

Title: A Randomized Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone (RVD) to High-Dose Treatment with Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age.

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New Hampshire Oncology and Hematology: [REDACTED]
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Oregon Health and Sciences University: [REDACTED]
Eastern Maine Healthcare: [REDACTED]
University of California at San Diego: [REDACTED]
Baylor College of Medicine: [REDACTED]
Ochsner Foundation [REDACTED]
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SUNY Upstate: [REDACTED]
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University of Pennsylvania: [REDACTED]
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Agent(s):

Lenalidomide - Celgene Corporation

Bortezomib - Millennium Pharmaceuticals, Inc. and commercially available

Dexamethasone – commercially available

Melphalan – commercially available

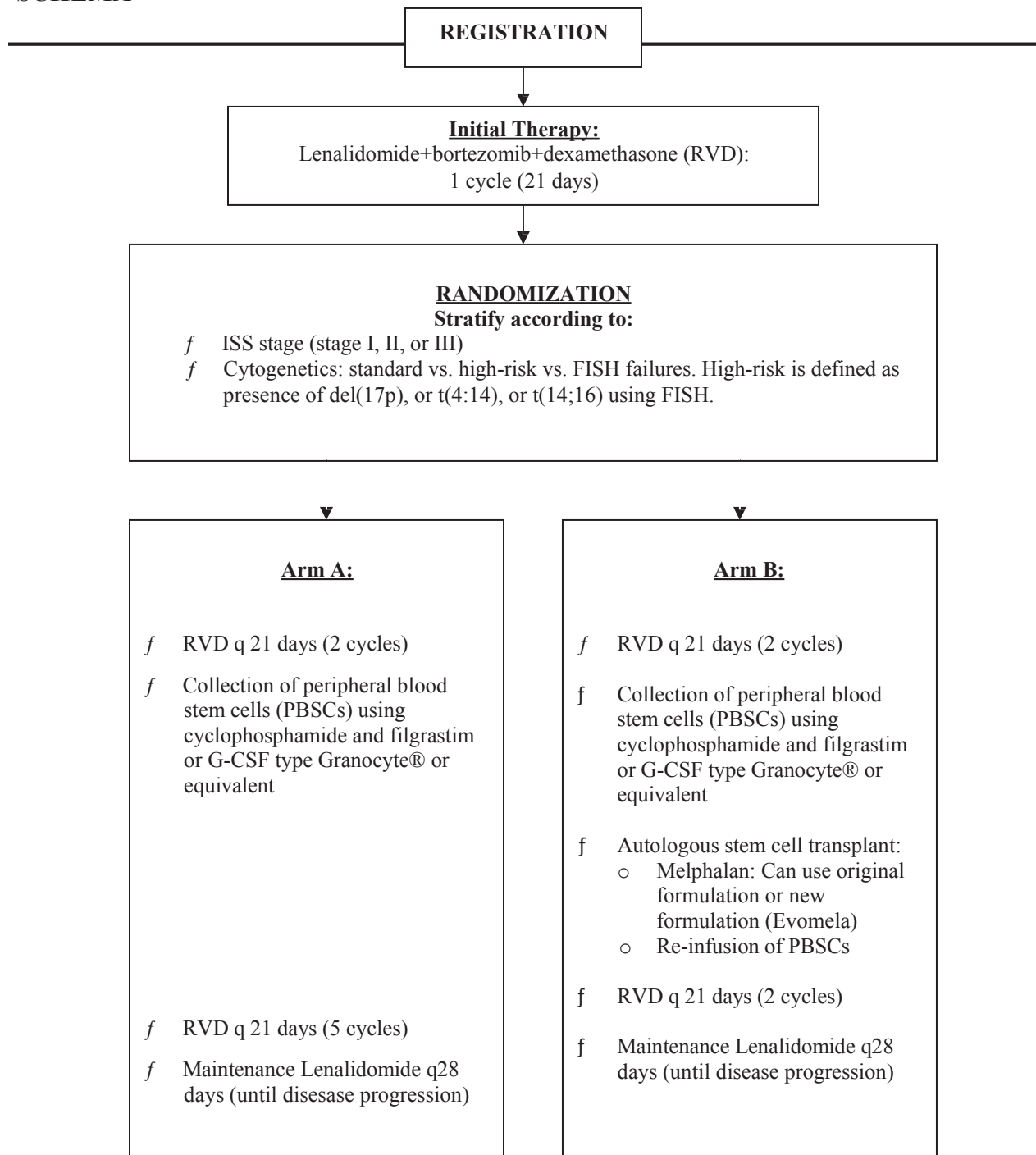
Cyclophosphamide – commercially available

Filgrastim – commercially available

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SCHEMA



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Abbreviations List

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Abbreviation	Definition
qC	degrees Celsius
PM	micromolar
20S	20S proteasome subunit
AE	adverse event
AIBW	adjusted ideal body weight
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
Bcl-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BM	Bone marrow
BMT	Bone marrow transplant
BSA	body surface area
BUN	Blood urea nitrogen
CAM	cell adhesion molecules
CBC	Complete blood count
Cm	Centimeter
CR	Complete Response
CRF	Case report form
CRO	Contact research organization
CRP	C-reactive protein
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
DAR	Drug accountability record
DLCO	Diffuse lung capacity
dL	deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
EBMT	European Group for Blood & Marrow Transplant

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ECG	Electrocardiography
	Echocardiogram
FCHO	
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
FDA	Food and Drug Administration
FLC	Free light chain
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GEP	Gene expression profiling
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HDT	High-dose therapy
HR	Hazard ratio
ht	Height
INB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonization
IL-6	Interleukin-6
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	International Staging
System IV	intravenous
INBD	I kappa B alpha-associated protein kinase
kg	kilogram
Ki	inhibitory constant
lbs	pounds
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
m ²	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MM	Multiple myeloma
MR	Minimal response
MRI	Magnetic resonance imaging

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MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NCI	National Cancer Institute
nCR	near complete response
NF- κ B	nuclear factor- κ B
Ng	nanogram
nM	nanomole
NYHA	New York Heart Association
OS	Overall survival
p21	p21(ras) farnesyl-protein transferase p27cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PBSC	Peripheral blood stem cells
PBSCT	Peripheral blood stem cell transplant
PD	Progressive disease
PE	Pulmonary embolism
PFS	Progression-free survival
PFT	Pulmonary function test
PK	pharmacokinetics
PR	Partial response
QACT	Quality Assurance for Clinical Trials
QOL	Quality of life
RR	Response rate
SAE	serious adverse event
SD	Stable disease
SGOT	serum glutamic oxaloacetic transaminase SGPT serum glutamic pyruvic transaminase
SPEP	serum protein electrophoresis

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Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse event
TTP	Time-to-progression
US	United States
USP	United States Pharmacopeia
UPEP	Urine protein electrophoresis
UTI	Urinary tract infection
VCAM-1	vascular cell adhesion molecule 1
VGPR	Very good partial response
WBC	White blood cells
w/w	weight-to-weight ratio
WWDSS	Worldwide Drug Safety Surveillance
wt	Weight

SYNOPSIS

Title	A Randomized Phase III study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone (RVD) to High-Dose Treatment with Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age.
Number of Centers	60
Rationale	<p><u>Treatment Regimen Rationale:</u> For fifteen years, high-dose therapy (HDT) has been the standard treatment for multiple myeloma (MM) in younger patients. In the 1990s, several randomized studies demonstrated the superiority of high-dose treatments versus conventional chemotherapies in terms of response (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004; Fermand et al., 1998; Blade et al., 2005), event-free survival (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004; Fermand et al., 1998; Blade et al., 2005) and overall survival (OS) (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004). The superiority of HDT over conventional-dose therapy is related to obtaining a higher rate of very good partial response (VGPR) or better, which in turn is correlated with longer PFS, but only in some studies with OS (Attal et al., 2007). Indeed, a recent meta-analysis by Koreth and colleagues demonstrated PFS and no OS advantage (Koreth et al., 2007).</p> <p>For the last 4-5 years, the arrival of novel therapies (thalidomide, bortezomib and lenalidomide) has revolutionized conventional therapeutic regimens. The use of these new therapies has improved complete response (CR) and VGPR rates of HDT as well as those of conventional-dose therapy, to such a point that these rates have now become similar in both groups of treatment. Thus, the arrival of novel therapies has brought into question the necessity of HDT as first-line therapy in young patients (Attal et al., 2007; Attal et al., 2007).</p> <p>The aim of the protocol is, therefore, to compare the results (in terms of efficacy, quality of life and cost) of HDT to those of conventional-dose treatment, with both treatment arms receiving novel drugs as part of induction, consolidation and maintenance.</p> <p><u>Rationale for the Conventional-Dose Arm (Arm A):</u></p> <p>Choice of treatment: Since the 1960s, the combination of melphalan + prednisone (MP) was the standard conventional-dose treatment for myeloma. Therefore, it was logical to evaluate new drugs in combination with MP. For the last 2 to 3 years, the combinations MP + thalidomide, MP + bortezomib, or MP + lenalidomide have become or are in the</p>

process of becoming new standards for the induction treatment of elderly patients (Palumbo et al., 2006; Facon et al., 2007; San Miguel et al., 2008; Palumbo et al., 2007). Other researchers, seeking to avoid the use of alkylating agents in induction treatment, have successfully evaluated combinations of dexamethasone and lenalidomide (Rajkumar et al., 2007). All of these new strategies have generated promising results, with PR rates between 70 and 80%, rates of VGPR between 42 and 50% and durations of response of approximately 24 months. However, these results remain greatly inferior to the results that are expected for the new high-dose strategies with more than 90% PR, including up to 80% VGPR (Attal et al., 2007). The only conventional-dose treatment that rivals these high-dose results is RVD, developed by the DFCI team, with 100% PR and 74% VGPR (Richardson et al., 2007; Richardson et al., 2008). It is therefore logical to select RVD for the conventional-dose arm in this protocol.

Maintenance therapy: Maintenance therapy used in the conventional-dose arm will be identical to that of the high-dose arm. Maintenance with lenalidomide (based on the results of the IFM 2005 study) will be used in an identical manner in both the high-dose and conventional-dose arms.

Treatment for relapse: To avoid penalizing (in terms of overall survival) patients in arm A, who will not receive a transplant in first-line treatment, the recommended treatment for relapse will be the use of high-dose melphalan with autologous peripheral blood stem cell transplant (PBSCT). A study conducted by Fermand et. al demonstrated that the overall survival of participants who receive transplant as first-line therapy is identical to overall survival of those who receive it as treatment for relapse (Fermand et al., 1998). Stem cells will, therefore, be collected from all participants after three cycles of RVD and used to support HDT/PBSCT in case of relapse for the conventional-dose participants, and after successful salvage therapy.

Rationale for HDT Arm (Arm B):

Induction: The combination of dexamethasone, adriamycin and vincristine (VAD regimen) was the standard induction regimen for a long time, although rates of response after VAD were mediocre: 75% PR (PR = 50% reduction in monoclonal component), including only 10% VGPR (VGPR = at least 90% reduction in monoclonal component) (Harousseau et al., 2007). Several randomized studies have recently demonstrated that the combination of dexamethasone and one of the new molecules, bortezomib (Harousseau et al., 2007) or thalidomide (Macro et al., 2006) made it possible to improve pre-transplant response rates. An Italian randomized study showed that the combination of dexamethasone, bortezomib and thalidomide made it possible to achieve still greater

improvement in the results of induction, obtaining 93% PR with 60% VGPR (Cavo et al., 2007). Finally, a multi-center study led by DFCI, in Boston, MA, has demonstrated that the combination of lenalidomide, bortezomib and dexamethasone (the so-called RVD regimen) has obtained 100% PR with 74% VGPR, with excellent tolerability (Richardson et al., 2007; Richardson et al., 2008). This regimen is currently the most promising current approach to induction, and will therefore be used in this protocol.

Collection of autologous peripheral blood stem cells: After conventional induction using VAD, mobilization of autologous peripheral blood stem cells (PBSC) has been performed by G-CSF alone. However, several studies that used lenalidomide as induction treatment suggest that mobilization by cyclophosphamide and G-CSF is preferable (Kumar et al., 2007). This combined mobilization will be used in this protocol.

High-dose therapy: The standard conditioning treatment is high-dose melphalan followed by autologous peripheral blood stem cell transplant (PBSCT) (Moreau et al., 2002). It has recently been reported that combined conditioning using melphalan and bortezomib made it possible to improve post-transplant response rates (Roussel et al., 2008). However, this improvement was mainly found in patients not receiving bortezomib as induction treatment. Since bortezomib will be used in induction and in consolidation in this protocol, transplant conditioning will use melphalan alone in order to reduce risks of neuropathy in this treatment arm.

Post-transplant consolidation: Ladetto and colleagues have reported that post-transplant consolidation using the combination of bortezomib, thalidomide and dexamethasone made it possible to convert 22% of VGPR into full, lasting molecular responses (PCR-) (Ladetto et al., 2007). In the IFM 2008 pilot study, the usefulness and safety of post-transplant consolidation with two cycles of the RVD combination is being tested. Based on the assumption that the results of this pilot study are satisfactory in terms of response and safety, two cycles of RVD has been chosen for consolidation in this protocol.

Post-transplant maintenance therapy: Results from a study by the

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Intergroupe Francophone du Myélome have demonstrated that post-transplant maintenance treatment with thalidomide made it possible to reduce tumor mass, prolong duration of response and improve survival (Attal et al., 2006). This result was recently confirmed by Spencer and colleagues (Spencer et al., 2007). However, the neurological toxicity of thalidomide is limiting with 68% neuropathy reported in the French study (Attal et al., 2006). The usefulness of lenalidomide (a thalidomide analogue with markedly reduced neurotoxicity) is currently being tested by the IFM

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	<p>with promising results to date (IFM 2005-02 protocol: 614 patients, enrollment completed on August 14, 2008, first interim analysis on January 4, 2010: PFS superiority of the lenalidomide maintenance arm, $p < 10^{-6}$). Based on the assumption that the results of this trial remain satisfactory, lenalidomide has been chosen as maintenance therapy in this protocol.</p>
Study design	<p>Phase III, multicenter, randomized, open-label study designed to evaluate the clinical benefit from the drug combination RVD without immediate high-dose therapy (HDT) followed by lenalidomide maintenance (Arm A) versus RVD plus HDT and PBSCT followed by lenalidomide maintenance (Arm B).</p>
Objectives	<p>To achieve the objectives of this study, data from this trial and a parallel trial in France will be combined together for analysis. To determine if, in the era of novel drugs, HDT is still necessary in the initial management of multiple myeloma in younger patients. HDT as compared to conventional dose treatment would be considered superior if it significantly prolongs progression-free survival (by at least 9 months).</p> <p><u>Primary objective:</u> To compare progression-free survival (PFS) between the Arm A and Arm B.</p> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none">x To compare the response rates (RR) between the two armsx To compare time to progression (TTP) between the two armsx To compare the overall survival (OS) between the two armsx To compare toxicity between the two armsx To define genetic prognostic groups evaluated by gene expression profiling (GEP)x To examine the best treatment in each GEP-defined prognostic group.x To compare quality of life (QOL) between the two armsx To collect medical resource utilization (MRU) information which may be used in economic evaluation models
Determination of the number of patients	<p>To achieve the objectives of this study, data from this trial and a parallel trial in France will be combined together for analysis. The primary objective of the study is to determine whether high-dose therapy with PBSCT (HDT/PBSCT) plus novel therapy is able to prolong progression-free compared to novel therapy alone. The median progression-free survival in the RVD arm is estimated to be 30 months. The intent-to-treat analysis of PFS will be performed using a stratified two-sided log-rank test with an overall type I error rate of 5%. The US study has been modified to</p>

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	<p>allow for maintenance until progression based on recent literature and the IFM sites will remain at 1 year of maintenance therapy. Therefore, the study has been modified to enroll 700 randomized patients from the IFM sites and 720 randomized patients from the US sites. The US study will have 90% power to detect at least a 30% reduction in the hazards. . Interim analysis of PFS will be performed at 33% and 69% information with full information defined as 329 failures. The study will be monitored for early stopping using repeated confidence intervals</p>
<p>Study duration</p>	<ul style="list-style-type: none"> x Planned 3 years of accrual and 3 years of follow-up x Inclusion period: Until time of disease progression x Follow-up period: Patients will be followed for survival
<p>Study Entry Criteria</p>	<p><u>Inclusion Criteria for Registration:</u> (Laboratory assessments must be performed within 21 days of initiation of protocol therapy unless otherwise noted; Bone marrow biopsy, skeletal survey, MRI, CT scans, and chest X-ray must be performed within 35 days of initiation of protocol therapy)</p> <ul style="list-style-type: none"> - Patients diagnosed with multiple myeloma based on International Myeloma Foundation 2003 Diagnostic Criteria. According to these criteria, the following must be met. <ul style="list-style-type: none"> o Monoclonal plasma cells in the bone marrow $\geq 10\%$ (or proven plasmocytic infiltration in bone marrow biopsy) and/or presence of a biopsy-proven plasmacytoma (within 35 days) o Monoclonal protein (M-protein) present in the serum and/or urine (within 21 days). o Myeloma-related organ dysfunction (1 or more) of the following. A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Note: Laboratory assessments used to support the CRAB criteria in the IMF 2003 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 These include: <ul style="list-style-type: none"> [C] Calcium elevation in the blood, defined as serum calcium > 10.5 mg/dl or upper limit of normal [R] Renal insufficiency (defined as serum creatinine above normal). [A] Anemia, defined as hemoglobin <10 g/dl or 2 g $<$ normal). [B] Lytic bone lesions or osteoporosis. If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then $> 30\%$ plasma cells are required in the bone marrow or proven plasmocytic infiltration in smoldering or indolent myeloma, but can also include symptomatic disease.

- Patients must have symptomatic myeloma with myeloma-related organ damage as defined above with laboratory assessments
- Patients must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. Measurable disease is defined as one or more of the following: serum M-protein ≥ 1 g/dl (except for patients with IgD or IgA myeloma – please see below), urine M-protein ≥ 200 mg/24h, and/or serum FLC assay: involved FLC level ≥ 10 mg/dl with abnormal serum FLC ratio. For patients with IgD or IgA myeloma, a serum M-protein of greater than or equal to 0.5 g/dl will suffice. Serum free light chain patients not measurable by adequate urine or serum M protein evaluation may be considered for inclusion.
- Age between 18 and 65 years at the time of signing the informed consent document.
- ECOG performance status ≤ 2 (Karnofsky $\geq 60\%$, see Appendix III)
- Negative HIV blood test within 21 days of initiation of protocol therapy. HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with lenalidomide, bortezomib and/or dexamethasone. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.
- 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.
- Females of childbearing potential* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/ml 10 to 14 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®) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide.
 - * A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) 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)
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
- Men must agree to use a latex condom during sexual contact with a

	<p>female of childbearing potential even if they have had a successful pregnancy precautions and risks of fetal exposure. See Appendix II: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.</p> <ul style="list-style-type: none">- Ability to understand and willingness to sign a written informed consent document. Voluntary written consent must be obtained before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care. <p><u>Exclusion Criteria for Registration:</u></p> <ul style="list-style-type: none">- Participants treated with any prior systemic therapy. Treatment by localized radiotherapy is not an exclusion criterion if an interval of at least 7 days between the end of radiotherapy and initiation of protocol therapy is observed. Intervals of less than 7 days between radiotherapy and initiation of protocol therapy will be considered on a case by case basis with the lead PI, provided toxicity is not a concern. Similarly, the dose of corticosteroids for the treatment of their myeloma received by the participant should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol therapy.- Primary amyloidosis (AL) or myeloma complicated by amylosis.- Participants receiving any other investigational agents.- Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.- Poor tolerability or known allergy to any of the study drugs or compounds of similar chemical or biologic composition to lenalidomide, bortezomib and/or dexamethasone.- Platelet count $< 50,000/\text{mm}^3$ within 21 days of initiation of protocol therapy for patients in whom $< 50\%$ of bone marrow nucleated cells are plasma cells; or platelet count $< 30,000/\text{mm}^3$ for patients in whom $\geq 50\%$ of bone marrow nucleated cells are plasma cells. Transfusion within 7 days of screening <i>is not allowed</i> to meet platelet eligibility criteria.- ANC $< 1,000$ cells/mm^3 within 21 days of initiation of protocol therapy. Growth factor within 7 days of screening <i>is not allowed</i> to meet ANC eligibility criteria.- Hemoglobin < 8 g/dL within 21 days of initiation of protocol therapy. Transfusion <i>may</i> be used to meet hemoglobin eligibility criteria.- Hepatic impairment, defined as bilirubin > 1.5 x institutional upper limit of normal (ULN) (Patients with benign hyperbilirubinemia (e.g., Gilbert's syndrome) are eligible) or AST (SGOT), or ALT (SGPT), or alkaline phosphatase ≥ 2 x ULN, within 21 days of initiation of protocol therapy. <p>Renal insufficiency at the time of screening, defined as serum</p>
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creatinine > 2.0 mg/dl or creatinine clearance < 50 ml/min (either actual or calculated), within 7 days of initiation of protocol therapy. Creatinine clearance will be the primary eligibility criteria in determining renal insufficiency. The Cockcroft-Gault formula should be used for calculating creatinine clearance values, and may be located in Section 3.2.10.

- Respiratory compromise, defined as ventilation tests with DLCO < 50%.
- Participant with clinical signs of heart or coronary failure, or evidence of LVEF < 40%.
- Participant with myocardial infarction within 6 months prior to enrollment or have New York Heart Association (NYHA) Class III or IV heart failure (See Appendix V), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
- Intercurrent illness including, but not limited to ongoing or active severe infection, known infection with hepatitis B or C virus, poorly controlled diabetes, severe uncontrolled psychiatric disorder or psychiatric illness/social situations that would limit compliance with study requirements. For patients with a positive hepatitis B antibody result, but no signs of active infection, participating sites must contact the study PI for approval.
- Participants with previous history of another malignant condition are excluded, except for localized cancers that have been adequately treated. This includes completely resected basal cell carcinoma or squamous cell carcinoma of the skin, in situ malignancy (e.g. DCIS of the breast), good risk prostate cancer after curative therapy and/or considered appropriate for watchful waiting (e.g. Gleason 6 or less, T2 or less and PSA < 10), and stage I cervical cancer. If invasive malignancy was experienced 2 or more years ago and confirmed as cured, these participants may be considered for the study on case by case basis with PI discussion and approval.
- Female participant who is pregnant or breast-feeding. Pregnant women are excluded from this study because lenalidomide is an immunomodulatory agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lenalidomide, breastfeeding should be discontinued if the mother is treated with lenalidomide. These potential risks may also apply to other agents used in this study. Lactating females must agree not to breast feed while taking lenalidomide.
- Inability to comply with an anti-thrombotic treatment regimen (e.g., administration of aspirin, enoxaparin, or low molecular weight heparin administration (type Innohep® or equivalent)

	<ul style="list-style-type: none"> - Peripheral neuropathy • Grade 2 on clinical examination, within 21 days of initiation of protocol therapy. <p><u>Inclusion and Exclusion Criteria for Randomization</u> After registration and prior to randomization, participants will receive one cycle of RVD. Participants are not required to meet additional eligibility or exclusion criteria prior to randomization procedures.</p> <p>Participants must have completed testing for the following randomization factors:</p> <ul style="list-style-type: none"> <i>f</i> ISS disease stage (stage I, II, or III) <i>f</i> Cytogenetics: standard vs. high-risk vs. FISH failures. High-risk is defined as presence of del(17p), or t(4:14), or t(14;16) using FISH. <i>f</i> Country (IFM vs. U.S. center)
<p>Treatment plan</p>	<p><u>Initial Therapy with 1 cycle of RVD:</u></p> <ul style="list-style-type: none"> x This cycle will last 21 days x Participants will receive 1 cycle of RVD x This cycle consists of: <ul style="list-style-type: none"> o Lenalidomide: Days 1 to 14 o Bortezomib: Days 1, 4, 8, and 11 o Dexamethasone: Days 1, 2, 4, 5, 8, 9, 11 and 12 x The following supportive care is required: aspirin, enoxaparin or low molecular weight heparin (type Innohep®) or equivalent; acyclovir or valaciclovir or equivalent, bisphosphonates (Zometa® or equivalent). x The following additional medications are strongly recommended: sulfamethoxazole and trimethoprim or equivalent; and amoxicillin or equivalent. x Erythropoietin is allowed <p><u>Arm A:</u></p> <p><u>RVD Therapy: Cycles 2-3</u></p> <ul style="list-style-type: none"> x Each cycle will last 21 days x Participant will receive 2 additional cycles of RVD x This cycle consists of: <ul style="list-style-type: none"> o Lenalidomide: Days 1 to 14 o Bortezomib: Days 1, 4, 8, and 11 o Dexamethasone: Days 1, 2, 4, 5, 8, 9, 11 and 12 x The following supportive care is required: aspirin, enoxaparin or low molecular weight heparin (type Innohep®) or equivalent; acyclovir or valaciclovir or equivalent, bisphosphonates (Zometa® or equivalent). x The following additional medications are strongly recommended: sulfamethoxazole and trimethoprim or equivalent; and amoxicillin or equivalent.

	<ul style="list-style-type: none">x Erythropoietin is allowed <p><u>PBSC Collection</u></p> <ul style="list-style-type: none">x Performed 21 ± 7 days after the last dose of lenalidomide in cycle 3 of initial RVD therapyx On cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent.x • 5 x 10⁶ CD34 cells/kg will be collected. <p><u>Consolidation Therapy with RVD: Cycles 4-8</u></p> <ul style="list-style-type: none">x Five cycles of RVD will be administered as consolidation therapyx Treatment schedule will be identical to that of initial treatment except for dexamethasone with reduced dosex The following supportive care is required: aspirin, enoxaparin or low molecular weight heparin (type Innohep®) or equivalent; acyclovir or valaciclovir or equivalent, bisphosphonates (Zometa® or equivalent).x The following additional medications are strongly recommended: sulfamethoxazole and trimethoprim or equivalent; and amoxicillin or equivalent.x Erythropoietin is allowed <p><u>Maintenance therapy</u></p> <ul style="list-style-type: none">x Maintenance therapy with lenalidomide will be initiated following consolidation therapy.x Lenalidomide will be initiated at a low dose for 3 months, after which dose escalation may occur if initial dose well tolerated.x Maintenance therapy will be continued until disease progression.x Bisphosphonates (Zometa® or equivalent) and erythropoietin are permitted and can be administered according to institutional practice. <p><u>Recommended treatment of relapse (Please note that no exclusion (wash-out) period is applied to this group)</u></p> <ul style="list-style-type: none">x Induction will vary according to the initial response and the time of relapse/progression – bortezomib-based therapy is recommended.x PBSCT conditioned by high-dose melphalan is recommendedx The following is recommended: melphalan administered over 2 consecutive days on Day minus 2 and Day minus 1, or as a single dose on Day minus 2, according to institutional practice. <p><u>Arm B:</u></p> <p><u>RVD Therapy: Cycles 2-3:</u></p> <ul style="list-style-type: none">x Each cycle will last 21 daysx Participant will receive 2 additional cycles of RVD
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	<ul style="list-style-type: none">x This cycle consists of:<ul style="list-style-type: none">o Lenalidomide: Days 1 to 14o Bortezomib: Days 1, 4, 8, and 11o Dexamethasone: Days 1, 2, 4, 5, 8, 9, 11 and 12x The following supportive care is required: aspirin, enoxaparin or low molecular weight heparin (type Innohep®) or equivalent; acyclovir or valaciclovir or equivalent, bisphosphonates (Zometa® or equivalent).x The following additional medications are strongly recommended: sulfamethoxazole and trimethoprim or equivalent; and amoxicillin or equivalent.x Erythropoietin is allowed <p><u>PBSC Collection</u></p> <ul style="list-style-type: none">x Performed 21 ± 7 days after the last dose of lenalidomide in cycle 3 of initial RVD therapyx On cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent.x • 5 x 10⁶ CD34 cells/kg will be collected. <p><u>PBSC Transplant</u></p> <ul style="list-style-type: none">x Conditioning: melphalan as a divided dose on Day minus 2 and Day minus 1, or as a single dose on Day minus 2, according to institutional practice if using the original formulation. If using Evomela, recommended on 2 consecutive days (Day minus 3 and Day minus 2), according to institutional practicex Reinfusion of PBSC on Day 0x Filgrastim will be administered starting on Day +5 and continuing until engraftment, or G-CSF type Neulasta® or equivalent will be administered on Day +2 post PBSC or as per institutional practice. <p><u>Consolidation Therapy with RVD for 2 cycles: Cycles 4 and 5</u></p> <ul style="list-style-type: none">x Two cycles of RVD will be administered as consolidation therapyx Treatment schedule will be identical to that of initial treatment except for dexamethasone with reduced dose.x The following supportive care is required: aspirin, enoxaparin or low molecular weight heparin (type Innohep®) or equivalent; acyclovir or valaciclovir or equivalent, bisphosphonates (Zometa® or equivalent).x The following additional medications are strongly recommended: sulfamethoxazole and trimethoprim or equivalent; and amoxicillin or equivalent.x Erythropoietin is allowed
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Maintenance therapy

	<ul style="list-style-type: none">x Maintenance therapy with lenalidomide will be initiated following consolidation therapy.x Lenalidomide will be initiated at a low dose for 3 months, after which dose escalation may occur if initial dose is well tolerated.x Maintenance therapy will be continued until disease progression.x Bisphosphonates (Zometa® or equivalent) and erythropoietin are permitted and can be administered according to institutional practice.
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1. OBJECTIVES

1.1 Study Design

To achieve the objectives of this study, data from this trial and a parallel trial in France will be combined together for analysis.

