporting

10.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

10.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

10.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. 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 Overall PI and study team.

The DSMC will review each protocol up to four times a year 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 with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; 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.

10.3 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.

10.4 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 all applicable regulatory requirement(s).

10.5 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.

10.6 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.

10.7 Records Retention

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

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

11.1.1 Primary Objectives

The main objective of this study is to evaluate the overall response rate (PR or better) after 4 cycles and the final induction cycle of combination therapy with lenalidomide, subcutaneous (SQ) bortezomib, and dexamethasone (RSQVD) in patients with newly diagnosed multiple myeloma.

All patients who start treatment and have at least one follow-up assessment will be included in the response analysis.

Evaluate the rate and severity of PN of SQ bortezomib in combination with lenalidomide, and dexamethasone after the 4th cycle among all patients, and after the final cycle of induction therapy for subjects who do not proceed with immediate autologous transplant and elect instead to complete 8 cycles of induction chemotherapy.

11.1.2 Secondary Objectives

Secondary objectives include safety, to assess neurologic toxicity, time to progression, progression-free survival, duration of response, and overall survival associated with the combination. For patients who elect to go on to stem cell transplant, exploratory endpoints will also be stem cell yield (number of CD34+ cells and days of harvesting) and engraftment parameters.

11.2 Sample Size, Accrual Rate and Study Duration

The main objective of this study is to evaluate the ORR (PR or better) after 4 cycles of lenalidomide, bortezomib (subcutaneous) and dexamethasone among newly diagnosed patients. In a previous study of this population, the observed ORR after 4 cycles was 74% (90% CI:[64,83]). This study was designed such that if and observed rate of at least 74% was observed the lower 90% confidence interval would be at least 64%. This clinical trial is designed to enroll 45 eligible patients. With 45 patients and an observed response rate of 77.8% (35/45) the lower limit on the 90% confidence interval is at least 64% (see table 14.1).

Lower bounds of CIs for the true but unknown overall response rate after 4 cycles using different possible observed response rates and a sample size of 45 eligible participants.

Observed overall response rate	N	# of successes	True response rate: lower bound of 90% CI	True response rate: lower bound of 95% CI
0.80	45	36	0.68	0.65
0.778	45	35	0.65	0.63
0.756	45	34	0.63	0.60
0.733	45	33	0.60	0.58

In the aforementioned study, the observed ORR after the final induction cycle was 100% (90% CI: [92,100]) in the phase II population. With 45 patients and an observed response rate of 97.8% (44/45) and 91.1% (41/45) the lower limit on the 90% confidence interval is at least 90% and 80%, respectively (see table 14.2).

Lower bounds of CIs for the true but unknown overall response rate after the final induction cycle using different possible observed response rates and a sample size of 45 eligible participants.

Observed overall response rate	N	# of successes	True response rate: lower bound of 90% CI	True response rate: lower bound of 95% CI
1	45	45	0.94	0.92
0.978	45	44	0.90	0.88
0.956	45	43	0.87	0.85
0.933	45	42	0.84	0.82
0.911	45	41	0.81	0.79

The rate of peripheral neuropathy after 4 cycles and at the end of the induction cycle will also be reported along with the 90% exact binomial confidence intervals. In the aforementioned study of this population, the observed rate of peripheral neuropathy at the end of the study was 80% (where all grades were included). We expect that the rate of peripheral neuropathy will be much less in this RSQVD regimen. For a sample of 45 patients, the 90% exact binomial confidence intervals will be no wider than ± 0.13.

Based on the accrual of 06-150, a similar protocol for frontline MM patients, we anticipate the accrual rate to be 3-4 patients/month. Therefore, accrual to this trial will complete in 12-15 months.

11.3 Stratification Factors

There are no stratification factors planned in this trial.

11.4 Analysis of Secondary Endpoints

The objective response rate after 8 cycles and the CR + nCR rate after 4 cycles will also be reported along with the 90% exact binomial confidence intervals.

Duration of treatment, number of cycles, total dose and dose intensity will be summarized. Dose modifications will also be summarized. Toxicities will be closely monitored throughout the study. The incidence of all AEs and treatment-related AEs will be listed and summarized by CTCAE preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner Serious adverse events will be listed and summarized in the same manner as all AEs. Adverse events with a fatal outcome will be listed.

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be listed.

