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TRANSPLANT
CLINICAL TRIALS NETWORK

A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma

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BMT CTN PROTOCOL 0702
Version 8.0

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Study Agents:
CC-5013 (lenalidomide) (NSC 703813) – Supplied by Celgene and distributed by Biologics, Inc. through the Revlimid REMS
PS-341 (bortezomib) (NSC 681239) – Supplied by Millennium and distributed by EMINENT Services Corporation

Cooperative Group participation will be facilitated by the Cancer Trials Support Unit (CTSU). Cooperative Group participation will be limited to U.S. Cooperative Group-approved transplant center sites. Endorsing Cooperative Groups: Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), SWOG.

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Case Western Reserve University Consortium
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Brigham & Women's Hospital
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West Virginia University Hospital
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*Non-BMT CTN centers meeting the study criteria will participate through the CTSU mechanism.

*BMT CTN centers with Cooperative Group affiliation may choose to participate through the BMT CTN or the CTSU mechanism.

CTSU Logistics are located in Appendix L of the protocol

CTSU Contacts for BMT CTN 0702

Fax site **pre**-approval documents listed in Appendix L, Table L-1 to the BMT CTN Data and Coordinating Center (DCC)/Emmes at 240-306-0963

Submit site registration documents listed in Appendix L, Table L-2:

CTSU Regulatory Office
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For patient enrollments:
Patient enrollments will be conducted by CTSU Patient Registration using the Oncology Patient Enrollment Network (OPEN). Fax patient enrollment documents to the CTSU Patient Registration desk as outlined in appendix L (CTSU Logistics) of this protocol.

For data submission:
Access the BMT CTN AdvantageEDC on-line system:
https://secure.emmes.com/bmt/jsp/login.jsp

Questions?

Regarding: • Registration requirements in Appendix L, Table L-1	Courtney Nelson, Protocol Coordinator Connie Weaver, Protocol Coordinator Brianne Allison, Data Manager Jennifer Romeril, RN, BSN, Adverse Event Coordinator
• BMT CTN AdvantageEDC system • Patient eligibility or treatment • Adverse Events in Appendix K	BMT CTN Data and Coordinating Center (DCC) The Emmes Corporation 401 N. Washington Street, Suite 700 Rockville, MD 20850 Phone: (301) 251-1161 FAX: (240) 306-0963 cnelson@emmes.com , cweaver@emmes.com
Regarding: • Registration requirements in Appendix L, Table L-2 • Protocol and supporting documents posted on the CTSU Website or the OPEN patient enrollment system	CTSU Regulatory Office Help Desk 1-888-651-CTSU (2878) CTSU General Information Line 1-888-823-5923 OR ctsucontact@westat.com

PROTOCOL SYNOPSIS – BMT CTN 0702 PROTOCOL

A Trial Single Autologous Transplant with or without RVD Consolidation versus Tandem Transplant and Maintenance Therapy for Patients with Multiple Myeloma

Co-Principal Investigators: Amrita Krishnan, MD, George Somlo, MD, and Edward Stadtmauer, MD

Study Design: The study is designed as a Phase III, multicenter trial of tandem autologous transplants plus maintenance therapy versus the strategy of single autologous transplant plus consolidation therapy with lenalidomide, bortezomib and dexamethasone (RVD) followed by maintenance therapy or single autologous transplant plus maintenance therapy as part of upfront treatment of multiple myeloma (MM). Lenalidomide will be used as maintenance therapy for three years in all arms.

Primary Objective: The primary objective of the randomized trial is to compare progression-free survival (PFS) between the three treatment arms as a pairwise comparison.

Secondary Objectives: Secondary objectives are to: compare disease response with rates of very good partial remission or better (VGPR, nCR, CR and sCR); compare the rate of CR conversion for patients not in CR at initiation of maintenance; compare overall survival (OS); compare the rate Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE); compare the incidence of infections; compare the rate of treatment-related mortality; assess the rate of non-compliance of therapy; and describe and compare quality of life in all three arms of the study.

Eligibility Criteria: Eligible patients are ≤ 70 years of age with Karnofsky scores ≥ 70, who have symptomatic MM requiring treatment, who have received at least two cycles of systemic therapy and who are within 2-12 months of initiation of the initial therapy. Patients must have available an autograft ≥ 4 x 10^6 CD34+ cells/kg patient weight.

Treatment Description: Mobilization therapy will not be specified for the study. Randomization to three treatment arms will be done prior to the first transplants. All patients will undergo a first autologous peripheral blood stem cell (PBSC) transplant with high-dose melphalan (200 mg/m^2 IV) given on Day –2. Upon recovery from the first transplant patients will receive either a second

autologous PBSC transplant with the same conditioning regimen as the first transplant or consolidation therapy with RVD (lenalidomide 15 mg/day on Days 1-14, dexamethasone 40mg on Days 1, 8 and 15, and bortezomib 1.3mg/m^2 on Days 1, 4, 8 and 11 of every 21 day cycle, patients will receive four cycles) or maintenance with lenalidomide (15 mg daily). All patients will also receive maintenance lenalidomide which will start after the second transplant, after the first autologous transplant or after consolidation therapy depending on the treatment arm. Maintenance therapy with lenalidomide will start at 10 mg daily for 3 months and increase to 15 mg daily. The duration of maintenance will be three years in all treatment arms.