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the clinical benefit from the drug combination lenalidomide, bortezomib and dexamethasone (RVD) without immediate high-dose therapy (HDT) and autologous peripheral blood stem cell transplant (PBSCT), followed by lenalidomide maintenance (Arm A) versus RVD plus HDT and PBSCT, followed by lenalidomide maintenance (Arm B). The aim of the protocol is to determine if, in the era of novel drugs, HDT is still necessary in the initial management of multiple myeloma (MM) in younger patients. “High-dose” chemotherapy (Arm B) will be considered superior if it significantly prolongs progression-free survival as compared to “conventional-dose” treatment (Arm A).

1.2 Primary Objectives

To compare progression-free survival (PFS) between Arm A and Arm B

1.3 Secondary Objectives

- x To compare the response rates (RR) between the two arms
- x To compare time to progression (TTP) between the two arms
- x To compare the overall survival (OS) between the two arms x

To compare the toxicity between the two arms

- x To define genetic prognostic groups evaluated by gene expression profiling (GEP)
- x To examine the best treatment in each Gene Expression Profile-defined prognostic group
- x To compare quality of life (QOL) between the two arms
- x To collect medical resource utilization (MRU) information which may be used in economic evaluation models.

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2. BACKGROUND

2.1 Study Agents

2.1.1 Lenalidomide (REVLIMID®)

Lenalidomide (REVLIMID®) is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF (Dredge et. al, 2005). In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production (Corral et. al, 1999). Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity (Schafer et. al, 2003).

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis (Davies et. al, 2001). In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone (Hideshima et. al, 2000).

2.1.1.1 Indications

Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Lenalidomide is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. All other uses are considered investigational.

2.1.1.2 Clinical Pharmacology

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell

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lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (C_{max}) by 36%. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in Phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25 mg, and 50 mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg (Wu et. al, 2004). Exposure (AUC) in MM participants is 57% higher than in healthy male volunteers.

2.1.1.3 Pharmacokinetic Parameters

Distribution:

In vitro (¹⁴C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Due to its structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. When there is no alternative, female of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective (barrier) method (e.g., male condom, diaphragm, or cervical cap), beginning at least 28 days prior to initiating treatment with lenalidomide, during therapy with lenalidomide, during therapy delay, and continuing for at least 28 days following discontinuation of

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lenalidomide therapy even if she has amenorrhea. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of participants. Counseling includes verification with the participant that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix I) will be supplied with each medication dispense.

2.1.1.4 Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE)

This drug has demonstrated a significantly increased risk of DVT and PE in participants with MM who were treated with lenalidomide combination therapy. Participants and physicians are advised to be observant for the signs and symptoms of thromboembolism. Participants should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide is required for participants enrolled in this current trial.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

2.1.1.5 Clinical Experience

A Phase I study in participants with refractory or relapsed MM was conducted to identify the maximum tolerated dose (MTD) and to evaluate the safety of lenalidomide given orally for up to 4 weeks at 5 mg/day, 10 mg/day, 25 mg/day and 50 mg/day. Secondary objectives included evaluation of response to lenalidomide, as well as pharmacokinetics and identification of surrogate markers to aid in defining mechanisms of action. Participants who tolerated study drug with acceptable toxicity and were without disease progression were permitted to continue on therapy beyond 28 days as part of an extension phase for over 1 year. Twenty-seven participants were enrolled, of whom 15 had undergone prior autologous stem cell transplantation and 16 had received prior thalidomide, with a median of 3 prior regimens (range 2-6). All participants had relapsed MM and 18 (72%) were refractory to salvage therapy. Two participants were removed from study on the first day of treatment due to rapid disease progression, which resulted in renal dysfunction and rendered them ineligible. The first group of 3 participants were treated for 28 d at 5 mg/d without any dose limiting toxicity (DLT). The second cohort of 3 participants commenced therapy at 10 mg/day. In one participant, DLT was encountered with grade (G) 2 fever as well as G3 leukopenia and neutropenia, resulting in removal from study before day 28. Two participants tolerated drug. Three additional participants were treated at 10 mg/day with no attributable toxicity within the first 28 days. In the third cohort of 3 participants at 25mg/day, drug was well tolerated within the first 28 days but G3 thrombocytopenia and G3 and G4 neutropenia occurred during the second month, resulting in 2 participants being removed from study. In the fourth cohort

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at 50mg/day, the first 3 participants tolerated treatment without DLT in the first 28 days and a subsequent 10 participants also tolerated drug without DLT within the first 28 days. However, subsequent G3 thrombocytopenia and G3/4 neutropenia in the extension phase prompted dose reduction and Granulocyte colony stimulating factor (GCSF) support in all participants. No significant somnolence, constipation or neuropathy was seen in any cohort. Median duration of therapy is currently 4 months [range 2 weeks – 14 months] and 11 participants continue on treatment. Maximal protein reductions seen during therapy in participants who have received > 28d of treatment are summarized below:

Table 2.1.1 M Protein Reductions in a Phase I Study with Lenalidomide

Dose [mg]	Pts [n]	< 25%	≥ 25% < 50%	≥ 50%	Progression
5	3	-	2	1	-
10	5	-	-	1	4
25	3	1	2	-	-
50	13	3	5	4	1
Subtotals	24	4 (17%)	9 (37%)	6 (25%)	5 (21%)

Thus, best responses in protein of > 25% have been seen in 15 of 24 evaluable pts (63%), and a <25% reduction has been seen in 4 participants to achieve stable disease or better in 19 of 24 (79%). Pharmacokinetics [days 1-4, and 28] have been completed in 24 participants and reveal rapid absorption (t max: 1-1.5 h); monophasic elimination (t ½: 3.1-4.2 h), and low to moderate interparticipant variability for AUC (11-52%) and C max (3-33%). Furthermore, there was no significant accumulation by day 28. In conclusion, these studies suggest Lenalidomide at the dose levels studied has anti-tumor activity, continuous pharmacokinetics (PK) with convenient daily oral dosing and acceptable toxicity in participants with relapsed and refractory multiple myeloma. (Richardson et al., 2002).

Given the myelosuppression beyond day 28 seen in all participants at 50 mg/day, this dose was considered to be the DLT, and thus the 25 mg/day dose level as a continuous daily schedule of administration was considered MTD. Given the activity of the drug seen at lower dose levels and the PK characteristics observed, 30 mg/day in divided or single daily dose was assessed for activity and safety, and to determine whether a divided dose schedule is superior. In addition, a 3-week on and one-week off schedule was assessed to determine if a cycling schedule would decrease the myelosuppression that was observed in earlier trials with daily dosing. In this phase II study, 70 participants with relapsed and refractory Myeloma were enrolled at several U.S. centers. Richardson et al. reported that 26% of participants required dose reduction due to myelosuppression in this study. Responses that were observed included 4% of participants with complete responses (CR), 17% with partial responses (PR) and 33% with minimal responses (MR). Progressive disease (PD) occurred in 15% of participants (Richardson et al., 2002). It was concluded that daily dosing was better tolerated than twice daily dosing because of a lower incidence and severity of myelosuppression.

Data from two phase III trials comparing lenalidomide + dexamethasone to single agent

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dexamethasone in participants with relapsed and/or refractory MM were first presented at the 10th International Multiple Myeloma Workshop in Sydney Australia (Weber et al., 2005; Dimopoulos et al., 2005). Participants who had received 1-3 prior therapies, and progressing on their last therapy were randomized to receive lenalidomide, 25 mg/d x 21 d, placebo d22-28 plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q 28d or placebo daily x 28 d plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q28d. The responses reported are summarized in Table 2.1.2 while the incidence of DVT and PE are summarized in Table 2.1.3 (WEBER et al., 2007; Dimopoulos et al., 2007). Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were also observed more often in the lenalidomide + dexamethasone group compared to the dexamethasone only group, however these events were generally manageable.

Table 2.1.2 Response Rates in Phase III Trials of Relapse refractory MM (Celgene MM-009 and MM-010)

	Weber et al. (NEJM, 2007)			Dimopoulos et al. (NEJM, 2007)		
	Lenalidomide + Dex (n=177)	Dex Alone (n=176)	P Value	Lenalidomide + Dex (n=176)	Dex Alone (n=175)	P Value
Overall Response (≥PR) Rate (%)	61%	19.9%	<0.001	60.2%	24%	<0.001
TTP (mo.)	11.1	4.7	<0.001	11.3	4.7	<0.001
OS (mo.)	29.6	20.2	<0.001	Not reached at time of publication	20.6	<0.001

Table 2.1.3 DVT & PE Risks in Phase III Trials of Relapse refractory MM (Celgene MM-009 and MM-010)

	Weber et al. (NEJM, 2007)		Dimopoulos et al. (NEJM, 2007)	
	Lenalidomide + Dex	Dex Alone	Lenalidomide + Dex	Dex Alone
Deep Vein Thrombosis (%)	11.9	3.4	4.0	3.4
Pulmonary Embolism (%)	3.4	0.6	4.5	1.1

2.1.2 Bortezomib (VELCADE) for Injection

2.1.2.1 Scientific Background

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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 (U.S. FDA) and is registered in Europe for the treatment of MM patients.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. 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 et al., 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 (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

Bortezomib is thought to be efficacious in MM via its inhibition of nuclear factor κ B (NF- κ B) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects (Hideshima et al., 2001).

2.1.2.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, bortezomib displays a rapid distribution phase ($t_{1/2\alpha} < 10$ minutes) followed by a longer elimination phase ($t_{1/2\beta}$ 5–15 hours). Bortezomib has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

The pharmacodynamic action of bortezomib is well established and can be measured through an *ex vivo* assay (20S proteasome activity) (Lightcap et al., 2000). This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with bortezomib in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of bortezomib. Further, intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

2.1.2.3 Nonclinical Toxicity

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Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose MTD. The MTDs were 0.25 mg/kg (1.5 mg/m²) and 0.067 mg/kg (0.8 mg/m²) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.1 mg/kg (0.6 mg/m²) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m²) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date. In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

Additional detailed information regarding the nonclinical pharmacology and toxicology of bortezomib may be found in the Investigator's Brochure.

2.1.2.4 Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in participants with solid tumors and hematological malignancies, and confirmed in phase 2 studies in participants with MM.

Bortezomib demonstrates multi-compartmental PK. Following IV administration of 1 mg/m² and 1.3 mg/m² dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 participants with MM and creatinine clearance values >50 mL/min participating in a PK study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m², respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in

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humans.

In participants with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m² in participants with MM, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in participants is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma bortezomib concentration over the range of 0.5 to 2ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma bortezomib concentrations.

2.1.2.5 Clinical Experience

It is estimated that more than 100,000 participants have been treated with bortezomib, including participants treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the U.S. NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since May 13, 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and DLT of bortezomib in a number of therapeutic settings involving participants with various advanced malignancies. In a Phase I trial in participants with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m²/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 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/m²/dose (3 participants with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m²/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m²/dose and DLT included hypotension, tachycardia, diarrhea, and syncope. In phase 1 clinical studies, anti-tumor activity was reported in participants with NHL, MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

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The safety and efficacy of bortezomib in participants with MM were investigated in two phase 2 clinical studies, studies M34100-024 (participants with first relapse) and M34100-025 (participants with second or greater relapse and refractory to their last prior therapy) (Jagganath et al., 2004; Richardson et al., 2002). In M34100-025, 202 heavily pre-treated participants with refractory multiple myeloma after at least 2 previous treatments received bortezomib, 1.3 mg/m² 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 (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of participants, with an additional 6% of participants meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of participants, and MR or better was observed in 35%. Seventy percent of participants experienced stable disease (SD) or better (Richardson et al., 2005).

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (TTP, RR, and survival) to participants with relapsed 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 QOL relative to high-dose dexamethasone.

A total of 669 participants were enrolled and 663 participants received study drug (bortezomib: 331; dexamethasone: 332). Participants randomized to bortezomib received 1.3 mg/m² I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m² bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Participants 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 four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The EBMT response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. The responses reported are summarized in Table 2.1.4.

Table 2.1.4 Response Rates in a Phase III Trial of Relapsed MM

	Bortezomib (n=331)	Dex (n=332)	P Value
CR+PR Rate (%)	38%	18%	<0.0001
CR+nCR Rate (%)	13%	2%	
CR Rate (%)	6%	<1%	<0.0001

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TTP (mo.)	6.2	3.5	<0.0001
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In participants who had received only one 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 participants on the bortezomib arm vs. participants on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib ($P=0.0005$).

In participants who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib ($P=.0098$).

Updated RR and survival data were reported for M34101-039 (Richardson ASH, 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, OS was significantly longer for participants on the bortezomib arm vs. participants on the dexamethasone arm. The median OS 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 one year was 80% for the bortezomib arm vs. 67% for the dexamethasone arm ($P=0.0002$).

Studies using bortezomib as monotherapy and in combination with other chemotherapy agents are continuing.

2.1.2.6 Potential Risks of Bortezomib

To date, more than 100,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

Prescribing physicians and health care practitioners are referred to their locally approved product label for bortezomib regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of bortezomib therapy are presented below. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m² twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

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Table 2.1.5 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

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, diarrhoea*, 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	

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Table 2.1.5 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

Observed Incidence	Preferred Term
Uncommon	Hyperbilirubinaemia, hepatitis*r
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster* (may cause lesions)
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bacteraemia*, 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 herpeticr, varicella, empyemar, fungal oesophagitisr
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*

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Table 2.1.5 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

Observed Incidence	Preferred Term
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 ^r
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 ^r
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE[®] (bortezomib) for Injection Investigator's Brochure Edition 14.

Most common = \geq 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

* Fatal outcomes have been reported.

^r Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

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Table 2.1.6 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence^a
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease ^b	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare

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Skin and subcutaneous system disorders

Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE[®] (bortezomib) for Injection Investigator's Brochure Edition 14.

- a Incidence is assigned using the following convention: very common (**t** 1/10); common (**t** 1/100 and 1/10); uncommon (**t** 1/1000 and 1/100); rare (**t** 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.

Other medical events of interest that are considered not causally related to bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Females of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of bortezomib may be found in the current Investigator's Brochure.

2.2 Study Disease: Multiple Myeloma

Multiple myeloma is a malignant proliferation of plasma cells. Accounting for 13% of all cases, it is the second most common hematologic malignancy. (Malpas et al., 1998; Cohen et al., 1998). Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines (e.g., IL-6), macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival (Klein et al., 1989; Vidriales and Anderson, 1996; Kawano et al., 1988). Processes that change the bone marrow microenvironment either retard the growth of the tumor or cause myeloma to undergo apoptosis (Anderson et al., 2006).

Patients develop symptoms when the tumor burden is greater than 10^{11} cells/mm³ (Durie and Salmon, 1975). Symptomatic multiple myeloma traditionally requires initiation of systemic therapy, which in the past has included melphalan-prednisone (MP) or another form of combination chemotherapy (Alexanian and Dimopoulos, 1994; Oken, 1994; Oken et al., 1997). Typically, 50% to 60% of patients achieve an objective response to these regimens, but less than 5% achieve a true complete remission with conventional chemotherapy. The FDA approval of novel agents, such as bortezomib, thalidomide, and lenalidomide has greatly enhanced myeloma therapy (Ghobrial et al., 2007). Moreover, current studies using multi-drug combinations have further improved results by reducing drug resistance (Dimopoulos et al., 2003). Although MM remains incurable, survival

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has been extended to ten years and beyond (Richardson et al., 2003; Richardson et al., 2005; Barlogie et al., 2006; Rajkumar et al., 2006; Weber et al., 2007; Dimopoulos et al., 2007).

Experience from around the world now suggests that high-dose alkylating agent chemotherapy followed by autologous hematopoietic stem cell transplantation can achieve high (40%) CR rates and a similar number of partial responses (Schlossman and Anderson, 1999). Synergetic bone marrow transplantation (BMT) has been done infrequently, but patients can remain progression-free for long intervals post-transplant (Bensinger et al., 1996). Despite an increased survival in most patients and long-term survival in a few patients, there is a clear need to improve this intensive therapeutic regimen. Unfortunately, relapses occur in the majority of patients treated with any of these high-dose therapy (HDT) approaches, and there are few, if any, cures. Furthermore, despite recent advances, once a relapse occurs after single or tandem high-dose therapies and BMT, there are relatively limited therapeutic regimens for effective treatment. The bone marrow (BM) reserve has been compromised, restricting the use of both chemotherapeutic and novel regimens to those without attendant myelosuppression, and whilst outcomes have improved with newer agents (please see below), sustained disease stabilization becomes progressively more difficult to achieve, and patients ultimately succumb to relapsed, refractory disease.

2.3 Treatment Regimen Rationale

For fifteen years, HDT has been the standard treatment for MM in younger patients. In the 1990s, several randomized studies demonstrated the superiority of high-dose treatments versus conventional chemotherapies in terms of response (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004; Fermand et al., 1998; Blade et al., 2005), event-free survival (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004; Fermand et al., 1998; Blade et al., 2005) and overall survival (OS) (Attal et al., 1996; Child et al., 2003; Palumbo et al., 2004). The superiority of HDT over conventional-dose therapy is related to obtaining a higher rate of very good partial response (VGPR) or better, which in turn is correlated with longer PFS, but only in some studies OS (Attal et al., 2007). Indeed, a recent meta-analysis by Koreth and colleagues demonstrated PFS and no OS advantage (Koreth et al., 2007).

For the last 4-5 years, the arrival of novel therapies (thalidomide, bortezomib and lenalidomide) has revolutionized conventional therapeutic regimens. The use of these new therapies has improved CR and VGPR rates of HDT as well as those of conventional-dose therapy, to such a point that these rates have now become similar in both groups of treatment. Thus, the arrival of novel therapies has brought into question the necessity of HDT as first-line therapy in young patients (Attal et al., 2007; Attal et al., 2007).

The aim of the protocol is, therefore, to compare the results (in terms of efficacy, quality of life and cost) of HDT to those of conventional-dose treatment, with both

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treatment arms receiving novel drugs as part of induction, consolidation and maintenance. To achieve the objectives of this study, data from this trial and a parallel trial in France will be combined together for analysis.

2.3.1 Rationale for Conventional-Dose Arm (Arm A)

2.3.1.1 Choice of treatment

Since the 1960s, the combination of melphalan + prednisone (MP) was the standard conventional-dose treatment for myeloma. Therefore, it was logical to evaluate new drugs in combination with MP. For the last 2 to 3 years, the combinations MP + thalidomide, MP + bortezomib, or MP + lenalidomide have become or are in the process of becoming new standards for the induction treatment of elderly patients (Palumbo et al., 2006; Facon et al., 2007; San Miguel et al., 2008; Palumbo et al., 2007). Other researchers, seeking to avoid the use of alkylating agents in induction treatment, have successfully evaluated combinations of dexamethasone and lenalidomide (Rajkumar et al., 2007). All of these new strategies have generated promising results, with PR rates between 70 and 80%, rates of VGPR between 42 and 50% and durations of response of approximately 24 months. However, these results remain greatly inferior to the results that are expected for the new high-dose strategies with more than 90% PR, including up to 80% VGPR (Attal et al., 2007). The only conventional-dose treatment that rivals these high-dose results is RVD, developed by the DFCI team, with 100% PR and 74% VGPR (Richardson et al., 2007; Richardson et al., 2008). It is therefore logical to select RVD for the conventional-dose arm in this protocol.

2.3.1.2 Maintenance therapy

Maintenance therapy used in the conventional-dose arm will be identical to that of the high-dose arm. Maintenance with lenalidomide (based on the results of the IFM 2005 study) will be used in an identical manner in both the high-dose and conventional-dose arms.

2.3.1.3 Treatment for relapse

To avoid penalizing (in terms of OS) patients in this arm, who will not receive a transplant in first-line treatment, the recommended treatment for relapse will be the use of high-dose melphalan with autologous PBSCT. A study conducted by Fermand et. al demonstrated that the OS of participants who receive transplant as first-line therapy is identical to OS of those who receive it as treatment for relapse (Fermand et al., 1998). Stem cells will, therefore, be collected from all participants after three cycles of RVD and used to support HDT/PBSCT in case of relapse for the conventional-dose participants, and after successful salvage therapy.

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2.3.2 Rationale for HDT Arm (Arm B)

2.3.2.1 Induction

The combination of dexamethasone, adriamycin and vincristine (VAD regimen) was the standard induction regimen for a long time, although rates of response after VAD were mediocre: 75% PR (PR = 50% reduction in monoclonal component), including only 10% VGPR (VGPR = at least 90% reduction in monoclonal component) (Harousseau et al., 2007). Several randomized studies have recently demonstrated that the combination of dexamethasone and one of the new molecules, bortezomib (Harousseau et al., 2007) or thalidomide (Macro et al., 2006) made it possible to improve pre-transplant response rates. An Italian randomized study showed that the combination of dexamethasone, bortezomib and thalidomide made it possible to achieve still greater improvement in the results of induction, obtaining 93% PR with 60% VGPR (Cavo et al., 2007). Finally, a multi-center study led by Dana-Farber Cancer Institute (DFCI), in Boston, MA, has demonstrated that the combination of lenalidomide, bortezomib and dexamethasone (the so-called RVD regimen) has obtained 100% PR with 74% VGPR, with excellent tolerability (Richardson et al., 2007; Richardson et al., 2008). This regimen is currently the most promising approach to induction, and will therefore be used in this protocol.

2.3.2.2 Collection of autologous peripheral blood stem cells

After conventional induction using VAD, mobilization of autologous peripheral blood stem cells (PBSC) has been performed by G-CSF alone. However, several studies that used lenalidomide as induction treatment suggest that mobilization by cyclophosphamide and G-CSF is preferable. This combined mobilization will be used in this protocol.

2.3.2.3 High-dose therapy

The standard conditioning treatment is high-dose melphalan followed by autologous PBSCT (Moreau et al., 2002). It has recently been reported that combined conditioning using melphalan and bortezomib made it possible to improve post-transplant response rates (Roussel et al., 2008). However, this improvement was mainly found in patients not receiving bortezomib as induction treatment. Since bortezomib will be used in induction and in consolidation in this protocol, transplant conditioning will use melphalan alone in order to reduce risks of neuropathy in this treatment arm.

2.3.2.4 Post-transplant consolidation

Ladetto and colleagues have reported that post-transplant consolidation using the combination of bortezomib, thalidomide and dexamethasone made it possible to convert 22% of VGPR into full, lasting molecular responses (PCR-) (Ladetto et al., 2007). In the IFM 2008 pilot study (enrollment completed in December 2009), the usefulness and safety of post-transplant consolidation with two cycles of the RVD regimen is being tested. The first analysis of the consolidation phase of this protocol is planned in October

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2010. Based on the assumption that the results of this pilot study are satisfactory in terms of response and safety, two cycles of RVD has been chosen for consolidation in this protocol.

2.3.2.5 Post-transplant maintenance therapy

Results from a study by the Intergroupe Francophone du Myelome have demonstrated that post-transplant maintenance treatment with thalidomide made it possible to reduce tumor mass, prolong duration of response and improve survival (Attal et al., 2006). This result was recently confirmed by Spencer and colleagues (Spencer et al., 2007). However, the neurological toxicity of thalidomide is limiting with 68% neuropathy reported in the French study (Attal et al., 2006). The usefulness of lenalidomide (a thalidomide analogue with markedly reduced neurotoxicity) is currently being tested by the IFM with promising results to date (IFM 2005-02 protocol: 614 patients, enrollment completed on August 14, 2008, superiority of the lenalidomide maintenance arm in terms of PFS ($p < 0.000001$) on the first intermediate analysis performed on January 4, 2010). Based on the assumption that the results of this trial remain satisfactory, lenalidomide has been chosen as maintenance therapy in this protocol.

2.3.3 Rationale for the type of trial and the primary endpoint

2.3.3.1 Non-inferiority testing

While, in the context of a therapeutic trial, the notion of gradual dose reduction involves a non-inferiority test, such a test is impossible to perform in this case, for at least two reasons:

- a- Sufficient past data is not available to make an estimated projection of overall survival for patients receiving these new compounds. Trials using these new compounds are recent, and many of them are not yet published. The short-term results are promising, but remain uncertain in the long-term. This lack of thorough understanding, therefore, makes it impossible to define a non-inferiority range that would be applicable to the therapeutic regimen to be tested in this current trial.
- b- The intermediate endpoint of event-free survival is not an endpoint that can be used in a non-inferiority test, because HDT will be offered in those participants who progress during maintenance therapy and did not receive it as first-line treatment. Fermand et al., in an intervention trial aiming to determine the best time to use HDT (initial versus relapse) demonstrated that event-free survival was very different between the groups (13 months versus 39 months), without, however, any difference in OS ($HR=1.02$, $p=0.92$)(Fermand et al., 1998).

2.3.3.2 Progression-Free Survival (PFS) as an endpoint

The aim of this protocol is to determine if, in the era of new drugs, HDT (with transplant) is still necessary in the initial management of myeloma in young patients. Considering the toxicity of the transplant, the specificity of the arrangements that it requires, and its

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cost, the continued use of transplant as first-line treatment will be considered clinically pertinent if it prolongs PFS by at least 9 months as compared to conventional-dose treatment. Currently, new protocols using combinations of new drugs at conventional doses (melphalan/prednisone/thalidomide (Palumbo et al., 2006; Facon et al., 2007); melphalan/prednisone/bortezomib (San Miguel et al., 2008); dexamethasone/lenalidomide (Rajkumar et al., 2007) yield PFS of around 24 months. The RVD combination could improve this result, and a PFS of 30 months may be obtained (Richardson et al., 2007; Richardson et al., 2008). The continued use of transplant in first-line treatment would be warranted if the PFS of the high-dose arm were greater than 39 months. The trial will be considered to be positive if the PFS of the high-dose arm is greater by at least 9 months than that of the conventional dose arm.

2.4 Correlative Studies Background

The purpose of this correlative research is to obtain peripheral blood and bone marrow samples from patients with multiple myeloma. This correlative research will provide a better understanding of the impact of copy number aberrations (CNAs) and their functional consequences on MM initiation and progression, as well as novel high value therapeutic targets for early intervention and new tools to personalize the strategy of treatment in MM patients at risk.

We propose to evaluate whether further stringent CR definition may be able to predict superior survival outcome. We will incorporate normalization of serum free light chain, molecular CR using ASO-PCR and immunophenotypic CR using multicolor flow cytometric immunophenotyping of MM cell in bone marrow to detect minimal residual disease.

In addition, we propose to identify genomic alterations to evaluate clinical outcome. We will evaluate the role of DNA copy number aberrations (CNAs) by high throughput SNP array analysis as well as genome sequencing and gene expression changes by expression array on response, and survival outcome. We will investigate mRNA splicing by exon array and microRNA profiles in the patients to correlate with clinical endpoints. We will investigate both the direct and indirect relationship between CNAs and gene expression changes.

Finally, we propose to investigate genomic changes at the time of progression or relapse and evaluate mechanisms underlying genomic instability. We will perform genome-wide SNP analyses, expression profiling and genome-wide sequencing on paired samples obtained at the time of diagnosis and at the time of progression or relapse identify genomic regions with amplifications, deletions, and changes in heterozygosity. We will evaluate the mutations in light of the known pattern of changes and identify those which may predict different clinical outcomes. Based on our data showing that elevated homologous recombination (HR) activity plays a significant role in ongoing genomic instability in myeloma we will also measure HR activity in primary myeloma samples to evaluate if it correlates with acquisition of new genomic changes as well as clinical outcome.