The time to event secondary endpoints are defined as follows: time to progression (time from registration to progression, censored at date last known progression-free for those who have not progressed), progression-free survival (time from registration to the disease progression or death from any cause, censored at date last known progression-free for those who have not progressed or died), duration of response (time from time of first response after treatment (first MR or PR, respectively) to the date of disease progression or death from any cause, or date last known progression-free and alive for those who have not progressed or died) and overall survival (time from registration to death from any cause or date last known alive for those who have not died). Overall survival, time to progression, progression free survival and the duration of response will be estimated using the method of Kaplan-Meier.

For patients who elect to go on to stem cell transplant, descriptive statistics (medians and ranges) will be used to describe the number of CD34+ cells, days of harvesting, and other quantitative engraftment parameters.

12. 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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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B BODY SURFACE AREA FORMULAS

DuBois Formula

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

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

Mosteller Formula

$$BSA\ (m^2) = \sqrt{([\ height\ (cm) \times weight\ (kg)]\ /\ 3600)}$$

[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.

Cockcroft-Gault formula

$$\text{Creatinine Clearance (ml/min)} = \frac{(140\text{-age}) \times \text{Body mass (kg)} \times 0.85\ (\text{female}) \text{ or } 1.0\ (\text{male})}{\text{serum creat (mg/dL)} \times 72}$$

APPENDIX C 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 D DECLARATION OF HELSINKI

Full detail of the World Medical Association Declaration of Helsinki can be accessed using the following link: http://ohsr.od.nih.gov/guidelines/helsinki.html

APPENDIX E 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 #_____

Participant Initials_____

Cycle #_____

PARTICIPANT SIGNATURE_____ DATE_____

APPENDIX F DURIE SALMON STAGE AND INTERNATIONAL STAGING SYSTEM (ISS) FOR MULTIPLE MYELOMA

Stage	Durie Salmon Stage	ISS Stage
I	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or ≤12 mg/dL • Bone x-ray, 0-1 lesion or solitary bone plasmacytoma only • Low M-component production rate — IgG value <5 g/dL; IgA value <3 g/Dl; urine light chain M-component on electrophoresis <4 g/24 h	Serum $B2$-microglobulin < 3.5 mg/L **AND** Serum albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III	Serum $B2$-microglobulin <3.5 mg/L, but serum albumin <3.5 g/dL **OR** Serum $B2$-microglobulin 3.5 to <5.5 mg/L, irrespective of serum albumin

III	One or more of the following: • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions (≥ 3 lesions) • High M-component production rate — IgG value >7 g/dL; IgA value >5 g/dL — Bence Jones protein >12 g/24 h	Serum *B*2-microglobulin ≥5.5 mg/L

Sub classification	**Durie Salmon Stage**
(either A or B)	• **A**: relatively normal renal function, with serum creatinine value <2 mg/dl • **B**: abnormal renal function, with serum creatinine value ≥2 mg/dl

Adapted from Durie *et al*. and Greipp *et al.*

APPENDIX G DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

DFCI IRB Protocol #: 14-508

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

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1. 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), Boston Children's Hospital (BCH), 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).). 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 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 Overall 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), etc) 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.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible for ensuring high- quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and saftey monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. 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, MD** 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.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member 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 applicable 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 reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
- 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.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS)
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.

- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- 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.
- Order, store and dispense 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.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. 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 for all consent versions.

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 Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB 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 (HIPPA). 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 statement. This authorization statement 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, with information regarding authorization for the disclosure of protected health information.

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. 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 should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center (Dana Farber Cancer Institute Research Project Manager):

- Copy of required laboratory tests including:
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist ***or*** Protocol Registration Form ***[whichever is applicable for this protocol]***

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

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 departures 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. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner.The Coordinating Center will provide training for the requirements for the reporting of violations.

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. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessents 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 are outlined in sections 6 and 7 of 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 7

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy

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 Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

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. As the Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the DF/HCC Multi-center Protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution.

The DF/HCC Lead Institution will implement on-site as well as virtual or remote monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. At a minimum, the DF/HCC Lead Institute will monitor each participating site twice a year while patients are receiving treatment, or as scheduling and finances allow. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary.

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.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at least monthly. The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur on a regular basis as scheduling and finances allow. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments.

Virtual (Remote) Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. 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 on-site audit will be scheduled by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records

may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit 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. 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 and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may 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. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.