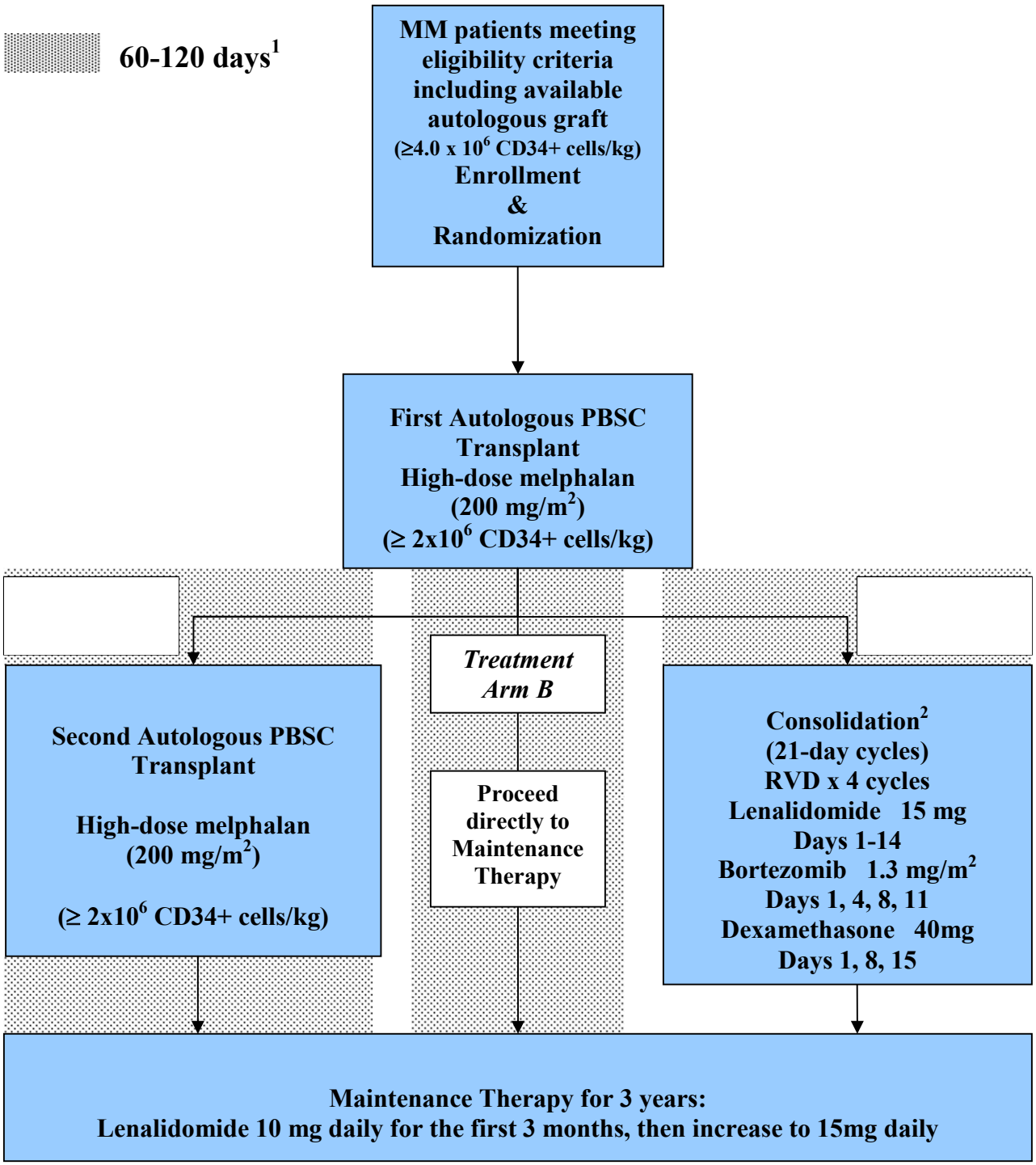
Quality of Life: The FACT-BMT and MOS SF-36 instruments will be used to describe the health-related quality of life (HQL) of patients. A secondary analysis will compare the HQL between the treatment arms. The self-report questionnaires will be performed prior to first and second transplants, consolidation therapy, and initiation of maintenance, after one year from randomization and yearly thereafter until four years from randomization for English and Spanish speaking patients.

Accrual Objective: 750 patients, allocated as 250 patients in each treatment arm.

Accrual Period: The estimated accrual period is three years.

Study Duration: Patients will be followed for 4 years from time of randomization. The primary analysis will occur at 38 months post randomization to enable patients who so desire to continue lenalidomide on an extended follow-up protocol.

Outline of Treatment Plan



[1] The recommended timing between the first and second intervention is 60 to 120 days, but not longer than 180 days.
[2] Consolidation can last from 84 to 180 days. Maintenance will start immediately after consolidation ends in patients meeting eligibility to initiate maintenance.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Multiple myeloma (MM), is characterized by malignant plasma cell proliferation, bone destruction and immunodeficiency, is a disease with a median age at diagnosis of approximately 70 years. It is responsible for about 1 percent of all cancer-related deaths in Western Countries.[1] Conventional treatments with chemotherapy and radiation therapy are non-curative but improve quality of life and duration of survival. Attempts to cure myeloma through high-dose therapy followed by autografting or allografting have largely failed due to a both relapsed disease and treatment-related mortality (TRM). High-dose therapy with autologous transplantation is safe and has low TRM (< 5%), but is associated with a continuing and nearly universal risk of disease progression and relapse. Even so, survival rates after autologous transplantation are superior to survival rates with continued conventional chemotherapy.[2] Recent data indicate that tandem autologous transplants are superior to a single procedure.2 However, those trials used conditioning regimens that would now be considered nonstandard (e.g., melphalan plus total body irradiation [TBI]) and doses of melphalan higher than the current standard.2

One approach to improving disease control with autologous transplantation is the use of post-transplant interventions, such as interferon and, more recently, anti-angiogenesis agents such as thalidomide. The Arkansas total therapy II trial showed that thalidomide combined with other agents resulted in superior event-free survival (EFS) compared to those same agents without thalidomide.[3] Furthermore the IFM 99 trial, a large randomized trial, demonstrated that thalidomide maintenance improves overall survival following tandem autologous transplantation in patients with elevated beta-2 microglobulin and absence of deletion 13 chromosome abnormalities.[4] Dexamethasone, an effective agent in the treatment of MM, has been combined with thalidomide resulting in synergy and no unexpected toxicities.[5] Initial results suggest that the combination of thalidomide and dexamethasone is well tolerated after autologous transplantation.[6]

A new immunomodulatory class of drugs (IMiDs®) such as lenalidomide has recently demonstrated high-response rates and favorable side effect profile in upfront and salvage trials. A Phase II trial at the Mayo Clinic used lenalidomide and dexamethasone as induction therapy. The overall response rate was 91%.[7] Lower doses of dexamethasone in combination with lenalidomide are also being studied for primary therapy. One-year survival rates with this combination appear promising. The Phase III MM009 trial of lenalidomide and dexamethasone versus dexamethasone alone for relapsed/refractory MM reported response rates of 61% with combination therapy compared to 22% with dexamethasone alone.[8]

Several new studies have explored combining lenalidomide with bortezomib for patients with relapsed refractory myeloma. Preclinical data indicates an additive effect when the two drugs are combined. Phase I and Phase II trials have been completed combining bortezomib 1.0mg/m^2 and lenalidomide 15mg daily for 14 days plus dexamethasone (RVD).[9] The Phase II trial showed

a response rate of 79% in patients with relapsed/refractory MM with no unacceptable non-hematologic toxicity. Bortezomib and lenalidomide have non-overlapping toxicities; this combination may be a good option earlier in the disease course. Trials are ongoing utilizing this regimen as upfront induction therapy.[10] In the proposed BMT CTN trial, patients will receive this regimen for four cycles after an autologous transplant. High response rates and low toxicity of this regimen may lead to a superior progression-free survival (PFS) and quality of life than a second autologous transplant. Since data from the APEX trial on bortezomib versus high-dose dexamethasone suggests that response to bortezomib is independent of cytogenetics, this regimen may be particularly attractive for patients with poor risk cytogenetics.[11]

This proposed study will explore several questions. First, it will answer the question of which of the following treatment approaches after an autologous transplant will offer the best PFS, overall survival (OS) and QOL: maintenance therapy with lenalidomide; intensive consolidation with a combination of new agents followed by maintenance lenalidomide; or a second course of high-dose melphalan and autologous transplant plus maintenance. Lenalidomide was chosen as the maintenance regimen in all arms based on its demonstrated efficacy in the salvage and upfront settings, ease of administration and acceptable side effect profile. The combination of lenalidomide, bortezomib and dexamethasone was chosen for intensive consolidation based on preclinical data showing synergy, and Phase I and Phase II data showing high response rates and favorable safety profiles.