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3. PARTICIPANT SELECTION

3.1 Inclusion Criteria for Registration

All laboratory assessments should be performed within 21 days of initiation of protocol therapy unless otherwise noted. Bone marrow biopsy, skeletal survey, MRI, CT scans, and chest X-ray within 35 days of initiation of protocol therapy are permitted to fulfill screening requirements.

3.1.1 Participants must have a diagnosis of MM, according to International Myeloma Foundation 2003 Diagnostic Criteria. According to these criteria, the following must be met:

- f* Monoclonal plasma cells in the bone marrow $\geq 10\%$ (or proven plasmocytic infiltration in bone marrow biopsy) and/or presence of a biopsy-proven plasmacytoma within 35 days of initiation of protocol therapy.
- f* Monoclonal protein (M-protein) present in the serum and/or urine
- f* Myeloma-related organ dysfunction (1 or more) of the following. A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. **Note:** Laboratory assessments used to support the CRAB criteria in the IMF 2003 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

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

[R] Renal insufficiency (defined as serum creatinine above normal).

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

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

Note: These criteria identify Stage IB (if the creatinine is > 2 mg/dl at marrow biopsy presentation) and Stages II and III A/B myeloma by Durie-Salmon stage. Stage

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IA becomes smoldering or indolent myeloma.

- 3.1.2 Participants must have documented symptomatic myeloma, with organ damage related to myeloma as defined above in section 3.1.1 with laboratory assessments
- 3.1.3 Participants must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. Measurable disease is defined as one or more of the following: serum M-protein \geq 1 g/dl (except patients with IgD or IgA myeloma), urine M-protein \geq 200 mg/24 h, and/or serum FLC assay: involved FLC level \geq 10 mg/dl with abnormal serum FLC ratio. For patients with IgD or IgA myeloma, a serum M-protein of greater than or equal to 0.5 g/dl will suffice. Free light chain patients not measurable by urine or serum evaluation may be considered for inclusion.
- 3.1.4 Age between 18 and 65 years at the time of signing the informed consent form.
- 3.1.5 ECOG performance status \leq 2 (Karnofsky \geq 60%, see Appendix III).
- 3.1.6 Negative HIV blood test within 21 days of study entry. HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic (PK) interactions with lenalidomide, bortezomib and/or dexamethasone. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.
- 3.1.7 All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.
- 3.1.8 Females of childbearing potential* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS®) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide.
- * A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) 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)
- 3.1.9 Females of childbearing potential must also agree to ongoing pregnancy testing.

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3.1.10 Men must agree to use a latex condom during sexual contact with a female of childbearing potential even if they have had a successful vasectomy. See Appendix II: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

3.1.11 Ability to understand and the willingness to sign a written informed consent document. Voluntary written informed consent must be obtained before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care.

3.2 Exclusion Criteria for Registration

All laboratory assessments should be performed within 21 days of initiation of protocol therapy.

- 3.2.1 Participant treated with any prior systemic therapy for myeloma. Treatment by localized radiotherapy is not an exclusion criterion if an interval of at least 7 days between the end of radiotherapy and initiation of protocol therapy is observed. Intervals of less than 7 days between radiotherapy and initiation of protocol therapy will be considered on a case by case basis with the lead PI, provided toxicity is not a concern. Similarly, the dose of corticosteroids received by the participant as part of initial therapy for myeloma should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol therapy (see Appendix XII for equivalence table).
- 3.2.2 Primary amyloidosis (AL) or myeloma complicated by amylosis.
- 3.2.3 Participants receiving any other investigational agents.
- 3.2.4 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- 3.2.5 Poor tolerability or known allergy to any of the study drugs or compounds of similar chemical or biologic composition to lenalidomide, bortezomib and/or dexamethasone.
- 3.2.6 Participants with platelet level $<50,000/\text{mm}^3$, within 21 days of initiation of protocol therapy for patients in whom $<50\%$ of bone marrow nucleated cells are plasma cells; or platelet count $<30,000/\text{mm}^3$ for patients in whom $\geq 50\%$

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of bone marrow nucleated cells are plasma cells. ***Transfusion within 7 days of screening is not allowed to meet platelet eligibility criteria.***

- 3.2.7 Participants with an absolute neutrophil count (ANC) $< 1000/\text{mm}^3$, within 21 days of initiation of protocol therapy. ***Growth factor within 7 days of screening is not allowed to meet ANC eligibility criteria.***
- 3.2.8 Participants with hemoglobin level < 8 g/dL, within 21 days of initiation of protocol therapy. Transfusion ***may*** be used to meet hemoglobin eligibility criteria.
- 3.2.9 Hepatic impairment, defined as total bilirubin > 1.5 x institutional ULN (Patients with benign hyperbilirubinemia (e.g., Gilbert's syndrome) are eligible.) or AST (SGOT), or ALT (SGPT), or alkaline phosphatase ≥ 2 x institutional ULN, within 21 days of initiation of protocol therapy.
- 3.2.10 Renal insufficiency at the time of screening, defined as serum creatinine > 2.0 mg/dL or creatinine clearance < 50 mL/min (either actual or calculated value may be used), within 7 days of initiation of protocol therapy. Creatinine clearance will be the primary eligibility criteria in determining renal insufficiency. The Cockcroft-Gault formula should be used for calculating creatinine clearance values:
- $$\frac{(140 - \text{age}) \times \text{Body mass (kg)}}{\text{serum creat (mg/dL)} \times 72} \times 0.85 \text{ (female) or } 1.0 \text{ (male)}$$
- 3.2.11 Respiratory compromise, defined as ventilation tests with DLCO $< 50\%$
- 3.2.12 Participant with clinical signs of heart or coronary failure, or evidence of left ventricular ejection fraction (LVEF) $< 40\%$. Participant with myocardial infarction within 6 months prior to enrollment or have New York Heart Association (NYHA) Class III or IV heart failure (see Appendix V), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conductive system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
- 3.2.13 Intercurrent illness including, but not limited to ongoing or active severe infection, known infection with hepatitis B or C virus, poorly controlled diabetes, severe uncontrolled psychiatric disorder or psychiatric illness/social situations that would limit compliance with study requirements. For patients with a positive hepatitis B antibody result, but no signs of active infection, participating sites must contact the study PI for approval.
- 3.2.14 Participants with previous history of another malignant condition are excluded, except for localized cancers that have been adequately treated. This includes

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completely resected basal cell carcinoma or squamous cell carcinoma of the skin, in situ malignancy (e.g. DCIS of the breast), good risk prostate cancer after curative therapy and/or considered appropriate for watchful waiting (e.g. Gleason 6 or less, T2 or less and PSA < 10) , and stage I cervical cancer. If invasive malignancy was experienced 2 or more years ago and confirmed as cured, these participants may be considered for the study on case by case basis with PI discussion and approval

3.2.15 Female participants pregnant or breast-feeding. Pregnant women are excluded from this study because lenalidomide is an immunomodulatory agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with lenalidomide, breastfeeding should be discontinued if the mother is treated with lenalidomide. These potential risks may also apply to other agents used in this study. Lactating females must agree not to breast feed while taking lenalidomide.

3.2.16 Inability to comply with an anti-thrombotic treatment regimen (e.g., administration of aspirin, enoxaparin, or low molecular weight heparin administration (type Innohep® or equivalent)

3.2.17 Peripheral neuropathy \geq Grade 2 on clinical examination, within 21 days of initiation of protocol therapy.

3.3 Inclusion and Exclusion Criteria for Randomization

After registration and prior to randomization, participants will receive 1 cycle of RVD. Participants are not required to meet additional eligibility or exclusion criteria prior to randomization procedures.

3.4 Inclusion of Women, Minorities and Other Underrepresented Populations

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

3.5 Screening Procedures

3.5.1 Registration Screening

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

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recorded. The following screening procedures must be performed within 21 days of initiation of protocol therapy. Results of skeletal survey, bone marrow biopsy, chest X-ray, MRI, and CT scans within 35 days of initiation of protocol therapy may be used to fulfill screening requirements:

- 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 re-reviewed.
- MM diagnosis will be confirmed and the disease stage at diagnosis (according to the criteria of Durie and Salmon, 1975; and the ISS published by Greipp et al., 2005 [See Appendix VII]) will be documented.
- Complete medical history will be obtained to include documentation of all treatments given for MM and all concomitant medications.
- Baseline Symptom Assessment, including neurotoxicity screening
- Physical examination to include measurement of vital signs, height, weight and calculation of body surface area (BSA).
- ECOG performance status will be evaluated (Appendix III)
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO₂, calcium, magnesium, phosphorous, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, lactate dehydrogenase (LDH), uric acid, TSH], beta 2-microglobulin, C-reactive protein (CRP), B-12 and Folate. Albumin should be measured using the nephelometric method when possible. However, standard institutional methods for measuring albumin are also allowed.
- CD4+ and CD8+ lymphocyte count
- HIV, Hepatitis B and Hepatitis C tests
- Urinalysis

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- 12-lead ECG
- LVEF measurement by multiple gate acquisition (MUGA) scan or echocardiogram (ECHO)
- Chest X-ray
- Pulmonary function tests (PFTs)
- Serum and urine M component quantification and immunofixation (SPEP, UPEP) and 24-hour urine collection for paraprotein measurement
- Assay of serum free light chains
- Serum or urine pregnancy test (sensitivity of at least 50 mIU/mL), for females of childbearing potential must be completed. The first test should be performed within 10-14 days, and the second test within 24 hours prior to initiation of lenalidomide. See Appendix II for more details and for the definition of females of childbearing potential used for this trial.
- Skeletal survey for quantification of bone lesions with magnetic resonance imaging (MRI) and CT scans as clinically indicated.
- Bone marrow aspiration to be evaluated for morphology and for cytogenetics by FISH methods, including marrow karyotype if possible. Bone marrow biopsy is also recommended. Results of bone marrow aspirate testing are needed in order to perform randomization.
- Bone marrow aspirate and blood collection for correlative studies (See Section 8 for specimen shipping and handling details):
 - x 6 mL of bone marrow aspirate will be collected in each of 2 purple top tubes (EDTA); 6 mL of blood will be collected in each of 4 purple top tubes (EDTA); 8.5 mL of blood will be collected in a proteomics tube; 10 mL of blood will be collected in a red top tube (no additive).

3.5.2 Randomization Screening

There are no additional screening test requirements for randomization. However, results of cytogenetics by FISH, and beta-2 microglobulin and albumin from registration screening tests are required in order to proceed with randomization because these laboratory results are stratification factors in the randomization. The Investigator is responsible for keeping a

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record of the reason(s) that participants do not proceed to randomization. This information will be collected in the database.

4. REGISTRATION PROCEDURES

4.1 General Registration Guidelines for All Institutions

Institutions will register eligible participants with an electronic central registration system as well as the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. **Registration must occur prior to the initiation of therapy.** Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants should begin protocol treatment within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator.

4.2 Registration Process for DF/HCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. Once eligibility criteria are confirmed following procedures described in Section 3, the patient must first be registered in the eCRF.
2. Eligible participants will be registered in the eCRF by the participating site. Registration must occur prior to the initiation of therapy (RVD Cycle 1, Day 1).
3. The participating institutions will register eligible participants to this study 24 hours a day, 7 days a week, using web-based registration: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link "Contact Technical Support". A user-specific login and password are required to access the website.
4. Participant study number will be automatically allocated by the online registration system based on the following format :

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(3 digits for the site number) – (3 digits for the patient number)

Note: Participant study number will be sequentially allocated for each site.

5. To be eligible for registration to the study, the participant must meet all inclusion and exclusion criteria listed on the eligibility checklist.

6. Information required for participant registration includes patient information (initials, date of birth, sex...), informed consent information, inclusion and exclusion criteria. Some biological parameters are also required in order to complete registration.

7. Once all registration information is entered and the web-based system verifies that inclusion and exclusion criteria are met, patient registration is confirmed. The site will receive an email confirmation with participant study number once the registration process is complete. **Patients must not begin study treatment prior to receiving email confirmation.**

8. To register the participant with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system, complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

9. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

10. The QACT Registrar will (a) validate eligibility, and (b) register the participant on the study.

11. The QACT Registrar will send an email confirmation of the registration to the person initiating the registration immediately following the registration.

If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.3 Registration Process for Other Participating Institutions

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. Once eligibility criteria are confirmed following procedures described in Section 3, the patient must be registered in the eCRF.

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2. Eligible participants will be registered in the eCRF by the participating site. Registration must occur prior to the initiation of therapy (RVD Cycle 1, Day 1).
3. The participating institutions will register eligible participants to this study 24 hours a day, 7 days a week, using web-based registration: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link “Contact Technical Support”. A user-specific login and password are required to access the website.
4. Participant study number will be automatically allocated by the online registration system based on the following format :

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(3 digits for the site number) – (3 digits for the patient number)

Note: Participant study number will be sequentially allocated for each site.

5. To be eligible for registration to the study, the participant must meet all inclusion and exclusion criteria listed on the eligibility checklist.

6. Information required for participant registration includes patient information (initials, date of birth, sex...), informed consent information, and inclusion and exclusion criteria. Some biological parameters are also required in order to complete registration.

7. Once all registration information is entered and the web-based system verifies that inclusion and exclusion criteria are met, patient registration is confirmed. The site will receive an email confirmation with participant study number once the registration process is complete.

8. In addition, the participant must be registered with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. The following documents should be completed by the research nurse or data manager and faxed () or emailed to the Regulatory Coordinator at

- x Eligibility checklist
- x Signed study consent form
- x HIPAA authorization form

9. To complete the registration process, the DFCI Regulatory Coordinator will:

- x Register the participant on the study with QACT
 - x Email the research nurse or data manager at the participating site to confirm eligibility and registration with QACT

Note: Registration with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

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If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the 10-106 research team of participant status changes as soon as possible.

4.4 General Randomization Guidelines for All Institutions

Randomization must occur 2-3 weeks after the initiation of cycle 1 of RVD and prior to cycle 2 of RVD.

For those patients who do not continue to randomization, the reason why patient was not randomized must be documented and will be collected in the database. Patients who do not continue to randomization will be withdrawn from the study. These patients are not followed for progression or survival. If a patient is randomized and does not receive randomized treatment, they are followed for progression and survival in order to perform the intent to treat analysis. The baseline information is also collected on these patients.

4.5 Randomization Process for DF/HCC Institutions

The randomization procedures are as follows:

1. The participating institution will randomize participants 24 hours a day, 7 days a week, using web-based randomization: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link "Contact Technical Support". A user-specific login and password are required to access the website.
2. Randomization information is entered on the web-based randomization system by the participating institution. Stratified permuted blocks will be used in the randomization using the following stratification factors. Stratification factor information will be requested at the time of randomization, and randomization will be blocked if the following data are not entered:
 - ISS Stage I vs. II vs. III. Institutions will provide Beta2- microglobulin level (mg/L) and serum albumin level (g/dL) entered from screening visit, and the randomization system will compute the ISS stage.
 - Standard vs. high risk vs. FISH failures. High-risk is defined as the presence of del(17p), or t(4;14), or t(14;16) using FISH.
 - Country (US)
3. Once participant randomization data is entered in the eCRF, the randomization system will allocate the treatment arm (A or B). The site will receive an email confirmation of treatment arm once the randomization process is complete.
4. Randomization assignment for must also be entered into the DF/HCC QACT central registration system. The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

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5. Enter the randomization assignment on the protocol-specific eligibility checklist.
6. Fax the eligibility checklist to the QACT at 617-632-2295.
7. The QACT Registrar will enter the randomization assignment into the QACT system.
8. The QACT Registrar will send an email confirmation that the randomization assignment has been entered to the person initiating the randomization immediately following the randomization.

4.6 Randomization Process for Other Participating Institutions

The randomization procedures are as follows:

1. The participating institution will randomize participants 24 hours a day, 7 days a week, using web-based randomization: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link “Contact Technical Support”. A user-specific login and password are required to access the website.
2. Randomization information is entered on the web-based randomization system by the participating institution. Stratified permuted blocks will be used in the randomization using the following stratification factors. Stratification factor information will be requested at the time of randomization, and randomization will be blocked if the following data are not entered:
 - ISS Stage I vs. II vs. III. Institutions will provide Beta2- microglobulin level (mg/L) and serum albumin level (g/dL) entered from screening visit, and the randomization system will compute the ISS stage.
 - Standard vs. high risk vs. FISH failures. High-risk is defined as the presence of del(17p), or t(4:14), or t(14;16) using FISH.
 - Country (US)
3. Once participant randomization data is entered in the eCRF, the randomization system will allocate the treatment arm (A or B). The site will receive an email confirmation of treatment arm once the randomization process is complete.

5 TREATMENT PLAN

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.

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Initial Therapy: 1 cycle of RVD

Initial Therapy with RVD for 1 Cycle					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent)	25 mg/day	Oral	Days 1-14 for 1 cycle	21 days (3 weeks)
Bortezomib	Doses should be administered 70-72 hours apart	1.3 mg/m ²	3-5 second IV injection	Days 1, 4, 8, and 11 for 1 cycle (+1 day window)	
Dexamethasone	Take with food; recommended to be taken in the morning	20 mg/day	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12 for 1 cycle (+1 day window). Should be given day of and day after Velcade.	

Arm A Treatment

Arm A: RVD Cycles 2-3					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent)	25 mg/day	Oral	Days 1-14 for 2 cycles (+ 7 day window is allowed between cycles)	21 days (3 weeks)
Bortezomib	Doses should be administered 70-72 hours apart	1.3 mg/m ²	3-5 second IV injection	Days 1, 4, 8, and 11 for 2 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits)	

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Dexamethasone	Take with food; recommended to be taken in the morning	20 mg/day	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12 for 2 cycles (+ 7 day is allowed between cycles and +1 day window for intra-cycle visits) Should be given day of and day after Velcade.	
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Arm A: PBSC Mobilization

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Cyclophosphamide	Per institutional guidelines; Mesna	3 g/m ²	IV	After cycle 3, 21 (± 7 days) days following the final lenalidomide dose	Single administration
Filgrastim or G-CSF type Granocyte® or equivalent	Per institutional guidelines	5 or 10 mcg/kg/day, according to institutional practice	Subcutaneous	Starting at least 24 hours and no more than 48 hours after cyclophosphamide dose until PBSC collection is complete	As needed for blood counts

Arm A: Consolidation Therapy with RVD Cycles 4-8

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent)	25 mg/day	Oral	Days 1-14 for 5 cycles (+ 7 day window is allowed between cycles)	21 days (3 weeks)

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Bortezomib	Doses should be administered 70-72 hours apart	1.3 mg/m ²	3-5 second IV injection	Days 1, 4, 8, and 11 for 5 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits)
Dexamethasone	Take with food; recommended to be taken in the morning	10 mg/day	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12 for 5 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits). Should be given day of and day after Velcade.

Arm A: Maintenance Therapy Until Disease Progression

Agent	Pre-medications;	Dose	Route	Schedule	Cycle
Lenalidomide	Recommended anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent) and as clinically indicated	10 mg/day (months 1-3); 15 mg/day (months 4-12, if initially well tolerated)	Oral	Within 3 weeks of completing RVD consolidation; Days 1-28 until disease progression (+ 14 day window is allowed between cycles)	28 days (4 weeks)

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Arm B Treatment

Arm B: RVD Cycles 2-3					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent)	25 mg/day	Oral	Days 1-14 for 2 cycles (+ 7 day window is allowed between cycle)	21 days (3 weeks)
Bortezomib	Doses should be administered 70-72 hours apart	1.3 mg/m ²	3-5 second IV injection*	Days 1, 4, 8, and 11 for 2 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits)	
Dexamethasone	Take with food; recommended to be taken in the morning	20 mg/day	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12 for 2 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits). Should be given day of and day after Velcade.	

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Arm B: PBSC Mobilization					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Cyclophosphamide	Per institutional guidelines; Mesna	3 g/m ²	IV	After cycle 3, 21 (± 7 days) days following the final lenalidomide dose	Single administration
Filgrastim or G-CSF type Granocyte® or equivalent	Per institutional guidelines	5 or 10 mcg/kg/day, according to institutional practice	Subcutaneous	Starting at least 24 hours and not more than 48 hours after cyclophosphamide dose until PBSC collection is complete	As needed for blood counts

Arm B: PBSC Transplant					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Melphalan (original formulation) OR Melphalan (Evomela formulation)	Per institutional guidelines	200 mg/m ² (100 mg/m ² /day if administered over 2 days)	IV	Day minus 2 and Day minus 1 or Day minus 2, according to institutional practice	1 or 2 days
	Per institutional guidelines	100 mg/ m ² Per day administered over 30 minutes over 2 days	IV	Day Minus 3 and Day minus 2 or according to institutional practice	2 days
PBSC reinfusion	Acetaminophen, Diphenhydramine	≥ 5x10 ⁶ cells/kg	IV	Day 0	Single administration

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Filgrastim or G-CSF type Neulasta® or equivalent	Per institutional guidelines	Filgrastim: 5 mcg/kg/day; G-CSF type Neulasta®: 6 mg; or according to institutional practice	Subcutaneous	For filgrastim: Daily, starting Day+5 until engraftment; For G-CSF type Neulasta®: on Day +2 after stem cell transplant; OR as per institutional practice	As needed for blood counts
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Arm B: Consolidation Therapy with RVD for 2 Cycles					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent)	25 mg/day	Oral	Beginning 60-110 days after PBSCT; Days 1-14 for 2 cycles (+ 7 day window is allowed between cycles)	21 days (3 weeks)
Bortezomib	Doses should be administered 70-72 hours apart	1.3 mg/m ²	3-5 second IV injection*	Beginning 60-110 days after PBSCT; Days 1, 4, 8, and 11 for 2 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits)	

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Dexamethasone	Take with food; recommended to be taken in the morning	10 mg/day	Oral	Beginning 60-110 days after PBSCT; Days 1, 2, 4, 5, 8, 9, 11 and 12 for 2 cycles (+ 7 day window is allowed between cycles and +1 day window for intra-cycle visits). Should be given day of and day after Velcade.	
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Arm B: Maintenance Therapy Until Disease Progression

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Lenalidomide	Recommended anti-thrombotic therapy (e.g., aspirin, enoxaparin or low molecular weight heparin type Innohep® or equivalent) and as clinically indicated	10 mg/day (months 1-3); 15 mg/day (months 4-12, if initially well tolerated)	Oral	Within 3 weeks of completing RVD consolidation; Days 1-28 until disease progression (+ 14 day and -7 day window is allowed between	28 days (4 weeks)

*Subcutaneous administration of Bortezomib may be considered in the event of \geq Grade 1-painful peripheral neuropathy; Study PI must approve such change in administration (see Section 6.3.4.3)

5.1 Pre-treatment Criteria

5.1.1 Initiation of New Cycle of RVD Therapy (Day 1)

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

f ANC \geq 1,000/ mm³ (growth factor support is permitted during cycles

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of RVD, with the exception of Cycle 1 Day 1; it is allowed on the same day as treatment administration)

- f* Platelet count $\geq 50,000/\text{mm}^3$ (platelet support is permitted during cycles of RVD; it is allowed on the same day as treatment administration)
 - * Patients' local lab results from the previous day may be used to fulfill criteria above only if performed within 24 hours from Day 1.**
- f* Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/other cardiac arrhythmia adverse event that may have occurred has resolved to \leq grade 1 severity.
- f* Any other lenalidomide or bortezomib-related adverse event that may have occurred has resolved to \leq grade 2 severity.
- f* Grade 1 with pain or grade 2 peripheral neuropathy requires dose modification, and grade 2 peripheral neuropathy with pain requires that bortezomib be held (See Section 6.3.4.3 for details).
- f* Herpes Zoster lesions are dry

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.

If lenalidomide is held during lenalidomide maintenance, and the patient comes back the following week to be re-evaluated, it is acceptable to only repeat the CBC with diff and the history and physical examination at that visit. However, please repeat the multiple myeloma restaging labs if more than 3 weeks has passed during a hold period.

The maximum amount of time for which a drug may be held due to toxicity is 6 weeks. However, treatment delay for more than 3 weeks (for any study treatment) will require authorization from the PI. If drug is held for more than 6 weeks due to toxicity, the participant will be removed from study treatment.

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- f* 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.
- f* 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.
- f* 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.
- f* If the new cycle is delayed due to bortezomib-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

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5.1.2 Intra-cycle RVD Therapy (Days 4, 8 and 11) (+ 1 day)

For intra-cycle dosing on Days 4, 8, and 11 (+ 1 day), the following criteria must be met:

- f* ANC \geq 750/mm³ (growth factor support is permitted)
- f* Platelet count \geq 30,000/mm³ (platelet support is permitted)

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*** Patients' local lab results from the previous day may be used to fulfill criteria above only if performed within 24 hours of specified visit date (Days 4, 8 and 11) (+ 1 day).**

Transfusion to support a platelet count of $\geq 50,000/\text{mm}^3$ at investigator discretion is permitted.

5.1.3 PBSC Collection and Transplant

Pre-treatment criteria for PBSC collection and PBSC transplant should be according to institutional standards.

5.1.4 Initiation of New Cycle of Lenalidomide Maintenance Therapy

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

- f* ANC $\geq 1,000/\text{mm}^3$ (growth factor support is permitted)
- f* Platelet count $\geq 50,000/\text{mm}^3$ (platelet support is permitted)
*** Patients' local lab results from the previous day may be used to fulfill criteria above only if performed within 24 hours from Day 1.**
- f* Any lenalidomide-related allergic reaction/hypersensitivity, neuropathy, or sinus bradycardia/other cardiac arrhythmia adverse event that may have occurred has resolved to \leq grade 1 severity.
- f* Any other lenalidomide-related adverse event that may have occurred has resolved to \leq grade 2 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. The maximum amount of time for which a drug may be held due to toxicity is 6 weeks. However, treatment delay for more than 3 weeks (for any study treatment) will require authorization from the PI. If drug is held for more than 6 weeks due to toxicity, the participant will be removed from study treatment.

Please also refer to section 6.3.4.2 for guidance regarding dosing modification guidelines for lenalidomide during maintenance.

5.2 Agent Administration

5.2.1 Initial Therapy with RVD for 1 Cycle for All Participants

5.2.1.1 Lenalidomide

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. Lenalidomide will be provided in accordance with the Celgene Corporation's

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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

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registered in, and must comply with, all requirements of the Revlimid REMS® program. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Participants will only receive treatment with lenalidomide for one cycle. Lenalidomide will be given as a single daily oral dose of 25 mg per day on days 1-14 followed by a 7-day rest period. A window of +7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Administration of lenalidomide will be at approximately the same time each day. Drug may be taken with or without food. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient can take the dose for that day. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. If a dose is missed, it should be taken as soon as possible on the same day. If a dose is vomited, the dose should not be made up and the participant should continue with the regular schedule of the drug at the next dose. A drug diary will be provided to participants to record oral administration of doses.

Participants who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Participants experiencing adverse events may need study treatment modifications (see Section 6.3).

The following document will be provided to all patients prior to receiving lenalidomide therapy:

- 1) The Lenalidomide Information Sheet (Appendix I) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment.
- 2) The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix II), which provides information regarding the risks to the fetus associated with lenalidomide exposure, the definition of Female of Childbearing Potential, pregnancy testing requirements for patients receiving lenalidomide who are females of childbearing potential, acceptable birth control methods for both female of childbearing potential and male patients receiving lenalidomide in the study, and requirements for counseling of all study patients receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide

5.2.1.2 Bortezomib

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Millennium Pharmaceuticals Incorporated will supply bortezomib for the study for the first 400 patients enrolled. Subsequent participants will receive bortezomab from the commercial supply. If the participant receives the drug from the commercial supply, this may lead to added costs for the participant or the participant's insurance company. Bortezomib will be administered at a dose of 1.3 mg/m². The appropriate amount of bortezomib will be drawn from the injection vial after reconstitution and administered as a 3-5 second IV injection/push followed by a standard saline flush or through a running IV line. Subcutaneous administration at a concentration of 2.5 mg/mL may be considered only in the presence of peripheral neuropathy (see Section 6.3.4.3), with approval granted by the Study PI.

Vials are for single use administration. Bortezomib should not be administered in participants who have a known allergy to bortezomib, boron or mannitol.

Participants will receive initial treatment with bortezomib for one cycle. Participants will receive bortezomib doses on Days 1, 4, 8 and 11 (+1 day window) of this cycle followed by a 10-day rest period. A window of +7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

Drug will be administered only to eligible participants under the supervision of the investigator or identified sub-investigator(s). Participants may be treated on an out-patient basis, if possible. 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 BSA. To calculate BSA, the DuBois formula is the preferred method. However, Mosteller is also acceptable. (Appendix IV). The dose should be calculated on Day 1 of the cycle, 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.

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.

5.2.1.3 Dexamethasone

Dexamethasone will be obtained by commercial supply in this study. This may lead to added costs for the participant or the participant's insurance company. It will be given as a single daily oral dose. Dexamethasone should be taken at approximately the same time each day. It is recommended that

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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.

Participants will receive treatment with dexamethasone for one cycle at 20 mg per day. Participants will receive dexamethasone doses on Days 1, 2, 4, 5, 8, 9, 11 and 12 of this cycle (+ 1 day window), followed by a 9-day rest period. A window of +7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.2 Arm A

5.2.2.1 RVD Cycles 2-3

5.2.2.1.1 Lenalidomide

Participants in Arm A will receive treatment with lenalidomide for two additional cycles prior to PBSC collection. See Section 5.2.1.1 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays). Dose modifications will be managed with 5mg capsules.

5.2.2.1.2 Bortezomib

Participants in Arm A will receive treatment with bortezomib for two additional cycles prior to PBSC collection. See Section 5.2.1.2 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. An intracycle window is allowed of +1 day. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.2.1.3 Dexamethasone

Participants in Arm A will receive treatment with dexamethasone for two additional cycles prior to PBSC collection. See Section 5.2.1.3 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. An intracycle window is allowed of +1 day. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.2.2 Autologous PBSC Collection 21 days after Cycle 3 of RVD

Following initial therapy with lenalidomide, bortezomib and dexamethasone, participants in Arm A will undergo collection of autologous PBSCs. The

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cyclophosphamide dose will be administered 21 days after the last dose of lenalidomide in cycle 3. A window of ± 7 days is allowed for scheduling. Participants will undergo stem cell mobilization with cyclophosphamide (IV) at a dose of 3 g/m². Filgrastim or G-CSF type Granocyte® or equivalent will be administered at a dose of 5 or 10 mcg/kg/day subcutaneously, according to institutional practice, starting at least 24 hours and not more than 48 hours after cyclophosphamide administration and continuing until the PBSC collection is complete. Filgrastim is preferred, but G-CSF type Granocyte® or equivalent is allowed for those sites who do not use filgrastim. For participants who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) (See Appendix XI) should be used for cyclophosphamide, filgrastim or G-CSF type Granocyte® or equivalent dosing. Beginning ten days after cyclophosphamide or start of G-CSF administration, according to institutional practice, participants must collect a minimum CD34 count of $\geq 5 \times 10^6$ cells/kg. In case of insufficient collection, collection of a minimum CD34 count of $\geq 2 \times 10^6$ cells/kg will be allowed.

If a participant is unable to collect a minimum of $\geq 2 \times 10^6$ cells/kg, it is suggested that an additional attempt at mobilization be performed using plerixafor. Plerixafor should be administered, in combination with filgrastim or G-CSF type Granocyte®, as follows:

- x Filgrastim or G-CSF type Granocyte® 10 mcg/kg/day subcutaneously every morning on mobilization days 1 through 5, and thereafter every morning until an adequate number of stem cells are collected
- x Plerixafor 0.24 mg/kg/day subcutaneously every evening beginning on mobilization day 4 and continuing daily for up to 4 consecutive days until an adequate number of stem cell are collected. The plerixafor dose should be based on actual weight.

Stem cell collection should be performed 10-11 hours after plerixafor administration.

If this additional mobilization attempt fails, a bone marrow sample may be taken and used in combination with PBSC.

If no stem cell product is obtained after all above attempts have been made, the participant will proceed with consolidation treatment with RVD cycles.

In the event of disease relapse or progression for participants on Arm A, an autologous PBSC transplant with high-dose melphalan is recommended, as described in Section 5.2.3.3. Induction will be variable depending on the response to the induction treatment and the time of relapse or progression.

5.2.2.3 Consolidation with RVD Cycles 4-8

Following PBSC collection, participants will undergo consolidation therapy with

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RVD. In case of grade 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain, bortezomib dose reduction is required (See Section 6.3.4.3 for detail). In case of grade 2 neuropathy with pain or neuropathy with a grade higher than 2 during consolidation treatment, hold bortezomib and administer lenalidomide and dexamethasone only for the remainder of consolidation.

5.2.2.3.1 Lenalidomide

Participants in Arm A will receive treatment with lenalidomide for five cycles during consolidation therapy. See Section 5.2.1.1 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays). Dose modifications will be managed with 5mg capsules.

5.2.2.3.2 Bortezomib

Participants in Arm A will receive treatment with bortezomib for five cycles during consolidation therapy. See Section 5.2.1.2 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. A window of +1 day is allowed for intra cycle visits. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.2.3.3 Dexamethasone

Participants in Arm A will receive treatment with dexamethasone for five cycles during consolidation therapy. Participants will receive dexamethasone **at 10 mg** per day on Days 1, 2, 4, 5, 8, 9, 11 and 12, followed by a 9-day rest period. See Section 5.2.1.3 all other details of administration. A window of +1 day is allowed for intra cycle visits. A window of + 7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.2.4 Lenalidomide Maintenance Therapy until Disease Progression

Celgene Corporation will supply lenalidomide as 5 mg capsules for oral administration. Drug will be shipped to the pharmacy at the study site in individual bottles. Lenalidomide investigational supplies are dispensed to the participant in individual bottles of capsules. Each bottle will identify the contents as study medication and bear the name of Celgene Corporation, quantity contained and standard caution statement as follows: Caution: New drug – Limited by Federal law to investigational use. Drug must be dispensed in the original packaging with the label clearly visible. For appropriate drug accountability, it is recommended that each bottle be marked with the institutional protocol number or Celgene tracking number (RV-MM-IFM-0444) upon receipt. Additional labels must not cover the Celgene label.

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Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Administration of lenalidomide will be at approximately the same time each day. Drug may be taken with or without food. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient can take the dose for that day. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. If a dose is 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.

Following completion of consolidation therapy, the participants in Arm A will undergo maintenance therapy with lenalidomide until disease progression. Participants should continue straight to maintenance therapy and may have up to 3 weeks following completion of RVD consolidation to begin maintenance. Drug will be taken orally at an initial dose of 10 mg/day, continuously for 28 days, of a 28-day cycle. A window of + 14 days and -7 days is allowed between lenalidomide treatment cycles. A dose increase to 15 mg/day will be allowed after 3 months at the initial dose, if the participant tolerates 10 mg/d without complication. In case of dose reduction during the previous cycle, and the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of lenalidomide. If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction of lenalidomide. Lenalidomide dose modifications are described in detail in Section 6.3 (Dose Modifications/Delays). Dose adaptations will be managed with 5 mg capsules.

If peripheral neuropathy worsens during maintenance therapy, lenalidomide dose will be reduced. If no improvement is seen with dose reduction of lenalidomide, the participant will be removed from study.

During maintenance therapy, lenalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules for 1 cycle of dosing. **Only enough lenalidomide for 1 cycle may be provided to the participant each cycle.**

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 6.3).

5.2.3 Arm B

5.2.3.1 RVD Cycles 2-3

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5.2.3.1.1 Lenalidomide

Participants in Arm B will receive treatment with lenalidomide for two additional cycles prior to PBSC collection. See Section 5.2.1.1 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays). Dose modifications will be managed with 5mg capsules.

5.2.3.1.2 Bortezomib

Participants in Arm B will receive treatment with bortezomib for two additional cycles prior to PBSC collection. See Section 5.2.1.2 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. A window of +1 day is allowed for intra cycle visits. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.3.1.3 Dexamethasone

Participants in Arm B will receive treatment with dexamethasone for two additional cycles prior to PBSC collection. See Section 5.2.1.3 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. A window of +1 day is allowed for intra cycle visits. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.3.2 Autologous PBSC Collection 21 days after cycle 3 of RVD

Following initial therapy with lenalidomide, bortezomib and dexamethasone, participants in Arm B will undergo collection of autologous PBSCs. This will occur 21 days after the last dose of lenalidomide in cycle 3. A window of ± 7 days is allowed for scheduling. See Section 5.2.2.2 for further detail of agent administration.

If no stem cell product is obtained after all above attempts have been made, the participant will proceed with consolidation treatment **with RVD for 5 cycles, instead of the planned 2 cycles.**

5.2.3.3 Autologous PBSC Transplant

Participants in Arm B will undergo conditioning for autologous PBSC transplant with melphalan. Melphalan will be administered either as a single dose of 200 mg/m² IV over 30 minutes on day minus 2 OR as a divided dose of 100 mg/m²/day IV over 2 days on day minus 2 and day minus 1 for a total dose of 200 mg/m². For participants who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) (See Appendix XI) should be used.

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A total of 5×10^6 cells/kg will be re-infused on day 0. A minimum of 2×10^6 cells/kg will be allowed in case of insufficient collection. Filgrastim will be administered at a dose of 5 mcg/kg/d subcutaneously, starting on day +5 following PBSC transplant. For participants who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) (See Appendix XI) should be used. Filgrastim will continue

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until ANC $\geq 1500/\text{mm}^3$ for 2 days or $\geq 5000/\text{mm}^3$ for one day, or per institutional guidelines. Filgrastim is preferred, but G-CSF type Neulasta® or equivalent is allowed for those sites who do not use filgrastim. G-CSF type Neulasta® should be administered at a dose of 6 mg subcutaneously, on day +2 following PBSC transplant. Administration of G-CSF per institutional practice is also permitted.

Supportive care will be administered as per institutional practice.

5.2.3.4 Consolidation with RVD for 2 cycles

Beginning 60-110 days after PBSC reinfusion, participants will undergo consolidation therapy with RVD. In case of grade 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain, bortezomib dose reduction is required (See Section 6.3.4.3 for detail). In case of grade 2 neuropathy with pain or neuropathy with a grade higher than 2 during consolidation treatment, hold bortezomib and administer lenalidomide and dexamethasone only for the remainder of consolidation

In discussion with the Principal Investigator and on a case-by-case basis, provisions may be made to start at a lower dose of lenalidomide for participants with inadequate hematologic parameters at 110 days following PBSC reinfusion.

5.2.3.4.1 Lenalidomide

Participants in Arm B will receive treatment with lenalidomide for two cycles during consolidation therapy. See Section 5.2.1.1 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays). Dose adaptations will be managed with 5 mg capsules.

5.2.3.4.2 Bortezomib

Participants in Arm B will receive treatment with bortezomib for two cycles during consolidation therapy. See Section 5.2.1.2 for details of administration. A window of + 7 days is allowed between RVD treatment cycles. A window of +1 day is allowed for intra cycle visits. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.3.4.3 Dexamethasone

Participants in Arm B will receive treatment with dexamethasone as a single daily oral dose of 10 mg per day for two cycles during consolidation therapy. Participants will receive dexamethasone doses on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each cycle, followed by a 9-day rest period. A window of + 7 days is allowed between RVD treatment cycles. See Section 5.2.1.3 for all other details of administration. A

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window of +1 day is allowed for intra cycle visits. Dose modification guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.2.3.5 Lenalidomide Maintenance Therapy until Disease Progression

Following completion of consolidation therapy, the participants in Arm B will undergo maintenance therapy with lenalidomide until disease progression. See Section 5.2.2.4 for details of administration. A window of + 14 days and -7 days is allowed between lenalidomide treatment cycles. Lenalidomide dose modifications are described in detail in Section 6.3 (Dose Modifications/Delays). Dose adaptations will be managed with 5 mg capsules.

If peripheral neuropathy worsens during maintenance therapy, lenalidomide dose will be reduced. If no improvement is seen with dose reduction of lenalidomide, the participant will be removed from study.

5.3 Definition of Dose-Limiting Toxicity

This section is Not Applicable.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Required Concomitant Therapy during cycles of RVD

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.

Thromboprophylaxis is required for all participants during cycles of RVD therapy. Participants may receive daily aspirin administration (81 or 325 mg), daily enoxaparin (40 mgs), or low molecular weight heparin (type Innohep® 4500 UI anti-Xa as needed) or equivalent to decrease the risk of thromboembolic complications. It is recommended that if the platelet count falls below $50,000/\text{mm}^3$, thromboprophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or above this level.

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

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Concomitant bisphosphonate therapy, according to institutional administration guidelines, is also required unless contraindicated.

5.4.2 Recommended Concomitant Therapy during cycles of RVD

It is strongly recommended that participants receive Pneumocystis Pneumonia prophylaxis using sulfamethoxazole and trimethoprim (1 tablet three times per week) or equivalent therapy and amoxicillin (1 g twice daily) or equivalent antibiotic therapy per institutional guidelines and at the discretion of the physician, unless the participant has a hypersensitivity to the agents.

It is also recommended that the following vitamins be administered with food as supplements 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.
- Cocoa butter: (rich in Vitamin E, xanthines and natural serotonins): Apply to extremities twice a day with gentle massage. Menthol-based creams can also be used for areas of numbness as needed.

Please note that all supplements (except emollient creams) should not be taken on days of bortezomib administration.

Other recommended therapy:

- Prophylactic antibiotics, according to individual institution guidelines.
- Mouth care is recommended.
- Erythropoietin is allowed.
- All supportive measures consistent with optimal participant care will be given throughout the study.

5.4.3 Concomitant Therapy during PBSC Collection and Transplant

During PBSC collection, participants will receive IV bolus of Mesna 600 mg/m² (or dose according to institutional practice) per dose on the day of cyclophosphamide administration. Mesna will be administered according to the following schedule or per institutional practice: 30 minutes prior to cyclophosphamide and 3, 6, and 9 hours after cyclophosphamide. A window of ± 30 minutes is allowed for administration of Mesna doses. The 9 hour dose may be given orally at double the IV dose (1200 mg/m²), and may be self-administered at home. If the 9 hour dose of Mesna is missed, it may be taken at a later time that same day. If the 9 hour dose of Mesna is vomited, it should not be retaken. A drug diary will be provided to

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participants to record oral administration of the 9 hour dose of Mesna. Alternatively, the Mesna dose may be mixed with the cyclophosphamide dose and administered IV over a period of 2 hours. For participants who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) should be used for dosing.

During PBSC transplant, participants must receive infection prophylaxis, hydration, and other supportive care according to standard institutional guidelines. Erythropoietin is also allowed.

5.4.4 Concomitant therapy during Lenalidomide Maintenance

Thromboprophylaxis is recommended and as clinically indicated (e.g., if the patient has experienced a thrombotic event during the study).

Other allowed therapy includes:

- Concomitant bisphosphonate therapy (Zometa® 4 mg/day monthly or equivalent), is permitted and can be administered according to institutional practice.
- G-CSF, as needed to support blood counts.
- Erythropoietin
- All supportive measures consistent with optimal participant care will be given throughout the study.

5.4.5 Other concomitant therapy

Radiotherapy for pain control of existing bone disease should be discussed with the study PI on a case by case basis.

5.5 Duration of Therapy/Criteria for early treatment discontinuation

Duration of therapy (RVD cycles, stem cell collection and transplant, maintenance) will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue for a total of 8 cycles of RVD therapy followed by 1 year of lenalidomide maintenance therapy (initial therapy and Arm A) or for a total of 5 cycles of RVD therapy (including stem cell transplant), followed by 1 year of lenalidomide maintenance therapy (initial therapy and Arm B), or until one of the following criteria applies:

- x Disease progression,
- x Treatment delay for toxicity for more than 6 weeks
- x Investigator judgment
- x Pregnancy or suspected pregnancy
- x Unacceptable adverse event(s)/Serious adverse event(s)
- x Participant decision*
- x Participant withdrawal of consent

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- x Non-protocol therapy for multiple myeloma or for other malignancy
- x Death

*Agrees to the use of collected data and to undergo follow-up assessments.

Patients who discontinue the treatment for a reason other than progressive disease (criteria listed above) will undergo disease assessments until disease progression. Once patient has progressed, he/she will be followed for survival data only.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed below applies:

- x Participant decision*
- x Participant withdrawal of consent
- x Participant registered but not randomized
- x Death

*Agrees to the use of previously collected data.

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. There is no exclusion (wash-out) period before start of another treatment.

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.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator: Paul Richardson at [REDACTED] (telephone) or [REDACTED]

5.7 Duration of FollowUp

Participants will be followed every two months (+/- 3 weeks) during the follow-up period after completion of treatment until disease progression or for up to 3 years after the last patient has been enrolled. Participants removed from study treatment for unacceptable adverse events will be followed for resolution or stabilization of the adverse event. Participants removed from study treatment for reasons other than progressive disease will be followed until disease progression unless the participant withdraws consent for follow-up. Following disease progression, a participant may be followed-up by telephone contact for survival. There is no exclusion (wash-out) period at the end of the study before start of another treatment.

5.8 Recommended treatment for relapse

5.8.1 For patients enrolled in Arm A: Induction will be variable depending on the response to the initial induction treatment and the time of relapse/progression.

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A stem cell transplant with high-dose melphalan conditioning is recommended.

The total dose of melphalan will depend on the patient's age at the time of relapse. The following doses are recommended:

- ” 65 years: 200 mg/m²
- > 65 years: 140 mg/m²

5.8.2 For patients enrolled in Arm B:

The relapsed treatment will be variable depending on the response to the initial induction treatment and the time of relapse/progression.

6 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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 after completion of therapy, with the exception of those participants who withdraw from treatment during RVD cycles, in whom adverse events will be collected until 60 days following the last treatment administration. Participants continuing to experience toxicity beyond the follow-up periods noted above may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities/Adverse Events

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

6.1.1 CAEPRs for CTEP-Supplied Investigational Agent(s)

This section is not applicable to the study.

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6.1.2 Adverse Event Lists for Lenalidomide

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

Events that have occurred in $\geq 10\%$ of individuals treated with lenalidomide include neutropenia, anemia, thrombocytopenia, fatigue, 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, and dyspnea.

Events that have occurred in $\geq 1\%$ of individuals treated with lenalidomide include risk of DVT, PE, and blood clots that could lead to stroke, heart attack, or organ failure, febrile neutropenia, atrial fibrillation, pneumonia or lung infections, sepsis, dehydration and renal failure.

Events that have occurred in $< 1\%$ of individuals treated with lenalidomide include rare treatment-emergent adverse events of angioedema, serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or an allergic skin reaction similar to that seen with thalidomide, tumor lysis syndrome (TLS), tumor flare reaction (TFR), and rhabdomyolysis. In addition, lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Patients will be instructed to inform their doctor if taking digoxin.

There may be an increased risk of second cancers in patients who are on lenalidomide maintenance therapy after a bone marrow transplant.

6.1.3 Adverse Event List for Bortezomib

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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* ^r , bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial diseaser, cardiopulmonary failurer
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, 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	

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Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class	
Observed Incidence	Preferred Term
Uncommon	Hyperbilirubinaemia, hepatitis* r
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster* (may cause lesions)
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bacteraemia*, 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 r , varicella, empyema r , fungal oesophagitis r
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*

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Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class	
Observed Incidence	Preferred Term
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 ^r
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 ^r
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE[®] (bortezomib) for Injection Investigator's Brochure Edition 14.

Most common = \geq 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

* Fatal outcomes have been reported.

^r Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

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**Reports of Adverse Reactions From Postmarketing
Experience**

System Organ Class Preferred Term	Observed Incidence ^a
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease ^b	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare

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Skin and subcutaneous system disorders

Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE[®] (bortezomib) for Injection Investigator's Brochure Edition 15.

- a Incidence is assigned using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1000$ and $< 1/100$); rare ($\geq 1/10,000$ 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.

6.1.4 Adverse Event List for Dexamethasone

Events that have occurred in 10-15% of individuals treated with dexamethasone include increased appetite, weight gain, sleep disturbance, hypertension, fluid retention, ankle swelling, bruising, infection, mood changes, slow wound healing, depression, and hyperglycemia, which may lead to fatigue, weight loss, excessive thirst and frequent urination.

Events that have occurred in 1-9% of individuals treated with dexamethasone include 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.

Events that have occurred in <1% of individuals treated with dexamethasone include blurred vision, personality changes, stomach ulcers with bleeding that may cause hematemesis, blood in the stool and abdominal pain.

Other, less frequent, events may include bowel perforation, irritation and bleeding of the esophagus, heart failure, allergic reaction that may lead to facial redness, shortness of breath, abdominal cramps and hypotension, convulsions, brain swelling, dizziness, cataracts, glaucoma and increased blood pressure in the eye, development of diabetes, pancreatic inflammation, abdominal swelling, hypokalemia, DVT or PE, malaise, swelling and/or redness of skin, allergic skin reactions, itching, hirsutism, muscle weakness or loss of muscle mass, rupture of tendons, menstrual cycle disturbances, facial puffiness, leading to the appearance of a "moon face" hormonal disturbances, and hiccups.

6.1.5 Adverse Event List for Stem Cell Collection

Events that have occurred in individuals undergoing stem cell collection include the following: tingling of the lips or fingers, and rarely, nausea, vomiting or muscle tightness, due to a sterile anticoagulant used to prevent

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blood from clotting in the collection machine; hypotension, hypertension or slow pulse; thrombocytopenia or anemia; return of migraine headaches (for participants with a history of migraines); serious or life-threatening reactions include allergic reactions, infections, seizures, air embolism or arrhythmias, but are extremely rare.

In addition, participants receive anticoagulant solution, which contains dextrose, during the collection procedure. Participants with a history of heart failure or kidney disease may retain some of this fluid causing increased weight or swelling of hands or feet, or shortness of breath. Participants with diabetes may experience hyperglycemia.

Participants on an Angiotensin Converting Enzyme (ACE) inhibitor may experience low blood pressure during the collection procedure, and these should not be taken before collection.

6.1.6 Adverse Event List for PBSC Transplant

The following is a list of adverse events that are associated with stem cell transplant.

Events that have occurred in >50% of individuals who have undergone stem cell transplant include neutropenia, thrombocytopenia, pancytopenia, anemia, fever and/or chills, flu-like symptoms, fatigue, loss of appetite and/or weight loss, diarrhea, nausea, vomiting, partial hair loss or thinning of hair, and rash or hives.

Events that have occurred in 1-50% of individuals who have undergone stem cell transplant include bone pain, inflammation of the throat and tongue, hyponatremia that may increase the risk of confusion or seizures, painful or difficult urination, bladder irritation, hematuria, abnormal kidney function or kidney damage, and abnormal thyroid function.

Events that have occurred in <1% of individuals who have undergone stem cell transplant include severe allergic reaction that may lead to tachycardia, wheezing, hypotension, sweating, swelling of the throat, facial rash, heart damage, bladder damage, lung inflammation or scarring of the lung, abnormal liver function, jaundice or liver failure, failure to engraft, life-threatening infection, hemolysis, mouth or throat sores, gastrointestinal bleeding, and death.

6.1.7 Study Procedure Risks

In addition to the risks of study drug, needle sticks for blood samples and/or bone marrow procedures may cause pain, bruising and rarely, infection at the site where blood is drawn.

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6.2 Hematologic Toxicity Management

Neutropenia: may be managed by G-CSF administration.

Anemia: may be managed by blood transfusion.

Thrombocytopenia: may be managed by platelet or blood transfusion.

6.3 Dose Modifications/Delays

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 CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). Dose modifications or delays will be done based on the toxicity experienced during a cycle of therapy or newly encountered on day 1 of each cycle. The participant may continue on therapy if the toxicity can be managed according to the dose modification guidelines as outlined below.

Once one of the treatment doses (lenalidomide, bortezomib, or dexamethasone) is reduced for toxicity, no re-escalation will be allowed with the exception of lenalidomide in case of renal insufficiency during RVD therapy. Reduction and/or temporary suspension of one agent and not the others is appropriate if toxicity is related primarily to one of the agents.

Drug may be held for no more than 6 weeks due to toxicity. However, treatment delay for more than 3 weeks (for any study treatment) will require authorization from the PI. During RVD cycles, if all three concerned treatments are held for more than 6 weeks, the patient will be withdrawn from the study treatment phase and will be followed until disease progression.

During RVD cycles 1-8 (Arm A) and RVD cycles 1-3 (Arm B), if all three drugs are held at the same time and two or more consecutive doses of bortezomib are missed, the patient may restart the cycle at Day 1 of treatment. **Participating sites should contact the study PI for approval prior to any RVD cycle restart.**

6.3.1 Dose Reduction Steps for Lenalidomide during RVD therapy

Starting dose of lenalidomide	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction	4 th Dose Reduction	5 th Dose Reduction
25 mg PO qd x 14 days every 21 days	20 mg PO qd x 14 days every 21 days	15 mg PO qd x 14 days every 21 days	10 mg PO qd x 14 days every 21 days	5 mg PO qd x 14 days every 21 days	Discontinue lenalidomide

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- x If the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of lenalidomide.

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- x 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.
- x 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 a one-level dose reduction.

6.3.2 Dose Reduction Steps for Bortezomib

Starting dose of bortezomib	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction
1.3 mg/m ² on days 1, 4, 8, and 11	1 mg/m ² on days 1, 4, 8, and 11	0.7 mg/m ² on days 1, 4, 8, and 11	Discontinue bortezomib

Dose modifications below 0.7 mg/m² twice weekly (e.g., to once weekly) will require prior PI permission and documentation. See Table 6.3.4.3 for separate dose modification guidelines for peripheral neuropathy.

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- x In case of dose reduction during initial RVD therapy, the participant will receive the reduced dose levels (the last level applied during initial therapy)
- x 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.
- x 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.

6.3.3 Dose Reductions Steps for Dexamethasone

Starting dose of dexamethasone	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction
20 mg/d on days 1, 2, 4, 5, 8, 9, 11 and 12	10 mg/d on days 1, 2, 4, 5, 8, 9, 11 and 12	5 mg/d on days 1, 2, 4, 5, 8, 9, 11 and 12	Discontinue dexamethasone

In case of dose reduction during initial RVD therapy, the participant will receive the reduced dose levels (the last level applied during initial therapy).

6.3.4 Dose Modification Guidelines

Each Adverse Event should be attributed to a specific study drug if possible so that dose modifications can be made accordingly. **Reduction and/or temporary suspension of one agent and not the others is appropriate if toxicity is related primarily to one of the agents.** Further clarification can be obtained in consultation

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with the PI. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity guidelines. Drug may be held for no more than 6 weeks to allow resolution of toxicity. The same dose modification guidelines will apply to maintenance cycles unless otherwise noted.