The study will also examine the effect of these approaches on high-risk patients such as those with deletion 13, t(4;14) and other poor risk cytogenetic abnormalities detected by either FISH analysis or standard metaphase karyotyping.

1.2. Rationale for Study

1.2.1. High-dose Melphalan as a Treatment for Multiple Myeloma

Until a decade ago, the prognosis of patients with MM had not significantly improved since the introduction of melphalan and prednisone, despite the introduction of several combination chemotherapy protocols. However, this changed with the use of high-dose melphalan and, more recently, newer agents. Pioneering studies by McElwain et al[12] demonstrated that treatment with high-doses of melphalan could induce responses in refractory myeloma. The responses were brief and were complicated by a high toxic death rate, ranging from 17%-31% in the initial series.[13,14] Nonetheless, these results stimulated interest in further studies to address the role of high-dose therapy in myeloma. The demonstration by Barlogie et al[15] that the toxicity of high-dose melphalan could be decreased by autologous bone marrow transplantation and that the addition of TBI increased response rates led to wider application of high-dose therapy using autologous bone marrow and, subsequently, peripheral blood stem cell (PBSC) support.

Multiple studies support a steep dose-response relationship for activity melphalan in MM. Doses up to 280 mg/m^2 have been used in myeloma and other malignancies.[16] In a Phase I trial involving MM patients, melphalan at a dose of 200 mg/m^2 was estimated to be the maximum tolerated dose for two cycles administered within 90 days.[17]

With bone marrow or PBSC support following high-dose melphalan, the toxic death rate is less than 3% in most studies.[4, 18] At a dose of 200 mg/m^2, high response rates in both untreated and previously treated patients are reported.[19, 3, 20, 21] Recent data indicate that melphalan 200 mg/m^2 is less toxic but equally effective as melphalan with TBI.[3, 22]

1.2.2. Tandem Autologous Transplantation

Barlogie et al showed the feasibility of tandem autologous PBSC transplants using melphalan 200 mg/m^2 for the first transplant and melphalan 200 mg/m^2 (79 patients) or melphalan 140 mg/m^2 plus TBI (1,125 cGy) (10 patients) for the second transplant. Of 123 patients, 87% completed one autologous transplantation and 76% completed a second autologous transplantation by 7.5 and 13 months, respectively, with a median interval between autologous transplantations of 4.5 months. Patients were hospitalized a median of 14 days with the first autologous transplantation and only six days with the second. Cumulative TRM during the first 12 months was 4%.[21] Barlogie reported a 40% complete response (CR) rate with tandem transplantation and a median EFS of 49 months, based on an intent to treat analysis in this single center experience. Overall, these results suggest that doses of melphalan of 140 mg/m^2 or higher, supported by hematopoietic stem cell infusion, provide a high-dose anti-myeloma regimen with acceptable toxicity.[23]

For responding patients, high-dose therapy followed by autologous PBSC rescue has been shown to be superior to continued treatment with conventional chemotherapy, leading to the widespread use of autologous transplantation for myeloma patients up to and beyond the age of 70.2. [20] Several studies, including preliminary data from the French IFM94 trial, suggest that tandem autologous transplants are superior to a single high-dose treatment.[19, 24] In the IFM study, the PFS and OS curves separated after three years with improved disease-free and overall survival at six years post-transplantation for the group that received tandem autologous transplants compared to those receiving single transplants. Median EFS times were 31 versus 37 months, 6-year EFS rates were was 19% versus 28% and 6-year overall survival rates were 26% versus 46% for single versus tandem transplants, respectively. The interim results of the "Bologna 96" trial presented at the 2002 ASH meeting further supported the role of tandem transplantation. In this randomized trial of single versus tandem autologous transplants as part of front line therapy for MM, both remission duration (44 months versus 27 months, p=0.005) and median EFS duration (44 months versus 27 months, p=0.05) were superior in the tandem autologous transplant arm.[24] However, different conditioning regimens were used in these trials and, as discussed above, subsequent randomized trials comparing melphalan/TBI to melphalan alone have demonstrated that single agent melphalan at 200 mg/m^2 has emerged as the preferred conditioning for autologous transplantation.[22] Additionally, the IFM 94 trial studied the benefit of the second transplant based on response to the first transplant, as a secondary endpoint and found that patients who achieved a CR or very good partial response (VGPR) after the first transplant did not benefit from the second transplant. Similarly, subgroup analysis of the Bologna 96 trial demonstrated that the benefits of tandem transplant were greatest in patients who failed to achieve a near CR with the first transplant. This raises the question of whether second transplants benefit all patients. Moreover, while TRM rates observed in these studies are low, patients continued to develop disease progression for many years, with only a minority patients remaining disease free at six years.

1.2.3. Post Autologous Transplant Consolidation Therapy

In recent years several new agents have emerged for the treatment of MM and have greatly altered the way the disease is treated.[8, 11, 25] Two novel agents with significant activity in both newly diagnosed and relapsed myeloma are bortezomib (Velcade®) and lenalidomide (Revlimid®).[8, 11] Bortezomib is FDA approved for the treatment of relapsed myeloma.[11] Recently studies also show high activity with this agent in the upfront setting with response rates of approximately 80%. Similarly, large Phase III trials demonstrate the efficacy of lenalidomide plus dexamethasone over dexamethasone alone for patients with relapsed myeloma.8 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. The combination of lenalidomide and dexamethasone is also being tested in the upfront setting and has evidence of high response rates. There is also evidence of incremental activity of these agents in combination with dexamethasone9 and alkylators such as melphalan.[26]

The combination of therapy with bortezomib, thalidomide and dexamethasone (VTD) in patients with myeloma achieves high CR rates in newly diagnosed patients and may even increase CR rates after subsequent autologous transplantation.[27] CR plus near CR rates (i.e. detectable paraproteins by immunofixation only) reached 38% after initial therapy with VTD compared to 7% with thalidomide dexamethasone.[27] Richardson and colleagues have used combined bortezomib and lenalidomide in patients with relapsed refractory myeloma and demonstrated that the combination is safe and efficacious.[9, 28] The dosing used in this BMT CTN trial mirrors that in the planned ECOG trial of RVD induction and consolidation in the nontransplant setting.