6.3.4.1 Drug Related Adverse Event Dose Modification Guidelines during RVD therapy

CTCAE Category	AGENTS	Toxicity During a Cycle
<p>≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5C) or Grade 4 neutropenia</p> <p>and/or</p> <p>Platelet count < 10,000/mm³ or G3 thrombocytopenia with bleeding</p>	<p>Lenalidomide</p>	<p>Hold therapy (interrupt). Follow CBC on day 4, 8, 11 (+1 day)</p> <p>Use of G-CSF is allowed and recommended.</p> <p>If neutropenia resolved to ≤ grade 2, resume lenalidomide with one level dose reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.</p> <p>If thrombocytopenia resolved to ≤ grade 2, resume lenalidomide with one dose level reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.</p>
	<p>Bortezomib</p>	<p>Hold therapy</p> <p>Use of platelet transfusion is allowed.</p> <p>If thrombocytopenia resolved to ≤ grade 2 and neutropenia resolves to ≤ grade 2 and if the Day 4,8 or 11 (+1 day) dose is held, that dose should be omitted and treatment should continue with next planned dose (i.e., if Day 8 is skipped, the next dosing day is Day 11) resume bortezomib at same dose.</p> <p>If thrombocytopenia resolved to ≤ grade 2 and neutropenia resolves to ≤ grade 2 and if any 2 or more doses were held due to toxicity (either consecutive or two or more in one cycle), then reduce the bortezomib dose by one level.</p>
<p>Non-blistering rash</p> <p>Grade 3</p>	<p>Lenalidomide</p>	<p>Hold (interrupt dose). Follow weekly.</p> <p>If the toxicity resolves to ≤ grade 1, restart lenalidomide with one level dose reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.</p>
<p>Non-blistering rash</p> <p>Grade 4</p>		<p>Discontinue lenalidomide study drug for grade 4 toxicity.</p>
<p>Desquamating (blistering) rash-any Grade or Erythema multiforme ≥ Grade 3</p>	<p>Lenalidomide</p>	<p>Discontinue lenalidomide study drug.</p>
<p>Sinus bradycardia/ other cardiac arrhythmia Grade 2</p>	<p>Lenalidomide</p>	<p>Hold (interrupt) dose. Follow at least weekly.</p> <p>If the toxicity resolves to ≤ grade 1 restart at next lower dose</p>

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Short title: Phase III Study of RVD versus RVD plus auto SCT in newly diagnosed MM participants

Version Date: November 30, 2016

		level.
Sinus bradycardia/ other cardiac arrhythmia Grade ≥ 3		Discontinue lenalidomide study drug for grade ≥ 3
Allergic reaction or hypersensitivity Grade 2-3	Lenalidomide	Hold (interrupt) dose. Follow at least weekly. If toxicity resolves to \leq grade 1 restart at next lower dose level
Allergic reaction or hypersensitivity Grade 4		Discontinue lenalidomide study drug.
Hyperthyroidism or Hypothyroidism	Lenalidomide	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide at investigator's discretion. For toxicity attributable to lenalidomide, reduce the dose by one dose level.
Peripheral Neuropathy	Bortezomib	See table 6.3.4.3
Neuropathy Grade 3	Lenalidomide	Hold (interrupt) dose. Follow at least weekly. If the toxicity resolves to \leq grade 1, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4		Discontinue lenalidomide.
Herpes Zoster reactivation any grade	Bortezomib	Hold therapy until lesions are dry. Increase antiviral from prophylactic to therapeutic dose for 10 days or until lesions are healing and dry.
Venous Thrombosis/embolism \geq Grade 3	Lenalidomide/ Bortezomib	Hold dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
Moderate renal impairment 30 μ Creat Clear<50 ml/min	Lenalidomide	10mg once daily. The dose may be escalated to 15mg/d after 2 cycles if the patient is tolerating the treatment
Severe renal impairment Creat Clear<30 ml/min (not requiring dialysis)		15mg every other day. The dose may be escalated to 10mg/d if the patient is tolerating the treatment.
Severe renal impairment Creat Clear<30 ml/min (requiring dialysis)		5mg once daily. On dialysis days, the dose should be administered following dialysis. Alternate etiology for severe renal impairment should be evaluated.
Other lenalidomide or bortezomib related non-hematologic toxicity Grade ≥ 3	Lenalidomide Bortezomib	Determine attribution of toxicity and hold appropriate therapy. If toxicity resolves to \leq grade 2, resume therapy with one level dose reduction.

*Patients with mild hepatic impairment (bilirubin < 1.5 u ULN) do not require a starting dose adjustment. In cases where a patient develops hepatic impairment on study, further investigation is needed to determine the cause of their hepatic impairment; in some instances, drug discontinuation may be necessary if the Investigator feels a perturbation in liver enzymes and/or bilirubin is related to bortezomib.

If a patient is no longer receiving Velcade at day 4 and 11, then the patient does not need to be brought in to complete the AE assessments and hematology labs on those days.

6.3.4.2 Dose Modifications for Lenalidomide during Maintenance Therapy

CTCAE Category	Toxicity During a Cycle
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<p>Hematologic Dose Modifications</p> <p>Absolute neutrophil count < 500/mm³</p>	<p>If with 15 mg/day, lenalidomide will be held and resumed at a dose of 10 mg/day when ANC \geq 500/mm³ and/or platelet count is \geq 30,000/mm³</p>
<p>and/or</p> <p>Platelet count < 30,000/mm³</p>	<p>If with 10 mg/day, lenalidomide will be held and resumed at a dose of 5 mg/day when ANC \geq 500/mm³ and/or platelet count is \geq 30,000/mm³.</p> <p>If with 5 mg/day, lenalidomide will be held and resumed at a dose of 5 mg/day for 21 of 28 days when ANC \geq 500/mm³ and/or platelet count is \geq 30,000/mm³.</p> <p>If with 5 mg/day for 21 of 28 days, lenalidomide will be discontinued definitively.</p> <p>Please note that ANC should be >1000 to initiate a new cycle but the dose is not reduced unless ANC <500. Please also refer to section 5.1.4 as well.</p>
<p>Neurologic Toxicity \geq Grade 3</p>	<p>If with 15 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 10 mg/day.</p> <p>If with 10 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 5 mg/day.</p> <p>If with 5 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 5 mg/day for 21 of 28 days.</p> <p>If with 5 mg/day for 21 of 28 days, lenalidomide will be discontinued definitively.</p>
<p>Cardiac Toxicity \geq Grade 2</p>	<p>If with 15 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 10 mg/day.</p> <p>If with 10 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 5 mg/day.</p> <p>If with 5 mg/day, lenalidomide will be held. If toxicity resolves to \leq grade 1, lenalidomide may be resumed at a dose of 5 mg/day for 21 of 28 days.</p> <p>If with 5 mg/day for 21 of 28 days, lenalidomide will be discontinued definitively.</p>
<p>Renal Failure</p> <p>30 ml/min \leq Creat Clear < 50 ml/min</p> <p>Creat Clear < 30 ml/min</p>	<p>Hold therapy.</p> <p>If creat clear \geq 50 ml/min, resume lenalidomide with one level dose reduction.</p> <p>Discontinue lenalidomide study drug. Alternate etiology for severe renal impairment should be evaluated.</p>

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Other Non-Hematologic Toxicity: Grade 3	Hold lenalidomide until toxicity resolves to \leq grade 2 and contact study PI. After consultation with the study PI, drug may be resumed at lower dose level, as described above.
Other Non-Hematologic Toxicity: Grade 4	Discontinue lenalidomide and contact study PI.

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

The neurotoxicity-directed questionnaire (Appendix IX) 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.

Please also refer to section 5.2.2.3 and section 5.2.23.4 for guidance regarding skipping consolidation therapy after mobilization or transplant.

Recommended Dose Modification for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy				
	If patient develops Grade 1 painful or Grade 2 (interfering with function but not with activities of daily living) PN	If G1 painful or G2 PN persists despite first dose reduction	If patient develops Grade 2 painful or Grade 3 (interfering with activities of daily living) PN	If patient develops Grade 4(sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis) PN
Starting dose of bortezomib	1st Dose Reduction	2nd Dose Reduction	Withhold bortezomib until toxicity resolves (Grade 1 or less)	Discontinue bortezomib
1.3 mg/m ² on days 1, 4, 8, and 11	1 mg/m ² on days 1, 4, 8, and 11	1.0 mg/m ² once per week (Can be IV or SC)	Resume dosing at 0.7 mg/m ² once per week (Can be IV or SC)	Discontinue bortezomib permanently
Grading based on CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE): http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .				

6.3.4.4 Dexamethasone Dose Modifications

Dexamethasone dose modifications		
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.

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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	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level.

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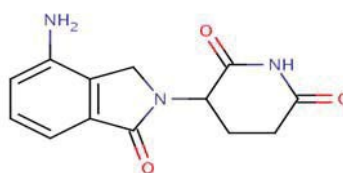
	interfering with function +/- interfering with activities of daily living	Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Lenalidomide (REVLIMID®)

7.1.1 Description

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



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

The empirical formula for lenalidomide is C₁₃H₁₃N₃O₃, and the gram molecular weight is 259.3.

7.1.2 Form

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

Lenalidomide is available for this study as 5 and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

7.1.3 Storage and Stability

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At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Lenalidomide should be stored according to manufacturer instructions reported on labels and storage temperature should not exceed 25°C. Sites must contact Celgene in the event of a temperature excursion via email at imsdistribution@celgene.com.

7.1.4 Handling

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

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

7.1.5 Availability

Celgene Corporation will supply lenalidomide, as 5 mg and 25 mg capsules for oral administration. Lenalidomide is an investigational agent and will be supplied free-of-charge. Drug will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for 1 cycle of dosing.

7.1.6 Preparation

Lenalidomide investigational supplies are dispensed to the participants in individual bottles of capsules. Each bottle will identify the contents as study medication and bear the name of Celgene Corporation, quantity contained and standard caution statement: Caution: New drug – Limited by Federal law to investigational use. Lenalidomide must be dispensed in the original packaging with the label clearly visible. For appropriate drug accountability, it is recommended that each bottle be marked with the institutional protocol number or Celgene tracking number (RV-MM-IFM-0444) upon receipt. Additional labels must not cover the Celgene label. Lenalidomide is an oral drug and does not require specific preparation details. **Only enough lenalidomide for 1 cycle may be provided to the participant at the beginning of each cycle.**

7.1.7 Administration

During initial therapy, each participant will be given lenalidomide as a single daily oral dose on Days 1-14 followed by a 7-day rest period, for 1 cycle.

In Arm A, each participant will be given lenalidomide as a single daily oral dose on Days 1-14 followed by a 7-day rest period, for two additional cycles, as initial therapy. Following collection of peripheral blood stem cells, participants in Arm A will then be given lenalidomide as a single daily oral dose on Days 1-14 followed by a 7-day rest period, for five cycles, as consolidation therapy. After completing consolidation therapy, participants in Arm A will receive lenalidomide as a single daily oral dose

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continuously for 28 days of a 28-day cycle, until disease progression. Participants will receive an initial dose of 10 mg/day. If this dose is well tolerated after three months at 10 mg/day, the participant may be dose escalated to 15 mg/day.

In Arm B, each participant will be given lenalidomide as a single daily oral dose on Days 1-14 followed by a 7-day rest period, for two additional cycles, as initial therapy. Following collection and reinfusion of peripheral blood stem cells, participants in Arm B will then be given lenalidomide as a single daily oral dose on Days 1-14 followed by a 7-day rest period, for two cycles, as consolidation therapy. After completing consolidation therapy, participants in Arm B will receive lenalidomide as a single daily oral dose continuously for 28 days of a 28-day cycle, until disease progression. Participants will receive an initial dose of 10 mg/day. If this dose is well tolerated after three months at 10 mg/day, the participant may be dose escalated to 15 mg/day.

A window of + 7 days is allowed between cycles of RVD.

A window of + 14 days and -7 days is allowed between cycles of lenalidomide maintenance.

At all times when dispensing lenalidomide protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants. Participants will be asked to bring any unused drug and empty drug containers to the study site at their next scheduled visit. Study staff will count and record the number of used and unused drug at each visit.

7.1.8 Ordering

The investigator or designee will order drug from Celgene Corporation, according to the ordering instructions provided by Celgene.

7.1.9 Accountability

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

7.1.10 Destruction and Return

Celgene will instruct the investigator on the return or destruction of unused lenalidomide. If any lenalidomide is lost or damaged, its disposition should be documented in the source documents. Lenalidomide supplies will be retained at the clinical site pending instructions for disposition by Celgene. Participants will be instructed to return all bottles (empty bottles or unused capsules).

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If instructed to do so by Celgene, empty bottles and unused supplies of lenalidomide should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

7.2 Bortezomib (VELCADE®)

7.2.1 Description

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

7.2.2 Form

Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in sterile, single use vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol. Bortezomib is manufactured by Millennium Pharmaceuticals Incorporated.

7.2.3 Storage and Stability

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Vials containing lyophilized bortezomib for Injection should be stored according to label requirements. Store at USP Controlled Room Temperature which is 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F). U.S. sites are instructed to use the following procedure in the event of a product complaint. 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 at 1-866-835-2233 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.

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 the sponsor will notify the investigator should this information be revised during the conduct of the study.

7.2.4 Compatibility

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Each vial of bortezomib for **intravenous administration** should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Each vial of bortezomib for **subcutaneous administration** should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 1.4 mL (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL.

7.2.5 Handling

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

7.2.6 Availability

Bortezomib is a commercially available agent and will be supplied free-of-charge from Millennium Pharmaceuticals Incorporated for the first 400 participants enrolled on this study. The remaining participants will receive Bortezomib from the commercial supply.

7.2.7 Preparation

Each vial of bortezomib for **intravenous administration** should be reconstituted in aseptic conditions (e.g., under a laminar flow biological cabinet (hood)) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. The reconstituted solution should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

****Attention**** The drug reconstitution for intravenous bortezomib **differs** from that of subcutaneous bortezomib, even though the same-sized commercial

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drug vial is used for both modes of administration. Please be sure that you have the correct route of administration and correct reconstitution.

Each vial of bortezomib for **subcutaneous administration** should be reconstituted in aseptic conditions (e.g., under a laminar flow biological cabinet (hood)) within eight hours before dosing with 1.4 mL (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. The reconstituted solution should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

7.2.8 Administration

During initial therapy, each participant will receive bortezomib as a 3-5 second IV push; subcutaneous administration may be allowed in the presence of \geq G1-painful peripheral neuropathy or if participants demonstrate poor peripheral veins (SQ administration due to poor venous access requires approval from the Study PI). Participants will receive bortezomib on days 1, 4, 8, and 11 (+1 day intracycle window), followed by a 10-day rest period, for 1 cycle.

In Arm A, each participant will receive bortezomib as a 3-5 second IV push or via subcutaneous administration (in presence of \geq G1-painful peripheral neuropathy) or if participants demonstrate poor peripheral veins (SQ administration due to poor venous access requires approval from the Study PI). Participants will receive bortezomib on days 1, 4, 8, and 11 (+1 day intracycle window), followed by a 10-day rest period, for two additional cycles, as initial therapy. Following collection of peripheral blood stem cells, participants in Arm A will then receive bortezomib as a 3-5 second IV push or via subcutaneous administration (in presence of \geq G1-painful peripheral neuropathy or compromised venous access- with Study PI approval) on Days 1, 4, 8 and 11 (+1 day intracycle window), followed by a 10-day rest period, for 5 cycles, as consolidation therapy.

In Arm B, each participant will receive bortezomib as a 3-5 second IV push or via subcutaneous administration (in presence of \geq G1-painful peripheral neuropathy or compromised venous access- with Study PI approval) on Days 1, 4, 8, and 11 (+1 day intracycle window), followed by a 10-day rest period, for two additional cycles, as initial therapy. Following collection and reinfusion of peripheral blood stem cells, participants in Arm B will then receive bortezomib as a 3-5 second IV push or via subcutaneous administration (in presence of \geq G1-painful peripheral neuropathy or compromised venous access- with Study PI approval) on Days 1, 4, 8 and 11 (+1 day

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intracycle window), followed by a 10-day rest period, for 2 cycles, as consolidation therapy.

For all treatment arms, 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.

A window of + 7 days is allowed between RVD treatment cycles. A +1 day intracycle window is allowed.

Drug will be administered only to eligible participants under the supervision of the investigator or identified sub-investigator(s). Participants may be treated on an outpatient basis, if possible. The pharmacist will prepare the drug under aseptic condition. The amount (in mg) of drug to be administered will be determined based on BSA. BSA is to be calculated based on body weight using the DuBois formula (Appendix IV). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a participant experiences a notable change in weight (eg, loss or gain of 5% body weight) within a cycle, as determined by an unscheduled weight assessment, then that participant's dose should be recalculated at that time.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds followed by a standard saline flush or through a running IV line; bortezomib may also be administered subcutaneously (at a concentration of 2.5 mg/mL) in presence of \geq G1-painful peripheral neuropathy or compromised venous access (SQ due to poor venous access requires approval from the Study PI). Vials are for single use administration.

7.2.9 Ordering

The investigator or designee will order drug supply from Millennium Pharmaceuticals for the first 400 participants enrolled globally on this study, according to the ordering instructions provided by Millennium. For subsequent participants, the investigator or designee will order drug supply from commercial supply.

7.2.10 Accountability

For the drug supplied by Millennium, the investigator or designee must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI DAR Form or another comparable drug accountability form. (See the CTEP home page at <http://ctep.cancer.gov> for the Procedures for Drug Accountability and Storage or to obtain a copy of the DAR.)

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It is not DF/HCC practice to record lot numbers for drugs from the commercial supply, so the drug accountability form will not be used for commercial drug.

7.2.11 Destruction and Return

Millennium will instruct the investigator on the destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Millennium.

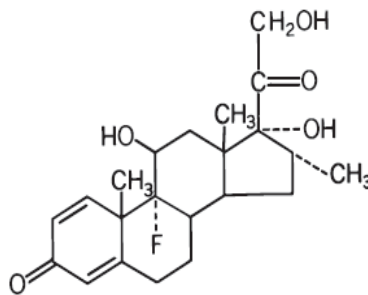
If instructed to do so by Millennium, unused supplies of bortezomib should be destroyed according to institutional policies. Destruction will be documented in the DAR Form.

7.3 Dexamethasone

7.3.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione. The empirical formula is C₂₂H₂₉FO₅ and the structural formula is:



Dexamethasone is stable in air and almost insoluble in water.

7.3.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) 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.

7.3.3 Storage and Stability

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At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Dexamethasone should be stored at controlled room temperature, 68-77°F (20-25°C) and not frozen, and according to label requirements.

7.3.4 Handling

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

7.3.5 Availability

Dexamethasone supply will be obtained through commercial supply.

7.3.6 Preparation

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

7.3.7 Administration

During initial therapy, each participant will receive dexamethasone as a single oral daily dose of 20 mg/d on Days 1, 2, 4, 5, 8, 9, 11 and 12 (+1 day intracycle window), followed by a 9-day rest period, for 1 cycle, as initial therapy.

In Arm A, each participant will receive dexamethasone as a single oral daily dose of 20 mg/d on Days 1, 2, 4, 5, 8, 9, 11 and 12 (+1 day intracycle window), followed by a 9-day rest period, for two additional cycles, as initial therapy. Following collection of peripheral blood stem cells, participants in Arm A will then receive dexamethasone as a single oral daily dose of 10 mg/d on Days 1, 2, 4, 5, 8, 9, 11 and 12 (+1 day intracycle window), followed by a 9-day rest period, for 5 cycles, as consolidation therapy.

In Arm B, each participant will receive dexamethasone as a single oral daily dose of 20 mg/d on Days 1, 2, 4, 5, 8, 9, 11 and 12 (+1 day intracycle window), followed by a 9-day rest period, for two additional cycles, as initial therapy. Following collection and reinfusion of peripheral blood stem cells, participants in Arm B will then receive dexamethasone as a single oral daily dose of 10 mg/d on Days 1, 2, 4, 5, 8, 9, 11 and 12 (+1 day intracycle window), followed by a 9-day rest period, for 2 cycles, as consolidation therapy.

A window of + 7 days is allowed between RVD treatment cycles.

7.3.8 Ordering

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

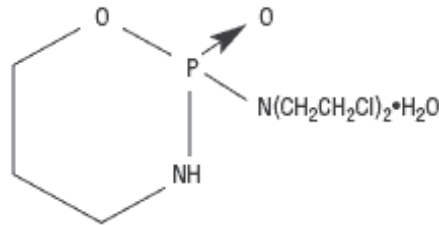
7.3.9 Destruction and Return

At the end of the study, unused supplies of dexamethasone should be destroyed and documented according to institutional policies.

7.4 Cyclophosphamide (Cytoxan®)

7.4.1 Description

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



An activated form of cyclophosphamide, phosphoramidate mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as to inhibition of protein synthesis. Cyclophosphamide is a potent immunosuppressant. It also causes marked and persistent inhibition of cholinesterase activity.

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic

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effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

7.4.2 Form

Cyclophosphamide for injection, USP, is a sterile white powder containing cyclophosphamide monohydrate. Cyclophosphamide is supplied in vials for single-dose use and is available as Intravenous Powder for Solution in the following strengths: 1 g, 2 g, 500 mg.

7.4.3 Storage and Stability

Reconstituted solutions of lyophilized cyclophosphamide and solutions prepared with bacteriostatic water are chemically and physically stable for 24 hours at room temperature or for 6 days in the refrigerator. Store vials at or below 77° F (25° C). Do not use cyclophosphamide vials if there are signs of discoloration.

7.4.4 Compatibility

The osmolarities of solutions of cyclophosphamide constituted with water and 0.9% sterile sodium chloride solution are as follows: 5 mL water per 100 mg cyclophosphamide (anhydrous) has osmolarity of 74 mOsm/L; 5 mL 0.9% sterile sodium chloride solution per 100 mg cyclophosphamide (anhydrous) has osmolarity of 374 mOsm/L.

7.4.5 Handling

Procedures for proper handling and disposal of anticancer drugs should be considered.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing cyclophosphamide sterile powder for injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

7.4.6 Availability

Cyclophosphamide supply will be obtained through commercial supply.

7.4.7 Preparation

Cyclophosphamide must be reconstituted using 0.9% sterile sodium chloride (NS) or Sterile Water for Injection (SWFI) as follows: 25 ml NS or SWFI for 500 mg of cyclophosphamide, 50 ml NS or SWFI for 1gm cyclophosphamide, 100 ml NS or SWFI for 2 gm cyclophosphamide.

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Cyclophosphamide may be prepared for parenteral use by infusion using either of the following dilution methods or according to standard institutional practice:

1. Cyclophosphamide reconstituted with 0.9% sterile sodium chloride may be infused following further dilution in the following:
Dextrose Injection, USP (5% dextrose)
Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
5% Dextrose and Ringer's Injection
Lactated Ringer's Injection, USP
2. Cyclophosphamide sterile powder may be prepared for parenteral use by infusion by adding Sterile Water for Injection, USP. *Cyclophosphamide, reconstituted in water, is hypotonic and should not be injected directly.* Prior to infusion, solutions of cyclophosphamide sterile powder reconstituted in Sterile Water for Injection, USP must be further diluted in one of the following:
Dextrose Injection, USP (5% dextrose)
Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sterile sodium chloride)
5% Dextrose and Ringer's Injection
Lactated Ringer's Injection, USP

7.4.8 Administration

Participants in Arm A and Arm B will receive cyclophosphamide 21 (\pm 7) days following the last dose of lenalidomide in cycle 3. Cyclophosphamide will be administered intravenously, at a total dose of 3 g/m², over a period of 2 hours or per institutional practice.

7.4.9 Ordering

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

7.4.10 Destruction and Return

At the end of the study, unused supplies of cyclophosphamide should be destroyed according to institutional policies.

7.5 Melphalan (new or old formulation)

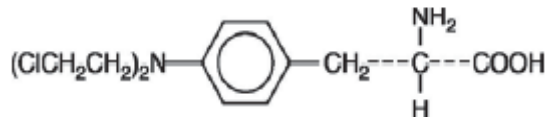
7.5.1 Description

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcosylsin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It

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is known chemically as 4-[bis(2-chloroethyl)amino]-*L*-phenylalanine. The molecular formula is $C_{13}H_{18}Cl_2N_2O_2$ and the molecular weight is 305.20. The structural formula is:



Melphalan is the active *L*-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the *D*-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the *L*-isomer. The racemic (*DL*-) form is known as merphalan or sarcolysin.

Melphalan is practically insoluble in water and has a pK_{a1} of ~ 2.5 .

Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

The pharmacokinetics of melphalan after IV administration has been extensively studied in adult patients. Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m²) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 mL/min/kg after the first course, to 5.5 mL/min/kg after the third course, but did not decrease appreciably after the third course. Mean (\pm SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m² were 1.2 ± 0.4 and 2.8 ± 1.9 mcg/mL, respectively.

The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Serum albumin is the major binding protein, while Γ_1 -acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.

7.5.2 Form

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The original formula for Melphalan for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan with 20 mg povidone added as an excipient.

The new formulation (Evomela) is supplied in a single carton containing one (1) vial. Each 50 mg vial contains a white to off-white lyophilized powder in single-dose vial for reconstitution (after reconstitution the solution is clear and colorless to light yellow). Each vial contains 50 mg melphalan free base equivalent to 56 mg melphalan hydrochloride.

7.5.3 Storage and Stability

The original formulation of melphalan should be stored at controlled room temperature 15° to 30° C (59° to 86° F) and protected from light. A precipitate forms if the reconstituted solution is stored at 5° C. Do not refrigerate the reconstituted product.

Store new formulation (Evomela) at room temperature 25°C (77°F). Temperature excursions are permitted between 15-30°C (59 86°F).

7.5.4 Compatibility

Original Melphalan for Injection should be reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6 mL, ethanol (96%) 0.52 mL, and Water for Injection to a total of 10 mL.

For the new formulation (Evomela), use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed) to reconstitute Evomela and make a 50 mg/10 mL (5 mg/ mL) nominal concentration of melphalan.

7.5.5 Handling

As with other toxic compounds, caution should be exercised in handling and preparing the solution of melphalan. Skin reactions associated with accidental exposure may occur. The use of gloves is recommended. If the solution of melphalan contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Procedures for proper handling and disposal of anticancer drugs should be considered.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product.

Care should be taken to avoid possible extravasation of melphalan and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

7.5.6 Availability

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.Either the original formulation or the new formulation can be used depending on local availability.

7.5.7 Preparation

FOR THE ORIGINAL FORMULATION®

Melphalan for Injection must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5-mg/mL solution of melphalan. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.

Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45 mg/mL. Use of standard institutional practice for dilution of melphalan is also allowed.

The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable.

For the new formulation of Melphalan

Use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.6 mL as directed) to reconstitute Evomela and make a 50 mg/10 mL (5 mg/ mL) nominal concentration of melphalan. The normal saline used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline. The reconstituted Evomela drug product is stable for 24 hours at refrigerated temperature (5o C) without any precipitation due to the high solubility. The reconstituted Evomela drug product is stable for 1 hour at room temperature. Calculate the required volume of Evomela needed for a patient's dose and withdraw that volume from the vial(s). Add the required volume of Evomela to the appropriate volume of 0.9% Sodium Chloride Injection, USP to a final concentration of 0.45 mg/mL. The Evomela admixture solution is stable for 4 hours at room temperature in addition to the 1 hour following reconstitution.. Infuse over 30 minutes via an injection port or central venous catheter. Evomela may cause local tissue damage should extravasation occur. Do not administer by direct injection into a peripheral vein. Administer Evomela by injecting slowly into a fast-running IV infusion via a central venous access line. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

7.5.8 Administration

The original formula for melphalan should be administered in carefully adjusted dosage by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use. Melphalan will be administered either

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as a single dose of 200 mg/m² i.v. over 30 minutes on day minus 2 OR as a divided dose of 100 mg/m²/day i.v. over 2 days on day minus 2 and day minus 1 for a total dose of 200 mg/m². For participants who weigh above 120% of their ideal body weight, the adjusted ideal body weight (AIBW) should be used (See Appendix XI for AIBW calculation).

The recommended dose of the new formulation (Evomela) for conditioning treatment is 100 mg/m² /day administered over 30 minutes by intravenous infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation (ASCT, Day 0). For patients who weigh more than 130% of their ideal body weight, body surface area should be calculated based on adjusted ideal body weight.

7.5.9 Ordering

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

7.5.10 Destruction and Return

At the end of the study, unused supplies of melphalan should be destroyed according to institutional policies.

8 CORRELATIVE/SPECIAL STUDIES

8.1 Proposed Study

This trial will provide samples from newly diagnosed and uniformly treated patients to comprehensively characterize the MM genome and epigenome, to define molecular events driving development and progression of MM, as well as to identify novel therapeutic targets, biomarkers, and preventative strategies.

We will attempt to obtain samples on all patients at the following time points: at diagnosis (initial therapy), at the time of response determination and at disease relapse. It is anticipated that approximately 70% of samples collected will be adequate for gene expression profiling (GEP) analysis.

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To evaluate whether further stringent CR definition may be able to predict superior survival outcome, we will evaluate normalization of serum free light chain, molecular CR using ASO-PCR and immunophenotypic CR using multicolor flow cytometric immunophenotyping of MM cell in bone marrow to detect minimal residual disease.

In order to identify genomic alterations and correlate with clinical outcome, the role of DNA CNAs by high throughput SNP array analysis as well as genome sequencing and gene expression changes by expression array will be analyzed for response and survival. mRNA splicing by exon array and microRNA profiles in study participants will be correlated with clinical endpoints. Both the direct and indirect relationship between CNAs and gene expression changes will also be investigated.

To investigate genomic changes at the time of progression or relapse and evaluate mechanisms underlying genomic instability, genome-wide SNP analyses, expression profiling and genome-wide sequencing on paired samples obtained at the time of diagnosis and at the time of progression or relapse will be performed to identify genomic regions with amplifications, deletions, and changes in heterozygosity. We will evaluate the mutations in light of the known pattern of changes and identify those which may predict different clinical outcomes. Based on data showing that elevated homologous recombination activity plays a significant role in ongoing genomic instability in myeloma HR activity in primary myeloma samples will be measured to correlate with acquisition of new genomic changes as well as clinical outcome.

Leftover specimen material from the correlative studies will be stored for future unspecified research.

8.2 Bone Marrow Aspirate Samples

Collection of bone marrow aspirate specimens for exploratory analysis will be mandatory for this trial. Collections will be obtained at screening, within 42 days of PBSCT, prior to lenalidomide maintenance, end of study treatment (post lenalidomide maintenance), RVD Cycle 4, Day 1 (Arm B only), at the time of confirmation of response (only if previous response assessment was VGPR or better), at the time of disease relapse or progression, and/or when necessary clinical bone marrow aspirate samples are obtained. This will not require extra access for participants. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute.

Additionally, participants have the option to consent for additional collection of bone marrow aspirate specimens for exploratory analysis. If a participant agrees to the optional samples, these samples will be collected once per year during the maintenance portion of the study. The procedure will be done sometime within 3 months before to 3 months after the anniversary date of the participant's biopsy which occurred prior to lenalidomide maintenance. If a participant is already in the lenalidomide maintenance portion of the main study, the biopsies and aspirations will start at the next anniversary

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date from the biopsy prior to lenalidomide maintenance (with a window of 3 months before or after the actual date).

These annual biopsies are recommended. In addition to the research samples, the results will be used to assess the participant's disease status and to check for any post treatment side effects (such as MDS)

U.S. participating sites are responsible for ordering supplies for collection and shipment of bone marrow specimens.

Specimens Required: 2 Purple Top Tubes (EDTA), 6mL each for U.S. sites. Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment.

Processing Information: There is no required processing for bone marrow samples at each participating site prior to shipment.

Shipping Information for Bone Marrow Aspirate Specimens:

Label all specimens with the following:

- f* Subject Initials
- f* Subject study number (will include protocol number)
- f* Visit at which sample was drawn (screening, response or relapse/progression)
- f* Date sample drawn (mm/dd/yyyy)
- f* Time sample drawn (24 hour clock)

Shipping Instructions: **Shipments must be sent on the day of collection and cannot be batched.**

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance.

2. An electronic copy (Word or Excel) of the sample list must also be sent via email. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

3. Please email [REDACTED] to notify of an incoming shipment.

4. Please ship Monday, Tuesday, Wednesday or Thursday as shipments cannot be received on weekends and/or on holidays.

Once drawn, samples may be shipped **ambient via overnight air** to:

[REDACTED]
Dana-Farber Cancer Institute

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450 Brookline Avenue, MA551
Boston, MA 02215
Phone: [REDACTED]
Fax: [REDACTED]

8.3 Peripheral Blood Samples

Collection of peripheral blood specimens (including serum and plasma) for exploratory analysis will be mandatory for this trial. Red top tube collections will be obtained at the same timepoints as bone marrow samples for correlative studies (see Section 8.2 for list of required timepoints). Purple top and proteomics tube collections will be obtained at screening and at the time of disease relapse or progression. These collections will be taken at the time of routine blood collection timepoints required for this study. Specimens will be processed on site according to instructions below and shipped (via traceable carrier) to Dana-Farber Cancer Institute. Once the shipment is received, samples will be subsequently processed, analyzed, and stored at Dana-Farber.

U.S. participating sites are responsible for ordering supplies for collection, processing and shipment of peripheral blood specimens, except for proteomics collection tubes. Proteomics tubes will be provided to the site by Dana-Farber Cancer Institute for U.S. sites. An initial shipment of proteomics tubes will be shipped to U.S. participating sites at the time of site initiation. Refill supplies of proteomics tubes may be requested by contacting [REDACTED]

Specimens Required:

- f* 4 Purple Top Tubes (EDTA), 6ml each
- f* 1 Proteomics Tube, 8.5 ml
- f* 1 Red Top Tube (No Additive), 10 ml
- f* Specimens must be collected Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment.

Shipping Information:

Label all specimens with the following:

- f* Subject Initials
- f* Subject study number (will include protocol number)
- f* Visit at which sample was drawn (screening, response or relapse/progression)
- f* Date sample drawn (mm/dd/yyyy)
- f* Time sample drawn (24 hour clock)

Processing Information: Once collected, the vacutainers will be placed on ice and processed and stored according to instructions below.

For Purple Top Tubes: There is no required processing for purple top tubes at each participating site prior to shipment.

For Proteomics and Red Top Tubes:

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1. Slowly invert tubes 8-10 times immediately after blood collection to mix the blood and additives (for proteomics tube).
2. After mixing, centrifuge as soon as possible, but within 2 hours, at 2500g (rcf) for 20 minutes at Room Temperature (RT) in a swing bucket or 45 degree fixed angle rotor.
3. Obtain four cryovials with yellow-colored caps and two cryovials with red-colored caps.
4. Remove the tube from the centrifuge and carefully take off the top. Place top to the side.
5. Using a micropipette, carefully remove the supernatant from the centrifuged tube. Discard the remaining pellet in the vacutainer in a biohazardous sharps bin.
6. Remove the cap from a cryovial with the free hand and aliquot the supernatant evenly (approximately 1 ml of plasma) as follows, one at a time.
 - a. Transfer the serum from the Red tube to two red-capped cryovials.
 - b. Transfer the plasma from the proteomics tube to four yellow-capped cryovials.
7. Replace cap on the cryovials and store at -70 to -80 degrees until shipment.

Shipping Instructions: Shipments must be sent on the day of collection and cannot be batched.

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance.
2. An electronic copy (Word or Excel) of the sample list must also be sent via email. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.
3. Please email [REDACTED] to notify of an incoming shipment.
4. Please ship Monday, Tuesday, Wednesday or Thursday as shipments cannot be received on weekends and/or on holidays.

Once drawn, samples may be shipped via overnight air ambient (for purple top tubes) and dry ice (for proteomics and red top tubes) to:

[REDACTED]
Dana-Farber Cancer Institute
450 Brookline Avenue, MA551
Boston, MA 02215
Phone: [REDACTED]
Fax: [REDACTED]

9 STUDY CALENDAR

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Screening evaluations are to be conducted within 21 days prior to initiation of protocol therapy with the exception of the myeloma diagnosis. Baseline assessments are to be conducted on Cycle 1, Day 1 of initial RVD therapy. If screening assessments are performed within 7 days of C1D1, disease assessments do not need to be repeated. All assessments must be performed prior to administration of any study medication. Study assessments and medications should be administered within ± 7 days of the protocol-specified date, unless otherwise noted. See below for detailed scheduled of assessments.

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<u>Initial Therapy</u> (RVD Cycle 1)	Screening d 21days from Initiation of protocol therapy ²¹	Treatment Days			
		Baseline Day 1 ¹²	Day 4 (+ 1 day)	Day 8 (+ 1 day)	Day 11 (+1 day)
Informed consent	X				
Inclusion/Exclusion criteria	X	X			
Complete Medical Hx	X	Update			
Confirmation Dx and status of disease and prior Rx	X	Update			
Baseline Symptom Assessment	X	X			
Record concurrent therapies/procedures	X	X	X	X	X
Record adverse events		X	X	X	X
Physical examination, ECOG	X	X			
Vital signs	X	X	X	X	X
Ht, Wt, BSA		X			
Directed Neurological exam ¹	X	X			
FACT/GOG NTx questionnaire		X			
QOL Assessment ¹⁹		X			
Pharmacoeconomic Assessment ²⁰		X			
Skeletal survey (CT or MRI as clinically indicated) ⁸	X ²¹	X ⁸			
Bone Marrow aspiration ²	X ²	X ^{8,9}			
12 Lead ECG ⁷	X	X ⁷			
Assessment of cardiac ejection fraction	X ²¹				
Pulmonary function tests	X ²¹				
Chest X-ray	X ²¹				
HIV/Hep B/Hep C	X				
Hematology ³	X	X	X	X	X
Serum chemistry ⁴	X	X ⁴		X ⁴	
TSH	X				
Beta 2 Microglobulin	X				
B-12, Folate	X				
C-Reactive Protein (CRP)	X				
Urinalysis (microscopic analysis, color)	X				
Pregnancy test ⁵	X ¹³	X ¹³		X ^{5,13}	
CD4+ and CD8+ lymphocyte count	X				
Serum and urine M component quantification, Immunofixation	X	X ⁹			
24hour urine for protein measurement	X	X ⁹			
Serum for FreeLite Testing ^{6,8}	X	X ⁸			
Collection of bone marrow, plasma and serum for Correlative Studies ¹¹	X				
Dispense study drug for next cycle ¹⁵		X ¹⁵			

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<u>Arm A</u>	Treatment Days Initial Therapy with RVD (RVD Cycles 2-3)				At time of cyclophosphamide	Treatment Days Consolidation Therapy with RVD (RVD Cycles 4-8)				Prior to Len. Maintenance	Len. Maintenance	End of Study Treatment and Follow-up
	Day 1 ¹²	Day 4 (+1 day)	Day 8 (+1 day)	Day 11 (+1 day)		Day 1 ¹²	Day 4 (+1 day)	Day 8 (+1 day)	Day 11 (+1 day)			
Record concurrent therapies/procedures	X	X	X	X	X	X	X	X	X	X	X	
Record adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, ECOG	X				X	X				X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Ht, Wt, BSA	X					X				X	X	X
Directed Neurological exam ¹	X					X				X		
FACT/GOG NTx questionnaire ¹⁹	X				X	X						X
QOL Assessment ¹⁹	X ¹⁹				X	X ¹⁹					X ¹⁹	X ¹⁹
Pharmacoeconomic assessment ²⁰	X ²⁰					X ²⁰					X ²⁰	X ²⁰
Skeletal survey (CT or MRI as clinically indicated) ⁵	X ⁸					X ⁸				X	X ⁸	X ⁸
Bone Marrow aspiration ²	X ^{8,9}					X ^{8,9}				X	X ^{8,9}	X ⁸
12 Lead ECG ⁷	X ⁷					X ⁷						
Hematology ²	X	X	X	X	X	X	X	X	X	X	X ²	
Serum chemistry ⁴	X ²		X ²			X ²		X ²		X	X	
TSH ¹⁷												X ¹⁷
Pregnancy test ⁵	X ^{2,13}		X ^{2,15}			X ^{2,15}		X ^{2,15}		X ^{2,15}	X ^{2,15}	X ^{2,15}
CD4+ and CD8+ lymphocyte count ¹⁸	X ¹⁸					X ¹⁸						
Serum and urine M component quantification, Immunofixation	X ⁹					X ⁹				X ⁹	X ⁹	X ¹⁶
24hour urine for protein measurement	X ⁹					X ⁹				X ⁹	X ⁹	X ¹⁶
Serum for FreeLite Testing ^{6,8}	X ⁸					X ⁸				X	X	X ¹⁶
Collection of bone marrow, peripheral blood for Correlative Studies ¹¹										X ²²		X ²²
Dispense study drug for next cycle	X					X					X	
Perform drug accountability	X					X					X	
Follow for Disease progression and survival												X ¹⁶

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Arm B	Treatment Days Initial Therapy with RVD (RVD Cycles 2-3)				At time of cyclophosphamide	Within 42d of PBST (Day 0)	Inpatient PBST Period	Treatment Days Consolidation Therapy with RVD (RVD Cycles 4-5)				Prior to Len. Maintenance	Len. Maintenance	End of Study Treatment and Follow-up
	Day 1 ¹²	Day 4 (+ 1 day)	Day 8 (+ 1 day)	Day 11 (+ 1 day)				Day 1 ¹²	Day 4 (+ 1 day)	Day 8 (+ 1 day)	Day 11 (+ 1 day)			
Record concurrent therapies/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, ECOG	X				X	X	X	X				X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ht, Wt, BSA	X					X		X				X	X	X
Directed Neurological exam ¹	X							X				X		
FACT/GOG NTx questionnaire ¹⁹	X							X					X	X
QOL assessment ¹⁹	X ¹⁹				X			X ¹⁹					X ¹⁹	X ²⁰
Pharmacoeconomic assessment ²⁰	X ²⁰							X ²⁰					X ²⁰	X ²⁰
Skeletal survey (CT or MRI as clinically indicated) ⁸	X ⁸					X		X ⁸			X	X ⁸	X ⁸	X ⁸
Bone Marrow aspiration ²	X ^{8,9}					X		X ^{8,9}			X	X ^{8,9}	X ⁸	X ⁸
12 Lead ECG ⁷	X ⁷					X		X ⁷						
Assessment of cardiac ejection fraction						X								
Pulmonary functions tests						X								
Chest X-ray						X								
Standard pre-PBST assessments (incl infectious disease serologies)						X								
HIV/Hep B/ Hep C						X								
PT/PTT						X								
Hematology ³	X	X	X	X	X	X	Daily	X	X	X	X	X	X ³	
Serum chemistry, ⁴	X ⁴		X ⁴			X	Daily ⁴	X ⁴		X ⁴		X	X	
TSH ¹⁷														X ¹⁷
Urinalysis (microscopic analysis, color)						X								
Pregnancy test ⁵	X ^{5,13}		X ^{5,13}			X ^{5,13}		X ^{5,13}		X ^{5,13}		X ^{5,13}	X ^{5,13}	X ^{5,13}
CD4+ and CD8+ lymphocyte count ¹⁸	X ¹⁸							X ¹⁸						
Serum and urine M component quantification, Immunofixation	X ⁹					X		X ⁹				X ⁹	X ⁹	X ¹⁶
24hour urine for protein measurement	X ⁹					X		X ⁹				X ⁹	X ⁹	X ¹⁶
Serum for FreeLite Testing ^{6,8}	X ⁸					X		X ⁸				X	X	X ¹⁶
Collection of bone marrow, peripheral blood for Correlative Studies ¹¹						X ²²		X ²²				X ²²	(X) ²²	X ²²
Dispense study drug for next cycle ¹⁵	X ¹⁵							X ¹⁵					X ¹⁵	
Perform drug accountability	X							X					X	
Follow for Disease progression and survival														X ¹⁶

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1. To include light touch, pinprick, proprioception, deep tendon reflexes of upper and lower extremities and query for paresthesia and numbness. (neuro consult if indicated)
2. To be evaluated for morphology and cytogenetics by FISH at screening and sample collection for correlative studies.
3. To include WBC, differential, Hgb, Hct and platelet count. During lenalidomide maintenance, recommended once a week for the first 2 months, once every 2 weeks for the next 2 months, and once a month thereafter; must be conducted once per month at minimum during this period. During follow-up, once every 2 weeks for the first 2 months, then once every month thereafter.
4. To include Na, K, Cl, CO₂, Ca, Mg, Phosphorous, BUN, Creatinine, glucose, albumin, total protein, alk phos, total Bili, SGOT/SGPT, LDH, and uric acid at screening, baseline, and Day 1 of subsequent cycles. On day 8, Na, K Cl, CO₂, Mg, BUN and Creatinine only are required. Serum chemistry labs may be performed more frequently (e.g., on days 4 and 11) if required per institutional practice.
5. Pregnancy tests for females of childbearing potential, defined as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has not had menses at any time in the preceding 24 consecutive months).
6. For all participants.
7. 12-lead ECG to be done at screening, Cycle 1, Day 1 of RVD, and Day 1 of odd cycles of RVD therapy.
8. To be completed if clinically indicated, at emergence of new symptoms, or at MD discretion. If participants consent to the optional biopsy samples as described in the consent, they will be collected yearly during lenalidomide maintenance.
9. M Protein response will be based on objective serum and/or urine M protein changes as measured every cycle. For participants not measured in their urine (such as SPEP or free light chain), 24 hour urines should be done every 3 months if possible but no less than every 6 months. Additional testing (BMBx, skeletal survey, scans) may be required to determine overall responses and confirm responses as indicated. Full response assessment, including skeletal survey and BMBx, will be performed at the end of the study.
10. If routine scheduled visit
11. See Section 8.0 for Correlative studies (bone marrow, plasma and serum) collection and processing instructions.
12. When a study investigator or Nurse Practitioner is unavailable for Day 1 of subsequent cycles, arrangements should be made for the participant to be evaluated by an alternate investigator. Safety labs (CBC and chemistry) will be redrawn on Day 1 and reviewed prior to the administration of drug.
13. Pregnancy tests must occur 10-14 days before lenalidomide administration and again within 24 hours prior to initiation of lenalidomide. Females of childbearing potential with regular or no menstruation must have a pregnancy test weekly for the first 28 days (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix IV: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
15. All participants must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done at on Day 1 of RVD (or at a minimum of every 28 days) and at drug discontinuation. 15. Only enough lenalidomide for 1 cycle of therapy may be provided to the participant each cycle.
16. Follow-up assessments will be performed every 2 months during the follow-up period after completion of treatment until disease progression or for up to 3 years after the last patient has been enrolled. These assessments include serum and urine protein electrophoresis, serum and urine immunofixation, immunoglobulins assay, and serum free light chain assay. Any additional follow-up

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assessments should be performed according to institutional practice. At these assessments, participants are followed for disease status, survival, long term toxicities and second malignancies. Once a participant progresses disease assessments are no longer required.

17. TSH will be performed at screening, at investigator's discretion as clinically indicated and at discontinuation. 18. The CD4+ and CD8+ lymphocyte counts are to be performed on Day 1 of every odd cycles of RVD therapy beyond Cycle 1. In cases where the tests are performed for the anticipated start of a scheduled cycle, which then becomes delayed, these tests do not need to be repeated at the delayed start date of that cycle.

19. Quality of life assessments should be performed at Baseline, RVD Cycle 2, Day 1, prior to cyclophosphamide, RVD Cycle 5, Day 1, RVD Cycle 8, Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Cycle 6, Day 1 of lenalidomide maintenance, at the end of study treatment, and at 2 years, and 3 years from the date of baseline assessments. The FACT/GOG NTx questionnaire should be performed at Baseline (Cycle 1, Day 1), RVD Cycle 2, Day 1, prior to cyclophosphamide, RVD Cycle 5, Day 1, RVD Cycle 8, Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Cycle 6, Day 1 of lenalidomide maintenance, at the end of study treatment, and at 2 years, and 3 years from the date of baseline assessments as well.

20. EQ-5D questionnaire should be administered at Baseline, RVD Cycle 2, Day 1, prior to cyclophosphamide, RVD Cycle 5, Day 1, RVD Cycle 8, Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Cycle 6, Day 1 of lenalidomide maintenance, at the end of study treatment, and at 2 years, and 3 years from the date of baseline assessments.

21. Results of bone marrow biopsy, skeletal survey, MRI, CT scans, and chest X-ray within 35 days of initiation of protocol therapy may be used to fulfill screening requirements

22. Bone marrow aspirate and red top peripheral blood tubes will be collected at screening, within 42 days of PBSCT, prior to lenalidomide maintenance, end of study treatment (post lenalidomide maintenance), RVD Cycle 4, Day 1 (Arm B only), at the time of confirmation of response (only if previous response is VGPR or better), at the time of disease relapse or progression. Additionally, optional samples are collected during lenalidomide maintenance. Yearly biopsies for participants in the maintenance phase are recommended to check disease status and to check for post treatment side effects. For the optional samples, they should be collected yearly +/- 3 months from the anniversary date of the biopsy prior to lenalidomide maintenance. For patients already in maintenance at the time of consent, biopsies should start at their next anniversary date (+/- 3 months). Purple top and proteomics tube collections will be obtained at screening and at the time of disease relapse or progression.

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10. MEASUREMENT OF EFFECT

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

Disease response by the Modified EBMT Response Criteria in Section 10.2.4.3 will also be collected on participants as a secondary measure.

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.

10.1 Antitumor Effect– Solid Tumors

This section is not applicable to this study.

10.2 Antitumor Effect – Hematologic Tumors

10.2.1 Definitions

This section is not applicable to this study.

10.2.2 Disease Parameters

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

- f* Serum M-protein ≥ 1 g/dl (except patients with IgD or IgA myeloma). For patients with IgD or IgA myeloma, a serum M-protein of greater than or equal to 0.5 g/dl will suffice.
- f* Urine M-protein ≥ 200 mg/24 h
- f* Serum FLC assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) provided serum FLC ratio is abnormal.

10.2.3 Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of initial therapy with RVD. 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

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aspiration and biopsy, as well as skeletal survey will be performed to determine overall response or confirm response.

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

10.2.4 Response Criteria

A six-week confirmation measurement for disease response assessments is required in this protocol.

10.2.4.1 International Myeloma Working Group Response Criteria

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have ‘measurable’ disease, as defined in Section 10.2.2. All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Stringent CR: CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow* by immunohistochemistry or immunofluorescence.**

*Confirmation with repeat bone marrow biopsy is not needed.

**Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2.

CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow.

*Confirmation with repeat bone marrow biopsy is not needed.

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours.

PR: ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to < 200mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (definition of measurable disease in Section 10.2.3). If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 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.

SD: Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.

PD: > 25% increase of serum M-protein (which must also be an absolute increase of ≥ 0.5 g/dL) and/or urine M-protein (which must also be an absolute increase of ≥ 200

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mg/24hr). If serum and urine M-protein are unmeasurable, there must be an absolute increase of ≥ 10 mg/dL between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells $\geq 10\%$. In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

10.2.4.2 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 qualify 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.

10.2.4.3 Modified EBMT Response Criteria

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Response	Criteria for Response ^a
Complete response (CR)	<p>Requires all of the following:</p> <p>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.</p> <p><5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks.^b</p> <p>No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).^c</p> <p>Disappearance of soft tissue plasmacytomas for at least six weeks.</p>
Near Complete Response (nCR)	<p>Requires the following:</p> <p>Same as CR, but immunofixation studies continue to show presence of the monoclonal protein</p>
Very Good Partial Response (VGPR)	<p>Requires the following:</p> <p>≥ 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.</p>
Partial response (PR)	<p>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:</p> <p>†50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart.</p> <p>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.</p> <p>†50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks.</p> <p>No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).^c</p>
Minimal response (MR)	<p>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:</p> <p>†25% to †49% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart.</p> <p>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.</p> <p>25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for at least six weeks.</p> <p>No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).^c</p>
No change (NC)	<p>Not meeting the criteria for MR or PD.</p>

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Response	Criteria for Response ^a
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.

10.2.5 Duration of Response and Endpoint Definitions

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

Duration of overall complete response: The duration of overall CR is measured as the time from initiation of CR to first documentation of disease

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progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Time to progression: Time to progression is defined as the time of randomization until progression. Patients who have died without evidence of progression are censored in the TTP analysis at the time of death and patients who are alive without progression are censored at the last disease assessment.

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

10.2.6 Progression-Free Survival

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

10.2.7 Response Review

Central review of disease response assessments is not planned.

10.3 Other Response Parameters

10.3.1 Quality of Life

Quality of Life (QOL) is a secondary endpoint of this study. Measurement of quality of life (QOL) has gained widespread acceptance as a means of assessing the effects of chronic illness on a patient's well being. Three QOL instruments will be evaluated in this study: The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core (QLQ-C30) (Appendix VIII), the EORTC QLQ-MY20 Multiple Myeloma module (Appendix X), and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-NTX) side-effects questionnaires (Appendix IX).

The EORTC QLQ-C30 is a cancer-specific, multi-dimensional core QOL instrument that incorporates nine multi-item scales including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting and pain) and a global health and quality of life scale. Six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) are included. Response options are a four point Likert scale from "not at all" to "very much" or a seven point Likert scale from "very poor" to "excellent." It is a reliable and valid measure of QOL in cancer patients. The EORTC has also developed a module specific for multiple myeloma (EORTC QLQ-MY20) to be used in conjunction with the C30 scale. This scale is designed to evaluate the effect of the disease and drug therapy in patients with myeloma. It provides four scales (disease symptoms, side effects, body image, future

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perspective). The instrument consists of a brief questionnaire that has been validated and utilized in many countries. The EORTC QLQ-C30 and MY20 together take on average 12 minutes to complete. (Aronson et. al, 1993; Hjermstad et. Al, 1995; Cocks et. al, 2007).

The questionnaire is designed to be self administered. However, a designated person at each site should be responsible for giving the surveys to participants and providing materials to assist in survey completion (a clipboard, pen, and envelope to enclose the survey in when completed). This person would also be responsible for collecting the completed survey, checking for missing items, and answering any questions that arise regarding the survey.

The QOL surveys should be administered before the participant sees the physician so that the interaction between the participant and physician does not influence the participant's answers to the questionnaire. Ideally, the questionnaire should also be completed before the participant is asked about adverse experiences and concurrent illnesses, again so that any discussions of health problems do not influence the participant's answer to the questionnaire. It is important that the components of the QOL survey be administered in the same order in all study sites.

Participants must have basic fluency in English in order to complete the QOL surveys provided. If a participant is not able to speak English, the individual administering the questionnaire must determine whether or not the participant has basic fluency in any of the languages in which the questionnaire is currently available (mostly European languages). Copies of alternative language questionnaires are available from the Coordinating Center. If the questionnaire is not currently available in a language in which the participant has basic fluency, translation services may be requested. Participants who are not able to see or read the questionnaire may have it read to them verbatim by study staff and their answers recorded.

If a participant asks the meaning of specific questions, study staff may assist the participant by rereading the question for them verbatim. However, the study staff must not attempt to interpret the question and/or participant responses or provide the participant score on the questionnaire. All participants should answer the questions based on what they think the questions mean, or the study results may be biased.

After the participant has completed the questionnaire, study staff will check that all of the questions have been answered and ask the participant to answer the incomplete item or items. If the participant is still unable to complete the question or refuses to answer an item or items, accept the questionnaire as incomplete. The physician should not be allowed to review the completed questionnaire.

QOL questionnaires will be administered at nine timepoints: baseline, RVD Cycle 2, Day 1, prior to cyclophosphamide administration, RVD Cycle 5 Day 1, RVD Cycle 8 Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Cycle 6 Day 1 of lenalidomide maintenance, at the end of study treatment, and at 2 years and 3 years from baseline.

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QOL domains will be compared between Arm A and Arm B, and include health related quality of life, distress, psychological functioning, physical well-being and functional well-being. Participant answers will be kept confidential and aggregated with information from many other participants before analysis.

10.3.2 Pharmaco-economics (Medical Resource Utilization)

Pharmacoeconomics is another secondary endpoint to the trial. Pharmacoeconomics assessment will measure the costs of the two treatment arms by comparing markers of resource utilization between Arm A and Arm B. During the study, medical resource utilization (MRU) data associated with medical encounters related to disease or myeloma therapies will be collected for all participants. Specifically, MRU is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, and diagnostic tests and procedures. The MRU data will be used to conduct economic analyses.

MRU data will be collected at the following timepoints: baseline, RVD Cycle 2, Day 1, prior to cyclophosphamide administration, RVD Cycle 5 Day 1, RVD Cycle 8 Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Cycle 6 Day 1 of lenalidomide maintenance, at the end of study treatment, and at 2 years and 3 years from baseline. Routine MRU elements such as diagnostic tests, blood tests and other related tests, and bone scans are collected using the case report forms in this trial.

Data related with hospitalization, reasons for hospitalization, duration of hospitalization, and outpatient visits will be collected. It should be noted that outpatient visits for drug administration will also be captured.

The EQ-5D will be used to capture participant-reported utilities for use in cost-utility analyses in this trial (See Appendix X). The EQ-5D contains a five item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It also contains a 0-100 visual analogue scale to measure current overall health and 9 optional sociodemographic questions. The EQ-5D takes approximately 1 minute to complete (Agency for Healthcare Research and Quality, 2005).

11. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the CTCAE version 4.0 NCI Common Terminology Criteria for Adverse Events. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>).

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

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Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency 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.

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

An adverse event is any change in health occurring in a person who is a participant in biomedical research, whether this change is related or not to the research or to the product that the research is being conducted on. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

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.

11.1.2 Serious adverse event (SAE) and events requiring expeditive reporting

A serious adverse event is an undesirable sign, symptom, or medical condition, regardless of causality that:

- x Results in death,
- x Is life-threatening. Life-threatening means that the participant 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;
- x Requires hospitalization or prolongation of existing 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 participant 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);
- x Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions;

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- x Is a congenital abnormality or birth defect;
- x Is an important medical event. An important medical event is an event that, when based upon appropriate medical judgment, 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, the development of drug dependency or drug abuse, or suspected transmission of infectious agents by medicinal product.

The following event must also be reported in an expedited manner:

- x Results in pregnancy (see section 11.1.3)

Any adverse event arising after study treatment discontinuation/study termination that is possibly related to study treatments/procedures must be reported regardless of the delay between event onset and study treatment discontinuation/study termination.

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

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

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

Please note the distinction between seriousness and severity of an AE. Severity is a measure of intensity of an event (mild, moderate, severe). However, the event itself may be of relatively minor medical significance; thus, a severe reaction may not necessarily be classified as a serious reaction. This differs from seriousness, which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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11.1.3 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, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about 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 the abnormal outcome meets any of the serious criteria, 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 IP 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.