The question to be addressed is whether this combination administered after an autologous transplant will provide equivalent EFS to a planned second transplant autologous transplant with high-dose melphalan. Most patients (60%) in the Richardson Phase I study had relapsed after prior autologous transplantation, hence it is anticipated that it will be feasible to administer four cycles of this regimen as post-transplant consolidation. Appropriate dose modifications for cytopenias will be built into the protocol. A recent trial of bortezomib, thalidomide and dexamethasone consolidation post single autologous transplant demonstrated that it is feasible to administer four cycles of consolidation. Furthermore, with this approach, a proportion of patients (22%) became PCR negative for molecularly detectable residual disease.[29]

1.2.4. Post Autologous Transplant Maintenance Therapy

Convincing clinical data indicate that high-dose therapy and autologous transplantation produces better outcomes than conventional chemotherapy for MM. In the randomized study by Attal et al, the probability of five-year event-free survival was 28% in patients treated with autologous transplant compared to 10% in those treated with conventional chemotherapy.2 As discussed earlier, tandem autologous transplants appeared to be superior to single autologous transplants in the IFM94 trial with six-year event free survival of 19 versus 28%.[19] However, it is unclear whether the benefit of the tandem approach will remain with the use of post-transplant

maintenance therapy or the use of newer agents such as bortezomib or lenalidomide for post-transplant consolidation as previously discussed.

Several agents have been used for post-transplant maintenance. Of these, interferon is the most extensively studied. The evidence regarding the role of interferon after autologous transplantation is conflicting. A single, relatively small, randomized trial showed a non-statistically significant trend to longer progression-free survival with interferon but no improvement in overall survival.[30] A moderately-sized retrospective EBMT study demonstrated a longer median PFS (29 versus 20 months; p=0.006) and longer OS (78 versus 47 months; p=0.007) in patients receiving post-transplant interferon.[29] Despite these results, interferon is not consistently used after transplantation, largely because of toxic side effects. Other agents used include corticosteroids; which have most commonly been given with thalidomide.[31, 32]

Thalidomide was first introduced in 1953 as a sedative hypnotic, but a large increase in incidence of newborns with limb malformations led to its withdrawal in 1960. The immunosuppressive activity of thalidomide was first noted and used in the therapy of lepromatous leprosy.[31, 33] Its activity in chronic GVHD was reported in 1988.[34] The exact mechanism of this activity is unknown but reports suggest diverse mechanisms including effects on cell-mediated and humoral immunity as well as cytokine modulation.[35], [36]

Thalidomide inhibits angiogenesis in animal models and is active in myeloma with response rates of 30% even in patients with advanced and refractory disease.[37] Thalidomide also, in pre-clinical studies, inhibits the production of IL-6 by peripheral blood mononuclear cells.[38, 39] Data suggest that IL-6 production by marrow stromal cells is important in the pathogenesis of MM.[39] There are reports of possible benefits of thalidomide therapy in MM associated with reduction of tumor burden as well as a marked decrease in microvessel density in the bone marrow. Singhal and colleagues reported significant anti- tumor activity of thalidomide in patients with advanced and high-risk MM.[40] Toxicities of thalidomide therapy are neurologic (somnolence, dizziness, confusion, tremors, loss of coordination, tingling, numbness), gastrointestinal (constipation, nausea, vomiting, and stomatitis), and constitutional (weakness, weight loss, fever). These toxicities are generally moderate with doses of thalidomide up to 400 mg/day.

Thalidomide has been used concomitantly with corticosteroids without unexpected toxicities and with possible synergistic effects.5 The optimal dose of thalidomide is not established, although toxicities are dose-related. Responses are reported even at 50 mg/day. Current trials generally target the maximum tolerated dose up to a daily dose of 200 mg/day.5, 6

The use of thalidomide as post-transplant maintenance has been studied in several randomized trials. The IFM 99-02 trial randomized patients after tandem autologous transplantation (using melphalan 140mg/m^2 for the first and melphalan 200mg/m^2 for the second transplant) to either no maintenance, maintenance with pamidronate or maintenance with thalidomide and pamidronate. Patients received thalidomide for a median of 15 months. The major treatment-related side effect was neuropathy (68% of patients). Patients who received thalidomide had improved EFS and OS. Of note, patients who achieved a VGPR after transplantation did not benefit from thalidomide maintenance. This suggests that the benefit of post-transplant thalidomide might result from upgrading responses.4

New IMiDs® such as lenalidomide are now commonly used in clinical practice. The side effect profile of lenalidomide is superior to that of thalidomide. In normal volunteers the most common adverse events with lenalidomide are rash and pruritus. Phase II trials of lenalidomide plus dexamethasone for upfront therapy of myeloma demonstrate high response rates.[41] Hence, based on both a more favorable side effect profile and higher CR rates, lenalidomide appears to be a superior drug for maintenance therapy. It is unknown whether use of post-transplant maintenance lenalidomide until disease progression will provide similar EFS and OS to either tandem transplantation or a single transplant followed by consolidation and maintenance.

The maximum tolerated dose (MTD) of lenalidomide as a daily dose is 25 mg with dose-limiting toxicity (DLT) being grade 3/4 myelosuppression. A randomized Phase II study has been reported that examined two higher dose schedules: 15 mg twice daily versus 30 mg daily on a 3 weeks on/1 week off schedule.[42] This study examined 70 patients randomized to the two schedules. Fifty-seven patients were analyzed for toxicity and 46 for response. In this heavily pre-treated group of patients, 24% had a CR or PR and only 16% had progressive disease. One patient developed grade 3 neuropathy. The most common grade 1 and 2 toxicities were fatigue, self-limited rash, muscle cramps and diarrhea. Grade 3 or 4 myelosuppression was seen in 26% (n=15) of patients. Eleven of these 15 patients had undergone a prior autologous transplant; most (n=11) were on the 15 mg twice a day dose. The daily dosing schedule is the simplest and provides the best opportunity for compliance. There is no evidence that an interrupted schedule enhances long-term tolerability or response. The starting dose of 10 mg in this BMT CTN trial was selected based on a high probability of hematologic tolerability after autologous transplantation. This is also the dose used in the ongoing CALGB 100104 trial of single autologous transplantation followed by either placebo or lenalidomide until disease progression.

1.3. Study Approach and Treatment

The introduction of autologous transplantation for MM significantly improved survival for this population of patients, yet the potential for further improvement remains. This study will answer the question of which of three post-transplant approaches (tandem transplantation, consolidation, or maintenance alone) offer superior EFS, OS, toxicity and quality of life.

Symptomatic patients with MM who have received at least two cycles of systemic therapy and who are within 2-12 months of the start of their initial therapy (exclusive of mobilization therapy) and who have an autologous graft with $\geq 4x10^6$ CD34+ cells/kg patient weight are potentially eligible for this study. All enrolled patients will receive high-dose (200 mg/m^2) melphalan with autologous PBSC support (minimum $2x10^6$ CD34+ cells/kg). Subsequent therapy will be based on randomization at the time of enrollment to either maintenance alone, consolidation followed by maintenance or a second transplant followed by maintenance.

The second phase of therapy will begin at least 60 days (preferably between 60 and 120 days) after the initial autograft, once the patient has recovered sufficiently from the acute toxicity of the high-dose melphalan regimen. Patients randomized to second transplant will undergo a second course of high-dose melphalan (200 mg/m^2) followed by autologous PBSC transplant. These patients will then be placed on lenalidomide 10 mg daily for three months then 15 mg as maintenance treatment. The duration of maintenance will be three years in all treatment arms or

until disease progression. Patients randomized to consolidation will receive four cycles of treatment with RVD (lenalidomide, bortezomib and dexamethasone) given approximately three weeks apart. They will receive lenalidomide maintenance (10 mg daily for three months then 15 mg) upon completion of the 4th cycle of RVD for three years. Patients on the maintenance arm will proceed directly to maintenance therapy with lenalidomide. The maintenance lenalidomide dose is 10 mg daily for the first three months, and, assuming that the 10 mg dose is tolerated well, increased to 15 mg daily. Patients will continue on maintenance lenalidomide for 3 years or until disease progression.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

The study is a Phase III randomized clinical trial to evaluate three treatment strategies after a single autologous transplant for patients with multiple myeloma (MM): second autologous transplant with the same conditioning regimen followed by maintenance with lenalidomide; maintenance alone; or consolidation with lenalidomide, bortezomib and dexamethasone combination followed by lenalidomide maintenance. Patients will be randomized at time of enrollment, which should occur within 7 days prior to the first high-dose melphalan conditioning regimen. Maintenance therapy with lenalidomide will be given for 3 years to all patients. The endpoints assessed will include progression-free survival (PFS), disease response at different time points according to the International Uniform Response Criteria, overall survival (OS), incidence of toxicities and infections, treatment-related mortality (TRM), rate of discontinuation of protocol therapy and quality of life. Analyses of outcomes will be stratified according to risk status defined by the presence of cytogenetic abnormalities and serum beta-2 microglobulin level (Section 3.1).[33]

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

Use of novel anti-myeloma agents will improve PFS after high-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) as compared to a second autologous transplantation.

2.2.2. Study Objectives

The primary objective of the randomized trial is to compare PFS as a time to event analysis through three years and two months (38 total months) of follow-up from randomization between the two single transplant arms and between each single transplant arm and the tandem transplant arm. It is expected that 38 months is the earliest time point at which a participant may have completed 3 years of maintenance. Point estimates and confidence intervals will be estimated at 1 and 2 years as well as 38 months post-randomization

Secondary objectives include:

- Comparing rates of very good partial responses or better (VGPR, nCR, CR and sCR) after the first and second year from randomization;
- Comparing the rate of CR conversion for patients not in CR at initiation of maintenance at 3 months, 6 months, 1, 2 and 3 years after initiation of maintenance;

- Comparing overall survival between treatment arms as a time to event analysis through 38 months of follow-up from randomization. Overall survival estimates will be described at 1 and 2 years as well as 38 months post-randomization;Comparing Grade ≥ 3 toxicities, graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0), that occur within time periods that end approximately after each autologous transplantation, consolidation and yearly until 3 years post-randomization or until disease progression Comparing the incidence of infections that occur within time periods that end approximately after each autologous transplantation, consolidation and yearly until completion of 38 months post-randomization;
- Comparing TRM as a time to event analysis through 38 months of follow-up from randomization;
- Tabulating the proportion of patients who do not proceed to their second or, if applicable, third phase of treatment or who discontinue consolidation or maintenance at any time point due to toxicitiy, noncompliance or other reasons; comparing the rate of non compliance with protocol therapy (autologous transplantations, consolidation and maintenance) yearly until completion of maintenance; and,
- Comparing quality of life prior to the first transplant, after each autologous transplantations, consolidation and yearly until 3 years post randomization or until disease progression.

2.3. Patient Eligibility

Patients must meet specified eligibility criteria to be registered on the study. Additional criteria must also be met to continue to successive stages of the protocol. All questions regarding eligibility criteria should be directed to the Protocol Coordinator at 301-251-1161.

2.3.1. Initial Patient Eligibility Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Patients meeting the criteria for symptomatic MM (Appendix A).
2. Patients who are 70 years of age, or younger, at time of enrollment.
3. Patients who have received at least two cycles of any regimen as initial systemic therapy and are within 2 - 12 months of the first dose of initial therapy.
4. Cardiac function: left ventricular ejection fraction at rest > 40%.
5. Hepatic: bilirubin < 1.5x the upper limit of normal and ALT and AST < 2.5x the upper limit of normal. (Patients who have been diagnosed with Gilbert's Disease are allowed to exceed the defined bilirubin value of 1.5x the upper limit of normal.)
6. Renal: Creatinine clearance of ≥ 40 mL/min, estimated or calculated.
7. Pulmonary: DLCO, FEV1, FVC > 50% of predicted value (corrected for hemoglobin).
8. Patients with an adequate autologous graft defined as a cryopreserved PBSC graft containing ≥ 4 x 10^6 CD34+ cells/kg patient weight. The graft may not be CD34+

selected or otherwise manipulated to remove tumor or other cells. The graft can be collected at the transplanting institution or by a referring center. The autograft must be stored so that there are two products each containing at least 2 x 10^6 CD34+ cells/kg patient weight.

9. Signed informed consent form.

2.3.2. Initial Patient Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. Patients who never fulfill the criteria for symptomatic MM (Appendix A).
2. Patients with purely non-secretory MM [absence of a monoclonal protein (M protein) in serum as measured by electrophoresis and immunofixation and the absence of Bence Jones protein in the urine defined by use of conventional electrophoresis and immunofixation techniques]. Patients with light chain MM detected in the serum by free light chain assay are eligible.
3. Patients with plasma cell leukemia.
4. Karnofsky performance score less than 70%.
5. Patients with >grade 2 sensory neuropathy* (CTCAE version 3.0).
6. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and progression of clinical symptoms).
7. Patients seropositive for the human immunodeficiency virus (HIV).
8. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix I), 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.
9. Patient has hypersensitivity to bortezomib, boron or mannitol.
10. Patient has received other investigational drugs with 14 days before enrollment.
11. Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs. Cancer treated with curative intent > 5 years previously is allowed.
12. Female patients who are pregnant (positive β-HCG) or breastfeeding.
13. Females of childbearing potential (FCBP)† or men who have sexual contact with FCBP unwilling to use contraceptive techniques (Appendix D) during the length of lenalidomide maintenance therapy.

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* According to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), grade 3 sensory neuropathy is sensory alteration or paresthesia that interferes with activities of daily living.

14. Prior allograft or prior autograft.
15. Patients who have received mid-intensity melphalan (>50 mg IV) as part of prior therapy.
16. Patients unable or unwilling to provide informed consent.
17. Prior organ transplant requiring immunosuppressive therapy.
18. Patients with disease progression prior to enrollment (see Section 3.3 for disease progression definition).
19. Patients who have received lenalidomide as initial therapy for MM and have experienced toxicities resulting in treatment discontinuation.
20. Patients who experienced thromboembolic events while on full anticoagulation during prior therapy with lenalidomide or thalidomide.
21. Patients unwilling to take DVT prophylaxis.
22. Patients who cannot undergo an intervention in any treatment arm due to a priori denial of medical costs coverage by third party payers.
23. Patients unable or unwilling to return to the transplant center for their assigned treatments.