Male Subjects

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

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]

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11.1.4 Expectedness

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

11.1.4.1 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 Investigator's Brochure or is included in the informed consent document as a potential risk. Scheduled hospitalizations for the study treatment, participant follow-up and medical conditions related to the progression of the disease are considered to be expected SAEs.

The investigator must evaluate all abnormal lab results to determine the clinical significance. If an abnormal result appears to be clinically significant, it must be considered to be an AE.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.4.2 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 Investigator's Brochure or when it is not included in the informed consent document as a potential risk.

11.1.5 Attribution (Causality)

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. It will be assigned by using the WHO causality method assessment linked to CTCAE grading system (as follows):

TERM

DESCRIPTION

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A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. The AE is clearly related to the study treatment.

LIKELY/PROBABLE

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition. The AE is likely related to the study treatment.

POSSIBLE

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. The AE may be related to the study treatment.

UNLIKELY

A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. 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 possibly study-related if causality criteria will be “certain/definite”, “likely/probable”, and “possible”.

The causality criteria “unlikely” and “unrelated” is intended to be used when the exclusion of drug causality of a clinical event seems most plausible. It will be used to define “not study-related” events.

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An event will also be considered as “concomitant drug-related”, “disease progression-related” or “other cause related”.

Causality will be assessed for each investigational treatment used in the trial (bortezomib and lenalidomide)

If a reported SAE is considered an unexpected and suspected serious adverse reaction (SUSAR), reporting/notification rules described below must be followed.

11.2 Adverse Event 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.

All AEs detected by the investigator or by the participant must be recorded on the appropriate study-specific CRFs, 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 for each AE.

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

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Each adverse event will be assessed to determine if it meets the criteria for SAE reporting. If an SAE occurs, expedited reporting will follow local policies, and regulations as appropriate.

Hematologic adverse events will be recorded/reported only if > grade 2 or if an action on study drug was required. Grade 3/4 myelosuppression during mobilization and transplant is expected and does not require reporting as an SAE. These events should be captured on the adverse event pages of the CRF only.

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11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the Principal Investigator.

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 Principal Investigator, the participating site's IRB, and others as described below.

11.4 Reporting to the Study Supporter

11.4.1. Serious Adverse Event Reporting

Serious adverse events (SAE) are defined above. The investigator must inform Celgene and Millennium in writing using an SAE form or MEDWATCH 3500A form of any fatal or life threatening SAE within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event and all other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event. The written report must be completed and supplied to Celgene and Millennium by facsimile within 24 hours but no later than 4 calendar days. The initial report must be as complete as possible and include at minimum the event term, seriousness criteria, intensity of the event and the causal relationship between the event and the investigational product(s). Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at <http://ctep.cancer.gov/reporting/ctc.html>. 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 report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-MM-IFM-0444) and Millennium tracking number (X05347) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene and Millennium. A copy of the fax transmission confirmation of the SAE report to Celgene and Millennium should be attached to the SAE and retained with the patient records. Celgene and Millennium may request follow-up information on reported SAE's.

Dana-Farber will be responsible for SAE reporting and management to the FDA, Celgene and Millennium and DFCI IRB.

All serious adverse events that occur from the date of informed consent signature, during treatment, or within 30 days of the last dose of treatment, with the

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exception of participants who withdraw from treatment during RVD cycles, in whom adverse events will be collected until 60 days following the last treatment administration, must be reported on a MEDWATCH FDA Form 3500A. This includes events meeting the criteria outlined in Section 11.1.2., as well as the following:

- x Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- x All Grade 4 (life-threatening or disabling) events unless they are expected AND specifically listed in the protocol as not requiring reporting.
- x 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 using the MEDWATCH FDA Form 3500A form. 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
Paul Richardson, MD

[REDACTED]
450 Brookline Avenue, LG-
Boston, MA 02215

Phone: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

Email: [REDACTED]

Dana-Farber will inform Celgene and Millennium of any SAE in writing using a MEDWATCH FDA Form 3500A within 24 hours of awareness. The Celgene tracking number (RV-MM-IFM-0444) and the protocol number should be included on SAE reports (or on the fax cover letter).

Information not available at the time of the initial report must be documented on a follow-up MEDWATCH Form 3500A.

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11.4.2 IND Action Letters and Safety Reports

The Coordinating Center will distribute IND Action Letters or Safety Reports occurring on this trial to all participating institutions for submission to their individual IRBs for action as required.

11.4.3 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported on the adverse event Case Report Form.

11.5 Reporting to the Institutional Review Board (IRB)

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

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB policies and procedures in reporting adverse events.

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

11.6 Reporting to the Food and Drug Administration (FDA)

The Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

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

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at <http://www.fda.gov/medwatch/getforms.htm>.

An annual safety report containing SAEs, expected SAEs and unexpected SAEs will be sent to the FDA and other applicable regulatory authority(ies). Celgene and Millennium

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will receive a copy of the Investigator IND annual report at the time of the investigator's submission to the FDA and/or other regulatory authorities.

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

This section is not applicable to this study.

11.8 Reporting to the Institutional Biosafety Committee (IBC)

This section is not applicable to this study.

11.9 Reporting to Hospital Risk Management

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

11.10 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 treatment administration, with the exception of participants who withdraw from treatment during RVD cycles, in whom adverse events will be collected until 60 days following the last treatment administration, 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.

After this period only SAEs considered reasonably study-related by the investigator must be reported to the sponsor (for example, delayed SAE) without limitation.

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

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Principal Investigator 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.

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12 DATA AND SAFETY MONITORING

12.1 Data Reporting

The investigator and/or individual designated by the investigator will be responsible for the following study functions: oversee logistics and monitoring of the study, create progress reports, verify case report form updating, request additional information and corrections to case report form, send correlative samples, SAE reporting to the sponsor and local regulatory authorities. This individual will work in accordance with standard operating procedures, in cooperation with the project management team and study monitor, as delegated by the study sponsor.

12.1.1 Method

Data will be collected via electronic CRF (eCRF) for this study, using an Oracle based system. Details for access to this electronic data capture system will be provided by the study sponsor.

12.1.2 Data Submission

The schedule for completion of electronic data can be located in the Site Study Manual.

12.1.3 Database Management and Confidentiality

Data will be entered into an electronic file. The identity of participants participating in the study will be made anonymous. Participants will be identified by a unique study identifier (study subject number). A participant identification list linking the subject number to the participant identifying information will be kept in a secure location at each participating study site.

The investigator will take measures to protect the privacy and security of personal information for each participant in this trial. No information that could allow identification of persons will be communicated to third parties other than those legally authorized to have access to this information and who are bound by professional confidentiality.

The data will be monitored. Queries will be generated and sent to the participating site. Responses to queries will be done directly in the database by the investigators and/or individual designated by the investigator. Tracking of changes by the user will be performed. A set of work instructions for data validation will be written.

12.2 Data Monitoring Committee (DMC) Meetings

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An independent Data Monitoring Committee (DMC) will be established for this trial. The objective of the DMC is to review safety, progress toward completion of study, and interim analyses of outcome data as designated in the Data and Safety Monitoring Charter (DSMC). Adverse events and serious adverse events will be reviewed by the DMC to determine the cause of these events and necessary measures will be taken to ensure participant safety. The DMC will meet at least once a year to review the trial for data and safety issues, and may be scheduled more frequently if needed to review safety (e.g., one face-to-face meeting per year with teleconference at other timepoints). Following each meeting, the DMC will provide the study team with information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing or terminating the trial. The DMC will provide a summary of the committee findings to the principal investigator. The principal investigator will communicate this information to the IRB as well as participating study investigators as necessary.

The DMC members will include physicians with expertise in the field of multiple myeloma and statisticians. These DMC members are not affiliated with the participating institutions, and are not directly involved with the conceptual design or analysis of the trial.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the sponsor. The investigator will grant the monitor or auditor access to the patient's original medical records. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

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

A clinical research assistant (CRA) delegated by the sponsor will regularly visit each study center at the time of setup of the trial, one or more times during the trial according to the pace of enrollment, and at the end of the trial. The Coordinating Center will be responsible for site initiation visits. These visits will be conducted as either an on-site visit or via webconference. If investigator meetings are planned they may be considered as initiation visits if agreed by the sponsor. Following site initiation, a commercial CRO will be responsible for on-site monitoring and close-out visits at participating sites. The frequency of site monitoring will be dependent on site enrollment, with the first visit occurring within two months of first participant enrollment. After the first

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monitoring visit, on-site monitoring will occur approximately once every three months or as accrual dictates.

The purpose of these visits is to monitor compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center as per monitoring guidelines requirements. See Appendix XIII, Section 9.3.1 for further detail on source document verification.

Access to the source documents will be given to the clinical research assistant based on the needs of monitoring of the trial and in compliance with GCP. Any visit will be subject to a monitoring report via a written description (tracking of visits).

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

12.4 Audit and inspection

In accordance with GCP, the investigators agree to comply with the requirements of the sponsor and the Regulatory Authorities with regard to an audit or inspection of the trial.

The audit may be performed at any of the stages of the study, from development of the protocol to publication of the results.

Regulatory authorities or the sponsor may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be granted by the investigator, who must provide support at all times for these activities.

The investigator will notify DFCI in the event of an audit request and DFCI will subsequently notify Celgene and Millennium of such request.

12.5 Drug Accountability

Drug accountability for the drug at all study sites (including all sub-sites) is the responsibility of the Principal Investigator. The investigator will ensure that the drug is used only in accordance with this protocol and will maintain documentation of investigational products inventory, dispensing and destruction.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

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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. Millennium and Celgene will be notified of all protocol modifications, and will be given opportunity to review and provide comment prior to IRB submission. Any changes in study conduct must be reported to the IRB and other regulatory authority(ies) in accordance with the governing regulations. 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. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB. The Principal Investigator will disseminate protocol amendment information to participating investigators. See Appendix XIII, Section 5.0 for details of protocol management, including protocol distribution, revisions and closure.

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Any deviation from the protocol must be fully documented in the source documents.

13.2 Informed Consent

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

13.3 Ethics and Good Clinical Practice (GCP)

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

- x E6 Good Clinical Practice: Consolidated Guidance
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

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- x US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
 - o Title 21 Part 11 – Electronic Records; Electronic Signatures
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
 - o Title 21 Part 50 – Protection of Human Subjects
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
 - o Title 21 Part 54 – Financial Disclosure by Clinical Investigators
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
 - o Title 21 Part 56 – Institutional Review Boards
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
 - o Title 21 Part 312 – Investigational New Drug Application
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- x State laws
- x DF/HCC research policies and procedures
<http://www.dfhc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/>

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

13.4 Study Documentation

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

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

13.5 Records Retention

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

13.6 Multi-center Guidelines

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Short title: Phase III Study of RVD versus RVD plus auto SCT in newly diagnosed MM participants

Version Date: November 30, 2016

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the Principal Investigator, Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix XIII).

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

- x Participating institutions will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the coordinating center who will forward to applicable parties as needed.

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

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

13.8 Investigator Responsibilities

The investigator agrees to perform the study in accordance with law no. 2004-806 of 9 August 2004 regarding the public health policy, and with decrees made in application of it, with the Declaration of Helsinki and with Good Clinical Practices. All data, all documents and reports may be subject to regulatory audits and inspections, which cannot be opposed based on medical secrecy.

The investigator will inform participants of the objectives and constraints of the study, of their rights to refuse to participate in the study or to quit it at any time. When information has been given to the potential participant and the investigator has made sure that the potential participant has understood the implications of participation in the study, the participant's written consent will be collected by one of the investigators in two original copies of the informed consent document. One original copy of the signed consent form will be given to the participant and the second original copy will be maintained by the investigator in the participant's study files.

All information collected is confidential. The investigator will take measures to protect the privacy and security of personal information for each study in this trial. No information that could allow participant identification will be communicated to third parties other than those representing the sponsor or regulatory authority, legally authorized to have access to this information and bound by professional secrecy.

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14. STATISTICAL CONSIDERATIONS

In the original study, the statistical plan was to compare the two arms stratified by country (IFM, US), cytogenetic risk and ISS. The original protocols for both the IFM and the US included maintenance lenalidomide for one year. Based on the NEJM maintenance paper (CALGB NEJM 2012) on the benefit of maintenance therapy the US protocol was revised October 16, 2012 to extend maintenance until progression. The accrual for the US was expanded to include 660 patients to address the question of conventional dose followed by maintenance until PD versus high dose therapy arm followed by maintenance until PD. The accrual for the IFM protocol was 700 patients to address the question of conventional dose followed by 1-year of maintenance vs. high dose therapy arm followed by 1-year of maintenance.

In February 2016, McCarthy et al presented results from a meta-analysis showing a 50% reduction in the hazards for continuous maintenance therapy (EHA February 2016). With a reduction in the failure rate, the time to the full information could be longer than expected in this study. Therefore, to account for this potential reduction in the hazard rates in both arms (the hazard ratio remains at 1.43), the sample size is increased to 720 randomized patients; based on patient drop out rates from registration to randomization, it is anticipated that 750 patients will need to be enrolled in order to reach the 720 randomization figure. With the increase from 660 to 720 randomized patients, the time to reach full information is 5 months earlier.

Details on the design changes are summarized below. The sections below include the original design (14.2.1), the October 16, 2012 design at the time the US maintenance treatment duration was modified (14.2.2), and the October 2016 change to increase the sample size to account for potential reduction in the hazard rates per arm (14.2.3).

14.1 Study Objectives/Endpoints and Stratification Factors

The primary objective of this randomized phase III study is to compare the progression-free survival (PFS) of Arms A (conventional dose arm) and Arm B (high dose therapy arm) in newly diagnosed myeloma patients who have completed 1 cycle of RVD. PFS is defined as the time from randomization until progression or death from any cause. Patients alive without confirmed progression will be censored at the time of the last disease evaluation. Deaths without progression are counted as failures even if they occur after the last disease evaluation. Patients are stratified by country (US vs. IFM), cytogenetics risk factors (standard, high risk, FISH failures) and ISS (Stage I vs. II vs. III). Patients will be randomized equally to the two arms using permuted blocks within stratification combinations.

The secondary objectives of the study are to compare the following outcomes between the two arms: the response rates (CR, at least VGPR), time to progression, overall survival, toxicity, quality of life and pharmaco-economics. The reasons that participants who received 1 cycle of therapy did not proceed to the randomization will be collected and reported. Prognostic groups defined by gene expression profiling will be defined in correlative studies. Time to progression

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(TTP) is defined as the time of randomization until progression. Patients who have died without evidence of progression are censored in the TTP analysis and patients who are alive without progression are censored at the last disease assessment. Overall survival is defined as the time of randomization to death. Patients are censored at the time last known alive.

The planned sample size for the US is 720 randomized patients and for the IFM is 700 randomized patients. It is anticipated that approximately 1% of the patients will register to the study and not proceed to randomization after 1 cycle of therapy.

14.2 Statistical Considerations for the Primary Objective

The primary objective of this protocol is to compare PFS of Arms A (conventional dose arm) and B (high dose arm). Protocols using combinations of new drugs at conventional doses using melphalan, prednisone and thalidomide (Palumbo et al., 2006; Facon et al., 2007), melphalan, prednisone and bortezomib (San Miguel et al., 2008), dexamethasone / lenalidomide (Rajkumar et al., 2007) resulted in PFS estimates of between 18- 24 months. The median value of progression-free survival of participants treated with RVD can thus be estimated at 30 months at the best (Richardson et al., 2007). The primary analysis of PFS will be performed using a stratified two-sided log-rank test with an overall type I error rate of 5%. The primary analysis will be intent to treat analysis of all randomized patients. Cases determined to be ineligible after randomization will be included in the analysis. PFS in each of the arms will be estimated using the method of Kaplan and Meier.

14.2.1 Original design: The IFM and DFCI studies combined have 92% power to detect a 23% reduction in the PFS hazard from 0.0231/month on conventional dose arm (Arm A) to 0.0177/month on high dose therapy arm (Arm B) using a stratified two-sided log-rank test with an overall type I error rate of 0.05. This corresponds to a hazard ratio (hazard of conventional dose Arm A/hazard of high dose Arm B) of 1.3. Full information under the alternative hypothesis is 658 failures. Assuming median PFS of 30 months on the RVD alone arm (Arm A) and the PFS time follows an exponential distribution, this difference corresponds to a 30% increase in median survival to 39 months for Arm B. Based on these medians and corresponding failure rates, the required number of failures will be observed with 1000 patients enrolled over 36 months with 36 months of follow-up. Two interim analyses were planned at approximately 33% and 69% information. In calendar times these are anticipated to be at approximately 30 months (prior to the end of enrollment) and 48 months with the final analyses planned at approximately 72 months. To preserve the overall type I error rate, critical values at the interim analysis will be determined using the Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary. The study will also be monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (RCI) methodology. At each interim analysis, the one-sided 97.5% repeated confidence upper limit on the hazard ratio will be computed using the critical value from the error spending function. If the upper limit lies below the target alternative hazard ratio (hazard of the conventional dose /hazard of the high dose) then the DMC may consider stopping the trial early in favor of the conventional dose arm.

14.2.2 Design modification for US study change to continuous maintenance therapy (October 16, 2012)

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Reason for design modifications: The original protocols for both studies included maintenance lenalidomide for one year. With the recent papers in the NEJM on the benefit of maintenance therapy the US protocol will be revised to extend maintenance until progression. The accrual for the US will be expanded to include 660 patients to address the question of conventional dose followed by maintenance until PD versus high dose therapy arm followed by maintenance until PD. The accrual for the IFM protocol will be 700 patients to address the question of conventional dose followed by 1-year of maintenance vs. high dose therapy arm followed by 1-year of maintenance.

US Study Design Change: With this amendment, the US study will be designed with 90% power to detect a 30% reduction in the PFS hazard from 0.0231/month on conventional dose arm (Arm A) with maintenance until PD to 0.0162/month on high dose therapy arm (Arm B) with maintenance until PD. (See justification for design change below for further details). A stratified two-sided log-rank test will be used with an overall type I error rate of 0.05. This corresponds to a hazard ratio (hazard of conventional dose Arm A/hazard of high dose Arm B) of 1.43. Full information under the alternative hypothesis is 329 failures. Assuming median PFS of 30 months on the RVD alone arm (Arm A) and the PFS time follow an exponential distribution, this difference corresponds to a 43% increase in median survival to 43 months for Arm B. A power of 90% was used in this study to adjust for the potential for cross over from the conventional dose arm to the high dose therapy arm prior to progression. Based on simulations allowing for constant cross over as well as varying patterns of cross over the power is reduced approximately 7-10% with up to 15% cross over at 3 years.

It is anticipated that the US accrual will reach 100 randomized patients by 24 months. Based on the medians and the corresponding failures rates as well as the extended follow-up among the initial 100 patients, the required number of failures will be observed with an additional 560 patients entered over 30 months with 18 months of follow-up for a total study time of 72 months (24 months accrual time for the initial 100 patients, 30 months accrual time for the additional 560 patients and 18 months of follow-up). Specifically, with 560 patients entered over 30 months (monthly accrual rate of 18-19 patients/month) with 18 months of follow-up approximately 261 events will be observed assuming an exponential distribution with the above specified medians and failure rates. Among the initial 100 patients, the minimum follow-up is extended from 36 months to 48 months and therefore, based on the exponential distribution approximately 68 failures are expected. Two interim analyses will occur at 33% and 69% information and the final analysis at full information. These results will be presented to the data- monitoring committee (DMC). At each DMC meeting toxicity results will be presented and interim analyses if at designated information times. To preserve the overall type I error rate, critical values at the interim analysis will be determined using the Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary. The study will also be monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (RCI) methodology. At each interim analysis, the one-sided 97.5% repeated confidence upper limit on the hazard ratio will be computed using the critical value from the error spending function.

Study monitoring for slow accrual: Based on concerns about US accrual, consideration will be given to closing the US study if the actual accrual rate is less than 80% of the targeted accrual

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rate of 18-19/month by the fall 2013 DMC Meeting and the impact of the CTN, Alliance and other additional sites proves inadequate to meet the amended goals for enrollment.

Justification for the design change: Assuming the median PFS in the conventional dose arm (Arm A) remains at 30 months, the change in the reduction percentage in the failure rates/month from 23% to 30% is reasonable based on the recent literature which indicates that the median PFS from the time of transplant may range from 42-49 months with lenalidomide maintenance following autologous transplant. Based on a retrospective evaluation of data at the DFCI a median PFS of 45 months was observed from the time of RVD C1 D2 therapy (Luskin, et al, ASH 2011). These estimates were also reported, albeit not directly and with various induction strategies, in two studies evaluating maintenance therapy: 1) IFM study NEJM, 2012 which reported median PFS 39 months from time of consolidation with DCEP and lenalidomide maintenance after various induction therapies (vincristine,dox,dex; VD, other) which is approximately 3 months from time of transplant and 10 months from time of diagnosis and 2) the CALGB NEJM 2012 which reported median PFS of 46 months from time of lenalidomide maintenance therapy after various induction therapies (bortezomib, lenalidomide, thalidomide, other) which is approximately 3 months from time of transplant. Note the CALGB study counts progression and death as an event in the primary endpoint. These numbers could be further increased by approximately 6 months to align with the time of randomization on this study (day 1 of cycle 2 RVD) and would be approximately 47-55 months. However, both of these studies excluded patients with progressive disease prior to the time of maintenance/consolidation. These patients would be included in this study and therefore, it is anticipated that the median PFS from the time of day 1 of cycle 2 RVD would be lower. With these patients included, a median PFS on the high dose therapy arm (Arm B) of approximately 43 months is reasonable based on the current literature.

The current literature also indicates that the median PFS on the conventional dose arm (Arm A) proposed in the original design (30 months) is reasonable. In the US upfront study (Richardson et al, 2010, Blood) the median PFS censoring at transplant is approximately 32 months extrapolating from the 24 month estimates. The median PFS from the time of induction was 28 vs. 35 months among the patients <65 years of age who received VAD+ thalidomide vs. PAD+bortezomib (Sonneveld, JCO, 2012). Similarly, the median PFS from the time of induction was 26 months vs. not reached (3-year estimates of 38 vs. 60%) among the patients <65 years of age who received MPR+/- lenalidomide maintenance vs. MEL200 +/- lenalidomide maintenance (Palumbo et al, EHA, 2012). However, this included patients who did not receive any maintenance therapy and therefore, the median PFS with maintenance can be anticipated to be higher than 26 months for MPR. The benefit of maintenance reported on this trial was a median PFS of 34 vs. 22 months from time of maintenance therapy for Mel200/MPR patients combined.

Impact of the US Study Design Change on the IFM Study : In the original design, the IFM and DFCI studies combined have 92% power to detect a 23% reduction in the PFS hazard from 0.0231/month on conventional dose arm (Arm A) to 0.0177/month on high dose therapy arm (Arm B) using a stratified two-sided log-rank test with an overall type I error rate of 0.05. Full information is 658 failures. Current accrual for the IFM protocol has been faster than expected with 700 randomized patients anticipated to be entered within 24 months. To maintain at least 80% power, patients will continue to be followed until 72 months with a minimum follow-up of 48

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months. This would result in 489 failures under the alternative (83% power). Two interim analyses will occur at 33% and 69% information and the final analysis at full information. To preserve the overall type I error rate, critical values at the interim analysis will be determined using the Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary. The study will also be monitored for early stopping using Jennison-Turnbull repeated confidence interval (RCI) methodology. At each interim analysis, the one-sided 97.5% repeated confidence upper limit on the hazard ratio will be computed using the critical value from the error spending function.

Proposed analysis for both the IFM and US Studies: A descriptive analysis will be performed to attempt to address a question comparing PFS and OS for maintenance lenalidomide for 1 year (700 patients) vs. maintenance lenalidomide until PD (660 patients) overall and by conventional dose (350 vs. 330 patients) /high dose therapy arm (350 vs. 330 patients).

14.2.3 Design modification for US study change to increase sample size to 720 patients (12 October 2016 date)

Reason for design modifications: In February 2016, McCarthy et al presented results from a meta-analysis showing a 50% reduction in the hazards for continuous maintenance therapy (EHA February 2016). With a reduction in the failure rate, the time to the full information could be longer than expected. Therefore, to account for this potential reduction in the hazard rate in both arms (the hazard ratio remains at 1.43) and reduce the time to full information by 5 months, the sample size is increased to 720 randomized patients. With 660 and 720 patients the total study time with the reduction in hazards is 113 and 118 months, respectively. To derive the number of months required to reach full information, the actual accrual patterns through August 2016 and projections for the remaining number of patients to reach full accrual are used in the calculations.

Study Design: This study is designed with 90% power to detect a 30% reduction in the PFS hazard of conventional dose arm (Arm A) with maintenance until PD to high dose therapy arm (Arm B) with maintenance until PD. A stratified two-sided log-rank test will be used with an overall type I error rate of 0.05. This corresponds to a hazard ratio (hazard of conventional dose Arm A/hazard of high dose Arm B) of 1.43. Full information under the alternative hypothesis is 329 failures. A power of 90% was used in this study to adjust for the potential for cross over from the conventional dose arm to the high dose therapy arm prior to progression. Based on simulations allowing for constant cross over as well as varying patterns of cross over the power is reduced approximately 7-10% with up to 15% cross over at 3 years.

The current accrual patterns are used to determine the time required to reach full information with 720 patients randomized. Table 14.1 lists the actual accrual through August 2016 and the projected number of patients in the remaining months to reach 720 patients. Based on the failures rates ($\lambda_A = 0.0231/2 = 0.01155$, $\lambda_B = 0.0162/2 = 0.0081$), exponential distribution, and the accrual pattern in Table 14.1, the required number of failures (329) will be observed at 33 months after the end of accrual (80 months) for a total study time of 113 months. This is 5 months earlier in time than when full information would be observed with 660 patients.

Two interim analyses will occur at 33% and 69% information and the final analysis at full information. These results will be presented to the data- monitoring committee (DMC). At each

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DMC meeting toxicity results will be presented and interim analyses if at designated information times. To preserve the overall type I error rate, critical values at the interim analysis will be determined using the Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary. The study will also be monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (RCI) methodology. At each interim analysis, the one-sided 97.5% repeated confidence upper limit on the hazard ratio will be computed using the critical value from the error spending function.

Proposed analysis for both the IFM and US Studies: A descriptive analysis will be performed to attempt to address a question comparing PFS and OS for maintenance lenalidomide for 1 year (700 patients) vs. maintenance lenalidomide until PD (720 patients) overall and by conventional dose (350 vs. 360 patients) /high dose therapy arm (350 vs. 360 patients).

Table 14.1. Actual Accrual Per Month from October 2010 through August 2016.
Numbers for September 2016 to the June 2017 are projected numbers.

Month	Accrual	Month	Accrual	Month	Accrual
2010-10	1	2013-01	10	2015-04	9
2010-11	1	2013-02	13	2015-05	13
2010-12	3	2013-03	7	2015-06	15
2011-01	0	2013-04	11	2015-07	16
2011-02	3	2013-05	5	2015-08	14
2011-03	4	2013-06	4	2015-09	14
2011-04	1	2013-07	6	2015-10	15
2011-05	2	2013-08	11	2015-11	18
2011-06	2	2013-09	15	2015-12	10
2011-07	3	2013-10	10	2016-01	8
2011-08	7	2013-11	5	2016-02	16
2011-09	4	2013-12	11	2016-03	20
2011-10	6	2014-01	9	2016-04	10
2011-11	4	2014-02	14	2016-05	17
2011-12	2	2014-03	9	2016-06	11
2012-01	3	2014-04	7	2016-07	8
2012-02	6	2014-05	10	2016-08	7
2012-03	4	2014-06	13	2016-09*	10
2012-04	5	2014-07	18	2016-10*	10
2012-05	10	2014-08	14	2016-11*	10
2012-06	4	2014-09	11	2016-12*	10
2012-07	4	2014-10	11	2017-1*	10
2012-08	7	2014-11	14	2017-2*	10
2012-09	8	2014-12	16	2017-3*	10
2012-10	10	2015-01	13	2017-4*	10
2012-11	6	2015-02	13	2017-5*	8
2012-12	4	2015-03	17		

*Projected accrual

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14.3 Analysis of Secondary Endpoints

The secondary objectives of the study are to compare the following outcomes between the two arms: the response rates (CR, at least VGPR), time to progression, overall survival, toxicity, quality of life and pharmaco-economics. Prognostic groups defined by gene expression profiling will be defined in correlative studies. Duration of response is defined as the time from beginning of response to progression or death. Time to progression (TTP) is defined as the time of randomization until progression. Patients who have died without evidence of progression are censored in the TTP analysis and patients who are alive without progression are censored at the last disease assessment. Overall survival is defined as the time of randomization to death. Patients are censored at the time last known alive.