2.3.3. Patient Eligibility Criteria for Second Autologous Transplant (Treatment Arm A)

In order to be eligible to continue on protocol and receive their second transplant (preferably between 60-120 days, but at least 60 days or not longer than 180 days post first autologous transplant), patients must have recovered sufficiently from their first transplant. Conditioning therapy for the second transplant must not start sooner than 60 days after the first autologous transplant.

Eligibility criteria for a second transplant are as follows:

1. Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
2. Liver and renal function tests within the inclusion criteria for initial autograft.
3. Off antibiotics and amphotericin B formulations, voriconazole or other anti-fungal therapy for the treatment of proven, probable or possible infections (defined in accordance with the EORTC/MSG criteria[34]). Patients who have completed treatment for an infection but are continuing antibiotics or anti-fungal therapy for prophylaxis are eligible to continue on protocol with approval of the Medical Monitor or one of the Protocol Chairs.
4. Completed administration of any radiotherapy as per Section 2.5.5.

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† A female of childbearing potential is 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).

5. Cardiac and pulmonary function within the inclusion criteria for initial autograft. Evaluation is only required if clinically indicated.
6. Renal: Creatinine clearance of ≥ 40 mL/min, estimated or calculated.
7. Women who are pregnant (positive β-HCG) or breastfeeding are ineligible to proceed to a second autologous transplant.

Patients unable to meet criteria for a second transplant (NOTE: beyond 180 days after the first auto transplant) but are still eligible for maintenance therapy (Section 2.3.5) should proceed to maintenance.

2.3.4. Patient Eligibility Criteria to begin RVD Consolidation (Treatment Arm C)

Patients must have recovered sufficiently from their first transplant to be eligible for consolidation therapy (preferably between 60-120 days, but at least 60 days or not longer than 180 days post first autologous transplant). Eligibility criteria for beginning consolidation therapy are as follows:

1. Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
2. Liver and renal function tests within the inclusion criteria for initial autograft. See Sections 2.4.4 and 2.4.5.1 of the protocol for details on lenalidomide dose modifications in the presence of impaired renal function.
3. Off antibiotics and amphotericin B formulations, voriconazole or other anti-fungal therapy for proven, probable or possible infections (defined in accordance with the EORTC/MSG criteria[34]). Patients who have been treated for an infection but are continuing antibiotics or anti-fungal therapy for prophylaxis are eligible to continue on protocol with approval of the Medical Monitor or one of the Protocol Chairs.
4. Completed administration of any radiotherapy as per Section 2.5.5.
5. Less than or equal to grade 2 sensory neuropathy within 14 days before start of consolidation.
6. Platelet count ≥75 $x10^9$/L (without transfusion in previous 7 days).
7. Absolute neutrophil count (ANC) ≥ 1.5$x10^9$/L without filgrastim administration within 7 days, or pegfilgrastim within 14 days of starting consolidation.
8. Requirements prior to taking lenalidomide: Females of childbearing potential (FCBP)‡ must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of beginning treatment with lenalidomide (prescriptions must be filled within 7 days) 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

‡ A female of childbearing potential is 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).

SAME TIME, at least 4 weeks before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Women who are breastfeeding are ineligible to proceed to RVD Consolidation. Men must agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendices D (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and E (Revlimid REMS®).

9. Patients must be willing to begin DVT prophylaxis.
10. Patients unable to meet criteria for consolidation (NOTE: within 180 days of the first autologous transplantation) or who develop unacceptable toxicity during consolidation (see Section 2.4.3) should be started on maintenance therapy as per Section 2.3.5.
11. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program.
12. All study participants must be willing and able to receive counseling and complete phone surveys as required by the Revlimid REMS® program.

2.3.5. Patient Eligibility Criteria to Begin Maintenance Therapy (All Treatment Arms)

Patients must have recovered sufficiently from their first or second transplant (preferably between 60-120 days, but at least 60 days or not longer than 180 days post autologous transplant – Treatment Arms A and B) or completion of consolidation therapy (at least 84 days or less than 180 days from initiation of consolidation therapy or after completion of 4 cycles of RVD – Treatment Arm C) in order to initiate lenalidomide maintenance therapy.

Criteria for starting maintenance therapy with lenalidomide are as follows:

1. Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
2. Off antibiotics and amphotericin B formulations, voriconazole or other anti-fungal therapy for treatment of proven, probable or possible infections (defined in accordance with the EORTC/MSG criteria[34]). Patients who completed treatment for an infection but are continuing antibiotics or anti-fungal therapy for prophylaxis are eligible to continue on protocol with approval of the Medical Monitor or one of the Protocol Chairs.
3. Completed administration of any radiotherapy as per Section 2.5.5.
4. Platelet count $\geq 75 \times 10^9$/L (without transfusion in previous 7 days).
5. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without filgrastim administration within 7 days, or pegfilgrastim within 14 days of measurement.
6. No contraindications to lenalidomide (patients who were previously exposed to lenalidomide and who either did not tolerate it or who developed severe adverse events that preclude future use of this medication).

7. Liver and renal function tests within the inclusion criteria for initial autograft. See Sections 2.4.4 and 2.4.5.1 of the protocol for details on lenalidomide dose modifications in the presence of impaired renal function.
8. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program.
9. All study participants must receive counseling and complete phone surveys as required by the Revlimid REMS® program.
10. Females of childbearing potential (FCBP)§ must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of beginning treatment with lenalidomide (prescriptions must be filled within 7 days) 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 4 weeks before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendices D (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and E (Revlimid REMS® program). Patients must be willing to begin DVT prophylaxis.

2.4. Study Treatments

The immediate pre-transplant evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study. Similarly, special orders and procedures will be those defined by the BMT CTN Manual of Procedures (MOP). All patients enrolled on this protocol will be hospitalized in accordance with the procedures for recipients of autologous transplants as defined by the treating institution. All questions regarding treatment should be directed to the Protocol Coordinator at 301-251-1161.

2.4.1. First Autologous Stem Cell Transplantation

§ A female of childbearing potential is a sexually mature woman 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).

Table 2.4.1 -- High-Dose Melphalan

	-2 OR -1	**0**	**+5, or per Institutional Guidelines, to Engraftment**
Melphalan[1] (200 mg/m^2 /IV)	X		
PBSC Infusion		X	
G-CSF[2] (5 μg/kg/day) SQ or IV until ANC ≥ 0.5 x10^9/L500 x 2 consecutive days			X

[1]Melphalan will be administered at a total dose of 200mg/m^2 in a single day -2 or -1; or divided intravenous dose according to institutional guidelines. Peripheral blood stem cell should be infusion at least 24 hours after completion of melphalan infusion.

[2] G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5 μg/kg/day (e.g. < 70kg use 300 microgram vial, 70 to 90 kg use 480 microgram vial and > 90 kg use 2 x 300 microgram vials).

2.4.1.1. Melphalan administration

Melphalan will be administered at a total dose of 200 mg/m^2 at the first autologous HCT in all patients and at the first and second autologous HCT for patients randomized to receive tandem autologous HCT (Treatment A). Melphalan will be given either as a single dose infused on Day –2 or -1; or in divided doses according to institutional guidelines. It is mandatory that the infusion of melphalan start within 60 minutes of preparation. Melphalan dose is based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

Ideal Body Weight Formulas:

Males IBW = 50 kg + (2.3 kg x number of inches greater than 60)
Females IBW = 45.5 kg + (2.3 kg x number of inches greater than 60)
For patients less than 5 feet, subtract 2.3 kg/inch

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.4.1.2. Peripheral blood stem cell infusion

All patients will receive an autologous graft with a minimum cell dose of 2.0 x 10^6 CD34+ cells/kg patient actual body weight per autologous transplantation. The graft may not be CD34+ selected or otherwise manipulated to remove tumor or other cells. The autologous graft may be infused on an outpatient basis. Patients must comply with all scheduled study visits whether receiving their transplant as an in-patient or an outpatient. Cryopreservation and thawing of product will be in keeping with FACT standards and local institutional practice.

2.4.2. Second Autologous Stem Cell Transplantation

Conditioning with high-dose melphalan (Section 2.4.1.1) for the second transplant will be initiated once the patient has recovered from the first autologous HCT (preferably between 60-120 days, but at least 60 days or less than 180 days post first autologous transplant). Recovery from the first autograft will be defined as patients achieving the clinical criteria in Section 2.3.3. If indicated, radiation to high-risk skeletal lesions may be given pre-transplant as per Section 2.5.5.

2.4.3. Consolidation Therapy (RVD)

Consolidation with RVD will initiate after recovery from the first autologous HCT in patients who fulfill criteria (Section 2.3.4). Patients will be given consolidation therapy for 4 cycles (1 cycle = 21 days) with the combination of lenalidomide (15 mg orally on days 1-14 of each cycle), bortezomib (1.3 mg/m^2 on days 1, 4, 8 and 11 of each cycle) and dexamethasone (40mg total dose per day given on Days 1, 8, and 15 of each cycle).

Table 2.4.3 - RVD Treatment Schedule

Dexamethasone	40 mg orally on Days 1, 8, 15
Lenalidomide	15 mg/day orally on Days 1-14
Bortezomib	1.3 mg/m^2 intravenously on Days 1, 4, 8, 11

Treatment modifications are based on toxicity. All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with BMT CTN specific definitions when appropriate. If toxicity is observed at any time during treatment, consolidation may be held depending on the severity and type of adverse event as described in Tables 2.4.4a and 2.4.4b. If the patient is not able to complete two cycles of consolidation within 3 months or 4 cycles within 6 months from starting consolidation due to toxicity, the patient will stop consolidation. Patients who do not tolerate consolidation therapy will proceed to maintenance therapy if there are no contraindications for lenalidomide based on previous exposure (see Section 2.3.5).

2.4.3.1. Bortezomib

The timing of any bortezomib dose can be adjusted by a day in the event of a holiday or other clinic closure as long as there are at least 72 hours between doses. Bortezomib should be infused intravenously as a rapid push (3 to 5 seconds) or subcutaneously according the manufacturer recommendations. For subcutaneous administration, the local injection site should be rotated to avoid an adverse reaction. Recommended injection sites for subcutaneous bortezomib include: bilateral upper and lower abdominal quadrants, bilateral proximal and distal anterior thighs. The dose of bortezomib to be administered (in milligrams) will be determined based on body surface area. Body surface area is to be calculated based on actual body weight. 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 patient experiences a

notable change in weight (e.g., loss or gain of ≥ 8 lbs or 3.6 kg) within a cycle, between cycles, or any time since initiation of consolidation, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time.

Subcutaneous Bortezomib Administration; Please refer to manufacturer instructions on administering Bortezomib subcutaneously.

Bortezomib dose will be adjusted for toxicity, if necessary (Table 2.4.4a for toxicities requiring adjustments). Once the dose of bortezomib has been reduced for toxicity, no dose re-escalation is permitted. Table 2.4.3.1 demonstrates the recommended dose reduction steps.

Table 2.4.3.1 -- Bortezomib Dose Reduction Steps

Bortezomib Dose Reduction Steps	
Starting Dose	**1.3 mg/m^2 intravenously on Days 1, 4, 8, 11 every 21 days** or **1.3 mg/m^2 subcutaneously on Days 1, 4, 8, 11 every 21 days**
Dose Level -1	1 mg/m^2 intravenously on Days 1, 4, 8, 11 every 21 days or 1 mg/m^2 subcutaneously on Days 1, 4, 8, 11 every 21 days
Dose Level -2	0.7 mg/m^2 intravenously on Days 1, 4, 8, 11 every 21 days or 0.7 mg/m^2 subcutaneously on Days 1, 4, 8, 11 every 21 days
Dose Level -3	Discontinue bortezomib

2.4.3.2. Lenalidomide

Lenalidomide dose will be adjusted for toxicity, if necessary (Table 2.4.4a for toxicities requiring adjustments). Once the dose of lenalidomide is reduced for toxicity, no dose-re-escalation is permitted. Table 2.4.3.2 demonstrates the recommended dose reduction steps.

Table 2.4.3.2 -- Lenalidomide Dose Reduction Steps during Consolidation Therapy

Lenalidomide Dose Reduction Steps	
Starting Dose	**15 mg daily for 14 days every 21 days**
Dose Level -1	10 mg daily for 14 days every 21 days
Dose Level -2	5 mg daily for 14 days every 21 days
Dose Level -3	Discontinue lenalidomide

2.4.3.3. Dexamethasone

The dose of dexamethasone will be reduced for toxicity, if necessary (Table 2.4.4b for toxicities requiring adjustments). Once the dose of dexamethasone is reduced for toxicity, no dose-re-escalation is permitted. Table 2.4.3.3 demonstrates the recommended dose reduction steps.