The proportion of patients with CR, proportion of patients with at least a CR/nCR and the proportion of patients with at least a VGPR will be compared rates between the two arms using Fisher's exact test. For response there is at least 80% power to detect differences of at least 11% in the 2 arms (Fisher's exact test, two-sided significance level of 0.05). The median duration of response will be compared using log-rank test.

14.4 Toxicity

The difference in the rate of all grade 3 or higher toxicities will be compared between the two groups using Fisher's exact test. There is at least 80% power to detect differences in the 2 arms of at least 10% in more common toxicities (>20%) and differences of at least 5% for rare toxicities (<10%), assuming two-sided Fisher's exact test, significance level of 0.05).

14.5 QOL Evaluations

The QOL will be measured using the The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core (QLQ-30), the MY20 questionnaire, and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-NTX) side-effects questionnaires. The questionnaires will be administered on 9 occasions: baseline (Cycle 1, Day 1), time of randomization (Cycle 2, Day 1), prior to cyclophosphamide administration. RVD Cycle 5 Day 1, Cycle 8 Day 1 (Arm A only), 20 days post PBSCT (Arm B only), Maintenance C6D1, End of treatment, and 2 years and 3 years from baseline.

The QOL domains to be compared between Arm A and Arm B include health related quality of life, distress, psychological functioning, physical well-being and functional well-being. Differences which can be detected with 80% power between the two arms in the change of scores from time of randomization are computed using a two-sided t-test with a 0.05/8 significance level assuming 1) standard deviations of 4, 8 and 12, 2) correlations of 0.5 and 0.8 between measurements, 3) assuming that the number of patients with QOL assessments is 100, 200, 400, and 700 with equal number of patients per arm. The effect sizes which can be detected

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for 100, 200, 400, and 700 patients are 0.73, 0.51, 0.36 and 0.25, respectively. These effect sizes translate into the following differences in QOL outcomes using the standard deviation of the scores and the correlation of repeated measures.

Assuming that between 100, 200, 400, and 700 participants complete the questionnaires and standard deviation of 4, the differences which can be detected with 80% power in the change of the score between the two arms is 3, 2, 1.4, 1.0 and 0.9, respectively, assuming the correlation is 0.5 and is 1.1, 0.8, 0.6, and 0.4 assuming the correlation is 0.8. With a standard deviation of 8, the differences which can be detected with 80% power in the change of the score between the two arms of 5.8, 3.1, 2.9 and 2.0, respectively, assuming correlation is 0.5 and 2.3, 1.6, 1.2, 0.8 assuming the correlation is 0.8, respectively for 100, 200, 400, 700 participants. With a standard deviation of 16, the differences which can be detected with 80% power in the change of the score between the two arms of 8.8, 6.1, 4.3, and 3.0, respectively, assuming correlation is 0.5 and 3.5, 2.5, 1.7, 1.2, assuming the correlation is 0.8, respectively for 100, 200, 400, 700 participants. Power estimates are based on the number of complete cases; and therefore, are conservative. In the analysis, multiple imputation methods will be used.

14.6 Pharmacoeconomics

The medical resource utilization will be evaluated in the two arms. Comparisons of continuous quantities will be done using the Wilcoxon-rank sum test. With an estimated 150 participants per arm, there is 80% power to detect an effect size of 0.39 using a two-sided test with a 0.05 significance level. With an estimated 350 participants per arm, there is 80% power to detect an effect size of 0.212 using a two-sided test with a 0.05 significance level.

14.7 Additional Analysis Information

Statistical analyses for this trial will be performed using the software programs SAS, R, Stata9. Patient characteristics will be summarized using proportions for discrete data and median for continuous variables with comparisons between arms performed using Fisher's exact test for discrete data and Mann-Whitney rank sum for continuous data. Time to event outcomes will be estimated using Kaplan-Meier methods and compared between groups using stratified log rank tests. Logistic regression models and Cox proportional hazard regression models will be implemented to evaluate the impact of baseline information on response and time to event outcomes. Evaluation of factors associated with better outcome will include characteristics of the patient and of the myeloma, biological and genetic markers. It will be performed using the same statistical tests (log rank and Cox model).

14.8 Correlative Studies

Although we will collect samples for all participants, it is expected that adequate correlative samples will be available on 70% of the patients. As a result correlative power

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calculations are based on 700 patients with 350 on each arm. These studies will look for early differences for correlative endpoints in terms of outcome (response) and later endpoints (PFS and OS).

14.9 Study Monitoring

The study will be monitored by an independent Data Monitoring Committee (DMC). The DMC will meet at least once a year and more often if needed (e.g., for safety review). For each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of the outcome data. Copies of the toxicity reports prepared by the DMC meetings will be distributed to the Principal Investigator. The Principal Investigator will then distribute to sub-investigators. Any DMC recommendations for changes to the study will be distributed to the Principal Investigator and then circulated to sub-investigators by the Principal Investigator. Further information is provided in Section 12.2.

14.10 Reporting and Exclusions

Intent to treat analysis will be used. Therefore, all patients randomized will be included in the analysis of the primary endpoint and toxicity.

15. PUBLICATION PLAN

Data from this trial will be reported once it is released from the DMC for publication. The final results of this study will be published in manuscript form in a major peer-reviewed journal. The 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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The results will be made public after the DMC has released the data. Detailed information on when the interim and final analyses occur are provided in section 14.0.

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APPENDICES

Appendix I: Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

- 1. Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy.

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

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

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

If you are a female not of childbearing potential:

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

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

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

2. Restrictions in sharing study drug and donating blood:

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

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

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Appendix II: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential or pregnant female, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential or pregnant female.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy
- Additional effective methods:
 - Male condom
 - Diaphragm
 - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

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- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through Revlimid REMS® program.

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Appendix III: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	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	20	Very sick, hospitalization indicated. Death not imminent.

	confined to bed or chair.	10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix IV: DuBois Formula for Body Surface Area

The preferred method of calculating BSA is using the DuBois formula that yields the following result in meters squared (m²):¹

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

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

Although the DuBois BSA formula is preferred, the Mosteller method is also acceptable.

Appendix V: The New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
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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 VI: 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>

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Appendix VII: Durie Salmon Stage and International Staging System (ISS) for Multiple Myeloma

Stage	Durie Salmon Stage	ISS Stage
I	<p>All of the following:</p> <p>Hemoglobin value >10 g/dL</p> <p>Serum calcium value normal or ≤ 12 mg/dL</p> <p>Bone x-ray, 0-1 lesion or solitary bone plasmacytoma only</p> <p>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</p>	<p>Serum B_2-microglobulin < 3.5 mg/L</p> <p>AND</p> <p>Serum albumin ≥ 3.5 g/dL</p>
II	<p>Neither stage I nor stage III</p>	<p>Serum B_2-microglobulin <3.5 mg/L, but serum albumin <3.5 g/dL</p> <p>OR</p> <p>Serum B_2-microglobulin 3.5 to <5.5 mg/L, irrespective of serum albumin</p>
III	<p>One or more of the following:</p> <p>Hemoglobin value <8.5 g/dL</p> <p>Serum calcium value >12 mg/dL</p> <p>Advanced lytic bone lesions (≥ 3 lesions)</p> <p>High M-component production rate — IgG value >7 g/dL; IgA value >5 g/dL — Bence Jones protein >12 g/24 h</p>	<p>Serum B_2-microglobulin ≥ 5.5 mg/L</p>

Short title: Phase III Study of RVD versus RVD plus auto SCT in newly diagnosed MM participants

Version Date: November 30, 2016

Adapted from Durie et al. and Greipp et al.

Appendix VIII: Quality of Life Assessment Tool

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

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During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

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Patient Signature: _____

Date: _____

Short title: Phase III Study of RVD versus RVD plus auto SCT in newly diagnosed MM participants
Version Date: November 30, 2016

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EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

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During the past week:

	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

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Patient Signature: _____

Date: _____

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Appendix IX: 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

Patient Signature: _____

Date: _____

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Appendix X: EQ-5D Questionnaire

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By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

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To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

Short title: Phase III Study of RVD versus RVD plus auto SCT in newly diagnosed MM participants
Version Date: November 30, 2016

Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

1. Have you experienced serious illness? Yes No
- in you yourself*
- in your family*
- in caring for others*
- PLEASE CHECK APPROPRIATE BOXES

2. What is your age in years ?

3. Are you: Male Female
-

4. Are you:
- a current smoker*
- an ex-smoker*
- a never smoker*
- PLEASE CHECK APPROPRIATE BOX

5. Do you now, or did you ever, work in health or social services? Yes No
-

If so, in what capacity?.....

PLEASE CHECK APPROPRIATE BOX

6. Which of the following best describes your main activity?
- employed (including self employment)*
- retired*
- keeping house*
- student*
- seeking work*
- other (please specify)*
- PLEASE CHECK APPROPRIATE BOX

7. What is the highest level of education you have completed?
- some high school or less*
- high school graduate or GED*
- vocational college or some college*
- college degree*
- professional or graduate degree*
- PLEASE CHECK APPROPRIATE BOX

8. If you know your zip code, please write it here

Patient Signature: _____

Date: _____

Appendix XI: Adjusted Ideal Body Weight (AIBW) Calculation

$$\text{AIBW} = \text{Ideal Body Weight} + (0.25) \times (\text{Actual Body Weight} - \text{Ideal Body Weight})$$

** All weights should be calculated in kilograms*

1 inch = 2.54 cm

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Ideal Body Weight Table

Males

Height (inches)	Weight (Kilograms)						
Age (yrs)	25-29	30-34	35-39	40-44	45-49	50-54	55up
59	55.5	56.8	57.7	59.1	60.0	60.5	60.9
60	56.4	57.7	58.6	60.0	60.9	61.4	61.8
61	57.3	58.6	59.5	60.9	61.8	62.3	62.7
62	58.3	59.5	60.5	61.8	62.7	63.2	63.6
63	59.5	60.9	61.8	63.2	64.1	64.5	65.0
64	60.9	62.3	63.6	64.5	65.5	65.9	66.4
65	62.7	64.1	65.5	66.4	67.3	67.7	68.2
66	64.5	65.9	67.3	68.2	69.1	69.5	70.0
67	66.4	67.7	69.1	70.0	70.9	71.4	71.8
68	68.2	70.0	71.4	72.3	73.2	73.6	74.1
69	70.0	71.8	73.6	74.6	75.5	75.9	76.4
70	71.8	74.1	75.9	76.8	77.7	78.2	78.6
71	74.1	76.4	78.2	79.5	80.5	80.9	81.4
72	76.8	79.1	80.9	82.3	83.2	83.6	84.1
73	79.5	81.8	83.6	85.0	86.4	86.8	87.3
74	82.3	84.5	86.8	88.2	89.5	90.0	90.5
75	85.0	87.3	89.5	91.4	92.7	93.2	93.6

Females

Height (inches)	Weight (kilograms)						
Age (yrs)	25-29	30-34	35-39	40-44	45-49	50-54	55up
59	52.7	54.1	55.5	57.3	58.6	59.5	60.0
60	53.6	55.0	56.4	58.2	59.5	60.5	60.9
61	54.5	55.9	57.3	59.1	60.5	61.4	62.3
62	55.5	56.8	58.6	60.5	61.8	62.7	63.6
63	56.8	58.2	60.0	61.8	63.2	64.1	65.0
64	58.6	60.0	61.8	63.2	64.5	65.5	66.4
65	60.0	61.8	63.6	65.0	66.4	67.3	68.2
66	61.8	63.6	65.5	66.8	68.6	69.1	69.6
67	63.6	65.5	67.3	68.6	70.5	71.4	71.8
68	65.5	67.3	69.1	70.5	72.3	73.6	74.1
69	67.3	69.1	70.9	72.3	74.1	75.5	75.9
70	69.1	70.5	72.3	73.6	75.5	77.3	78.6
71	70.5	71.8	73.6	75.5	77.3	79.1	80.5
72	72.3	73.6	75.0	76.8	78.6	80.5	82.7

(From *Surgical Adjuvant Program*. Buffalo, New York, Roswell Park Memorial Institute)

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Appendix XII: Corticosteroids Equivalence Table

Corticosteroids type (dose=1mg)	Dexamethasone Equivalence Dose (mg)
Hydrocortisone	0.04
Prednisone	0.15
Prednisolone	0.15
Methylprednisolone	0.19
Betamethasone	1.25

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APPENDIX XIII

DFCI Protocol # 10-106

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

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1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations (21 CFR Part 11); Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with

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Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. *Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates are not viewed as outside sites in this definition.*

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CH, BWH) will be the Lead Institution and will be 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 (CTEP, FDA, OBA etc.).

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A participating institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The participating institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair (DF/HCC Principal Investigator), Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Paul Richardson, MD will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the

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protocol.

- Assure all participating institutions are using the correct version of the protocol.
- Monitor progress and overall conduct of the study at all participating institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. CTEP, FDA, OBA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with CTEP/PIO Office (CTEP trials) or FDA (sponsor-investigator IND trials) or OBA (gene therapy trials), as applicable.
- Identify participating institutions and obtain accrual commitments. The title page must include the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e. Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution (Dana-Farber Cancer Institute) will ensure that all participating sites within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and Health Insurance Portability and Accountability Act (HIPAA) requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of Institutional Review Board (IRB) approvals from all participating institutions.
- Maintain CTEP, FDA or OBA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute external Serious Adverse Event safety reports.
- Monitor and audit Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Provide Central Participant Registration for DF/HCC participants.
- Confirm eligibility and consent of DF/HCC participants.

2.3 Participating Institution

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The Participating Institution(s) will be identified on the title page for each protocol. In addition, each participating institution will provide to the Lead Institution or designee a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.

The general responsibilities for each participating institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Update Coordinating Center (Lead Institution or designee) with research staff changes on a timely basis.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center (Lead Institution or designee).
- Submit Serious Adverse Event reports and pregnancy reports to local IRB and directly to the Coordinating Center (Lead Institution or designee).
- Submit deviations and violations to local IRB and the Coordinating Center (Lead Institution or designee).
- For protocols using investigational agents, the participating institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company).

3.0 DF/HCC QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS

The DF/HCC QACT is a unit that has been developed to computerize, manage, and monitor data for DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to monitor DF/HCC trials.

3.1 Organizational Structure

The DF/HCC Quality Assurance Office for Clinical Trials administrative structure consists of:

DF/HCC Quality Assurance Officer for Clinical Trials: Oversees the functions of the DF/HCC QACT.

QACT Assistant Director for Monitoring: Provides direct oversight to the QACT Protocol Registrars and Clinical Research Auditors.

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The DF/HCC Protocol Registrars are responsible for the confirmation of each participant's eligibility and consent prior to protocol registration.

If funded and QACT approved, the DF/HCC Clinical Research Auditors may assist the Lead Institution in their auditing responsibilities for multi-center trials. The QACT auditor is responsible for systematically evaluating participant safety, protocol compliance, institutional SOPs, ICH GCP and Federal regulation compliance, data accuracy and investigational drug handling to assure a high standard of quality for DF/HCC trials.

4.0 PROTOCOL DEVELOPMENT

4.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and if applicable CTEP Multi-center, FDA or OBA Guidelines. Further, the Protocol Chair will be the single liaison with the CTEP/PIO, the FDA or OBA, as applicable.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify participating institutions and obtain accrual commitments. The title page must include the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

4.2 Coordinating Center Support Function

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The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all participating sites (conference call, emails, etc). Conference calls with sites will occur at least monthly and more often if needed.
- Maintain documentation of all communications.

5.0 PROTOCOL MANAGEMENT

The Coordinating Center (Lead Institution of designee) is responsible for assuring that each Participating Institution in the DF/HCC Multi-center Protocol has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Lead Institution or designee must maintain copies of all IRB approvals, for each participating institution.

5.1 Protocol Distribution

The final approved protocol and any subsequent amended protocols will be distributed to participating centers by the Coordinating Center.

5.2 Protocol Revisions and Closures

The participating institutions will receive e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

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Non life-threatening revisions: Participating institutions will receive email notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating institutions will receive email notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

Protocol Closures and Temporary Holds: Participating institutions will receive e-mail notification of protocol closures and temporary holds, with follow-up by mail from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

5.3 Informed Consent Requirements

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is DF/HCC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

5.4 IRB/IEC Documentation

The following must be on file with the DF/HCC Lead Institution or designee prior to participant registration:

- Approval Letter of the institution's IRB (An Expedited IRB first approval is NOT acceptable)
- IRB approval for all amendments

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It is the individual institution's responsibility to notify its IRB of protocol revisions. Participating institutions will have 90 days from receipt to provide the DF/HCC Lead Institution or designee their IRB approval for Major Amendments to a protocol.

DF/HCC defines a Major Amendment as: A substantive change in the study which may increase or decrease the risk to study participants. Major revisions require full IRB approval. The following criteria are examples of revisions to a protocol that are considered to be major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention
- Change of device
- Change in primary objective evaluation process

5.5 IRB Re-Approval

Annual IRB re-approval from the Participating institution is required in order to register participants onto a protocol. There is no grace period for annual re-approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution or designee from the Participating Institutions on or before the anniversary of the previous approval date.

5.6 Participant Confidentiality and Authorization Statement

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

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In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol participating institutions) must use.

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

5.7 Participant Registration and Randomization

5.7.1 Registration Process for DF/HCC Institutions

Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible. The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. Once eligibility criteria are confirmed following procedures described in Section 3, the patient must first be registered in the eCRF.

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- Eligible participants will be registered in the eCRF by the participating site. Registration must occur prior to the initiation of therapy (RVD Cycle 1, Day 1).
- The participating institutions will register eligible participants to this study 24 hours a day, 7 days a week, using web-based registration: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link “Contact Technical Support”. A user-specific login and password are required to access the website.
- Participant study number will be automatically allocated by the online registration system based on the following format :

||_|_| - |_|_|_|_|

(3digits for the site number) – (3digits for the patient number)

Note: Participant study number will be sequentially allocated for each site.

- **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**
- Information required for participant registration includes patient information (initials, date of birth, sex...), informed consent information, inclusion and exclusion criteria. Some biological parameters are also required in order to complete registration.
- Once all registration information is entered and the web-based system verifies that inclusion and exclusion criteria are met, patient registration is confirmed. The site will receive an email confirmation with participant study number once the registration process is complete. **Patients must not begin study treatment prior to receiving email confirmation.**
- To register the participant with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system, complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant’s medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**
- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.
- The QACT Registrar will (a) validate eligibility, and (b) register the participant on the study.
- The QACT Registrar will send an email confirmation of the registration to the person initiating the registration immediately following the registration.

If a participant does not receive protocol therapy following registration, the participant’s protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

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5.7.2 Registration Process for Other Participating Institutions

Eligible participants will be registered with a central registration system by the site. Registration must occur prior to the initiation of therapy. Following registration, participants should begin protocol treatment within 72 hours or as soon as possible.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. Once eligibility criteria are confirmed following procedures described in Section 3, the patient must be registered in the eCRF.
- Eligible participants will be registered in the eCRF by the participating site. Registration must occur prior to the initiation of therapy (RVD Cycle 1, Day 1).
- The participating institutions will register eligible participants to this study 24 hours a day, 7 days a week, using web-based registration: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link “Contact Technical Support”. A user-specific login and password are required to access the website.
- Participant study number will be automatically allocated by the online registration system based on the following format :

|_|_|_| - |_|_|_|

(3digits for the site number) – (3digits for the patient number)

_____ Note: Participant study number will be sequentially allocated for each site.

- **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**
- Information required for participant registration includes patient information (initials, date of birth, sex...), informed consent information, inclusion and exclusion criteria. Some biological parameters are also required in order to complete registration.
- Once all registration information is entered and the web-based system verifies that inclusion and exclusion criteria are met, patient registration is confirmed. The site will receive an email confirmation with participant study number once the registration process is complete.
- In addition, the participant must be registered with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. The following

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documents should be completed by the research nurse or data manager and faxed
[REDACTED] or emailed to the DFCI Study Coordinator at

[REDACTED]:

- Eligibility checklist
- Signed study consent form
- HIPAA authorization form
- To complete the registration process, the DFCI Study Coordinator will:
 - Register the participant on the study with QACT
 - Email the research nurse or data manager at the participating site to confirm eligibility and registration with QACT

Note: Registration with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the Study Coordinator of participant status changes as soon as possible.

5.7.3 Randomization Process for DF/HCC Institutions

Randomization assignment for participants from DF/HCC must be entered into the DF/HCC QACT central registration system. The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

Randomization must occur 2-3 weeks after the initiation of cycle 1 of RVD and prior to cycle 2 of RVD.

The randomization procedures are as follows:

- The participating institution will randomize participants 24 hours a day, 7 days a week, using web-based randomization: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link "Contact Technical Support". A user-specific login and password are required to access the website.
- Randomization information is entered on the web-based randomization system by the participating institution. Stratified permuted blocks will be used in the randomization using the following stratification factors. Stratification factor information will be requested at the time of randomization, and randomization will be blocked if the following data are not entered:
 - ISS Stage I vs. II vs. III. Institutions will provide Beta2- microglobulin level (mg/L) and serum albumin level (g/dL) entered from screening visit, and the randomization system will compute the ISS stage.

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- Standard vs. high risk vs. FISH failures. High-risk is defined as the presence of del(17p), or t(4:14), or t(14;16) using FISH.
- Country (US)
- Once participant randomization data is entered in the eCRF, the randomization system will allocate the treatment arm (A or B). The site will receive an email confirmation of treatment arm once the randomization process is complete.
- Randomization assignment for must also be entered into the DF/HCC QACT central registration system. The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.
- Enter the randomization assignment on the protocol-specific eligibility checklist.
- Fax the eligibility checklist to the QACT at 617-632-2295.
- The QACT Registrar will enter the randomization assignment into the QACT system.
 - The QACT Registrar will send an email confirmation that the randomization assignment has been entered to the person initiating the randomization immediately following the randomization.

5.7.4 Randomization Process for Other Participating Institutions

Randomization must occur 2-3 weeks after the initiation of cycle 1 of RVD and prior to cycle 2 of RVD.

The randomization procedures are as follows:

- The participating institution will randomize participants 24 hours a day, 7 days a week, using web-based randomization: <https://www.ifm-online.fr/csonline>. For assistance or questions, the technical support team can be contacted using the link “Contact Technical Support”. A user-specific login and password are required to access the website.
- Randomization information is entered on the web-based randomization system by the participating institution. Stratified permuted blocks will be used in the randomization using the following stratification factors. Stratification factor information will be requested at the time of randomization, and randomization will be blocked if the following data are not entered:
 - ISS Stage I vs. II vs. III. Institutions will provide Beta2- microglobulin level (mg/L) and serum albumin level (g/dL) entered from screening visit, and the randomization system will compute the ISS stage.
 - Standard vs. high risk vs. FISH failures. High-risk is defined as the presence of del(17p), or t(4:14), or t(14;16) using FISH.
 - Country (US)

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- Once participant randomization data is entered in the eCRF, the randomization system will allocate the treatment arm (A or B). The site will receive an email confirmation of treatment arm once the randomization process is complete.
- In addition, the participant must be registered with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. The randomization assignment should be entered on the protocol-specific eligibility checklist by the research nurse or data manager at the participating site, and faxed (617-632-4301) or emailed (ajantha_nithi@dfci.harvard.edu) to the DFCI Study Coordinator.
- The DFCI Study Coordinator will randomize the participant on the study with QACT and email the research nurse or data manager at the participating site to confirm randomization with QACT.

Note: Randomization with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday.

5.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a protocol case number. This number is unique to the participant on this trial and must be used for eCRF completion and written on all data and QACT correspondence for the participant.

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5.9 DF/HCC Multi-center Protocol Registration Policy

5.9.1 Initiation of Therapy: Participants must be registered with the web-based registration system before receiving treatment. Treatment may not be initiated until the site receives an e-mailed copy of the participant's Registration Confirmation memo from the web-based registration system. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy.

5.9.2 Eligibility Exceptions: The web-based registration system will make no exceptions to the eligibility requirements for a protocol. In addition, the Cancer Therapy Evaluation Program (CTEP) specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements.

5.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to this protocol will be emailed to the registering institution upon completion of the registration. Treatment may not be initiated until the site receives thee-mailed copy of the registration confirmation memo.

5.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned protocol case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

5.10 Schedule of Data Submission

Electronic case report forms will be used for data collection in this study, and can be accessed using the following website: <https://www.ifm-online.fr/csonline>. Completion and submission guidelines for these eCRFs can be located in the Study Manual.

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5.11 Missing and Deficient Data

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data: If study forms are received with missing or questionable data, the submitting institution will receive a query from the database.

6.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is generally specified in the protocol.

Participating sites should order their own agent directly from the supplier regardless of the supplier (i.e., NCI or a pharmaceutical company).

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/IEC. If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent. 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.

7.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents 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 to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria assigned to the protocol (CTEP Version 4.0) and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and IRB.

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

7.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, the development of drug dependency or abuse; or suspected transmission of an infectious agent by a medicinal product.

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm.

7.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol, Section 11.0.

In addition, the Participating Institutions must report the serious adverse events to the Protocol Chair and the Coordinating Center (Lead Institution) following the DFCI IRB SAE Reporting Requirements.

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The Lead Institution will maintain documentation of all Adverse Event Reporting and be responsible for communicating all SAEs to all Participating sites.

7.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, the Protocol Chair is responsible for reviewing all IND Safety Reports and forwarding the IND Safety Reports to the Participating Institutions. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

8.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all institutions participating in the DF/HCC Multi-center Protocol.

8.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject 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.

8.2 Reporting Procedures

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The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol exceptions, deviations and violations.

The Protocol Chair 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 DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the participating site's own IRB, per its institutional policy.

A copy of the participating institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair 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.

9.0 QUALITY ASSURANCE

The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality assurance oversight for the DF/HCC Multi-center Protocol.

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9.1 Ongoing Monitoring of Protocol Compliance

Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. For this trial, a commercial contract research organization (CRO) will perform the ongoing protocol compliance monitoring with the support of the Lead Institution or designee, participating institution's Coordinators, the Principal Investigators, and the Protocol Chair. A Clinical Research Associate (CRA) from the commercial CRO will perform on-site monitoring visits to participating sites throughout the course of the trial and at study close-out.

9.2 Evaluation of Participating Institution Performance

9.2.1 ELIGIBILITY CHECKLIST: An eligibility checklist for each participant is completed within the web-based registration system prior to registration on protocol. Eligibility criteria and informed consent documentation are verified by the CRA during on-site monitoring.

9.2.5 ACCRUAL OF ELIGIBLE PARTICIPANTS: ANNUAL ACCRUAL RATES FOR ELIGIBLE PARTICIPANTS ENROLLED ONTO THERAPEUTIC CLINICAL TRIALS IS CALCULATED FOR EACH INSTITUTION. INSTITUTIONS ARE EXPECTED TO MAINTAIN THE MINIMUM ANNUAL AVERAGE ACCRUAL AS DEFINED BY THE PROTOCOL GRANT OR CONTRACT.

9.3 On-Site Auditing

9.3.1 DF/HCC Sponsored Trials

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The participating institutions will be subject to on-site monitoring conducted by a commercial contract research organization (CRO).

The Lead Institution or designee will be responsible for site initiation visits. These visits will be conducted as either an on-site visit or via webconference. If investigator meetings are planned, they may be considered as initiation visits if agreed by the sponsor. Following site initiation, a commercial CRO will be responsible for on-site monitoring and close-out visits at participating sites. A CRA, delegated by the sponsor, will visit each study center one or more times during the trial according to the pace of enrollment, and at the end of the trial. The frequency of site monitoring will be dependent on site enrollment, with the first visit occurring within two months of first participant enrollment. After the first monitoring visit, on-site monitoring will occur approximately once every three months or as accrual dictates.

The purpose of these visits is to monitor compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center. Source document verification will be performed on 30% of the data and will include review of inclusion and exclusion criteria, safety data, and data related to study endpoints and disease response.

During the course of the study, communication with participating sites will occur at least monthly via teleconference and more often if needed.

9.3.2 Participating Institution

It is the participating institution's responsibility to notify the DF/HCC Lead Institution or designee of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

The DF/HCC Lead Institution or designee will notify Celgene and Millennium of audit requests.

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9.3.3 Coordinating Center (Lead Institution or designee)

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

9.4 Sub-Standard Performance

The Protocol Chair, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions: Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, and adherence to protocol requirements will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

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