Table 2.4.3.3 -- Dexamethasone Dose Reduction Steps

Dexamethasone Dose Reduction Steps	
Starting Dose	**40 mg orally on days 1, 8, 15 every 21 days**
Dose Level -1	20 mg orally on days 1, 8, 15 every 21 days
Dose Level -2	10 mg orally on days 1, 8, 15 every 21 days
Dose Level -3	Discontinue dexamethasone

2.4.4. Treatment Modification Guidelines for Consolidation Therapy

Table 2.4.4a - Treatment Modification Guidelines for Lenalidomide and Bortezomib

Grade by NCI CTCAE# [1]	**Day 1-10 of Cycle**	**> Day 10 of Cycle**
Neutropenia **≥ Grade 3** (< 1000 /mm^3)	Hold (interrupt) all therapy. If neutropenia has resolved to ≤ grade 2, restart lenalidomide at next lower dose level and continue the cycle until Day 14. Bortezomib should be resumed without dose reduction.	Omit therapy for remainder of cycle. If neutropenia is the only toxicity for which a dose reduction is required, then G-CSF may be used and the dose maintained for the next cycle at the investigators discretion.
	If persistence of this AE after all dose modifications of lenalidomide are completed, dose modifications with bortezomib should be initiated when neutropenia has resolved to ≤ grade 2.	
Thrombocytopenia **≥ Grade 3** (<50,0000/mm^3)	Hold (interrupt) all therapy. If applicable, hold anti-coagulation. If thrombocytopenia resolves to ≤ grade 2 restart bortezomib at next lower dose level (Day 1 infusion) and lenalidomide should be resumed at the same dose level and continue until Day 14. If applicable, restart anti-coagulation.	Omit lenalidomide and bortezomib for remainder of the cycle. If applicable, hold anti-coagulation. On Day 1 on the next cycle restart bortezomib at the next lower dose level provided thrombocytopenia has resolved to ≤ Grade 2. Lenalidomide should be started at the same dose. If applicable, restart anti-coagulation.
	If persistent or recurrence after all dose modifications are completed for bortezomib, hold therapy and restart with next lower level of lenalidomide after resolution of toxicity to grade 2 or less. <u>If patient on DVT/PE prophylaxis or treatment, discontinuation or modifications of anticoagulation should be considered by the treating physician.</u>	
Non-blistering rash **Grade 2- 3** (Generalized rash ≥ 25% BSA)	Hold (interrupt) all therapy: Follow weekly. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Resume bortezomib at same dose level. Bortezomib dose reduction start after all dose reductions with lenalidomide were done	Omit lenalidomide and bortezomib for remainder of cycle.
Non-blistering rash **Grade 4**	Discontinue all therapy.	Discontinue all therapy.
Desquamating (blistering) rash **any Grade**	Discontinue lenalidomide and bortezomib.	
Erythema multiforme **≥ Grade 3** (Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated)	Discontinue lenalidomide. If toxicity resolves to < grade 1 restart consolidation without lenalidomide.	

Grade by NCI CTCAE# [1]	Day 1-10 of Cycle	> Day 10 of Cycle
Sinus bradycardia/ other cardiac arrhythmia **Grade 2** (Non urgent, medical intervention indicated OR Moderate)	Hold (interrupt) all therapy. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level and continue the cycle until Day 14. No dose adjustments with bortezomib are required.	Omit lenalidomide for the remainder of the cycle.
Sinus bradycardia/ other cardiac arrhythmia **≥ Grade 3** (Incompletely controlled or controlled with device- e.g. pacemaker or Severe)	Discontinue lenalidomide. If toxicity resolves to < grade 1 restart consolidation without lenalidomide	
Allergic reaction or hypersensitivity **Grade 2-3** (flushing; urticaria; dyspnea; drug fever≥ 38ºC – symptomatic bronchospasm; parenteral meds indicated)	Hold (interrupt) all therapy. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level and continue the cycle until Day 14.Bortezomib should be resumed at the same dose level.	Omit lenalidomide for the remainder of the cycle.
Allergic reaction or hypersensitivity **Grade 4** (anaphylaxis)	Discontinue protocol therapy	
Venous thrombosis/embolism **≥ Grade 3** (DVT or cardiac thrombosis; intervention indicated)	Hold (interrupt) all therapy and start anticoagulation. Restart therapy per institutional guidelines.	
Glomerular filtration rate (Creatinine Clearance) **≥ Grade 3** (≤ 25%LLN, chronic dialysis not indicated)	Hold (interrupt) all therapy. If creatinine clearance has improved to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 14.	Omit therapy for remainder of cycle. On Day 1 on the next cycle restart at next lower dose level provided creatinine clearance has improved to ≤ Grade 2.
Other non-hematologic toxicity assessed as Lenalidomide-related **≥ Grade 3**	Hold (interrupt) lenalidomide. If the toxicity resolves to ≤ grade 2 restart lenalidomide at next lower dose level and continue the cycle until Day 14.	Omit lenalidomide for remainder of cycle.
Other non-hematologic toxicity assessed as Bortezomib-related **≥ Grade 3**	Hold (interrupt) bortezomib. If the toxicity resolves to ≤ grade 2 restart bortezomib at next lower dose level and continue the cycle until Day 14.	Omit bortezomib for remainder of cycle.
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, Evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (at next lower dose level).	
Peripheral Neuropathy[2] Grade 2 with pain or Grade 3	Hold (interrupt) all therapy. If the toxicity resolves to <Grade 1 restart therapy after with reduction of bortezomib by two dose levels; if this results in discontinuation of bortezomib, continue therapy with other drugs. If toxicity recurs after bortezomib has been stopped, discontinue lenalidomide and resume therapy with dexamethasone alone	
Peripheral Neuropathy[2] Grade 4	Discontinue bortezomib and lenalidomide	
Constipation Grade 1-2	Initiate bowel regimen and maintain dose level.	

Grade by NCI CTCAE# [1]	**Day 1-10 of Cycle**	**> Day 10 of Cycle**
Constipation > Grade 3	Hold therapy with lenalidomide till adverse event resolves to grade 1 or less. Restart therapy with next lower dose level of lenalidomide after resolution of toxicity.	
Pregnancy[3]	Discontinue lenalidomide study drug.	

[1]Please consult NCI CTCAE version 3.0 http://ctep.cancer.gov/reporting/ for complete **Grade** descriptions. The **"≥ Grade 3"** descriptions listed above are minimums.
[2]The neurotoxicity-directed questionnaire (see Appendix J) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient 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.
[3]If a subject, or the partner of a male study subject, misses her period or if her pregnancy test or her menstrual bleeding is abnormal, pregnancy testing and counseling must be performed (Section 4.4.5).

Table 2.4.4b: Treatment Modification Guidelines for Dexamethasone

CTCAE* category	**Adverse event**	**Dosage change/intervention**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by one dose level
	Grade 3 (requiring hospitalization or surgery)	Hold therapy with all drugs until symptoms adequately controlled. After toxicity resolves to grade 1 or less, restart therapy with study drugs with dexamethasone dose reduction by one level, along with concurrent therapy with H2 blockers, sucralfate, or proton pump inhibitor as appropriate. If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	Hold therapy with all drugs until symptoms adequately controlled. After toxicity resolves to grade 1 or less restart therapy with study drugs but discontinue dexamethasone permanently
Cardiovascular	Edema Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by one level
Neurology	Confusion or Mood alteration Grade ≥ 2 (interfering with function +/- interfering with activities of daily living)	Omit dexamethasone from current cycle. If symptoms resolve to grade 1 or less, restart with next cycle with dexamethasone dose reduction by one level.
Musculoskeletal	Muscle weakness Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living) Grade ≥3	Decrease dexamethasone dose by one dose level Omit dexamethasone dose from current cycle. If symptoms resolve to grade 1 or less, restart next cycle with dexamethasone dose reduction by one level.
Metabolic	Hyperglycemia Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dexamethasone dose by one dose level
Other	Other non-hematologic toxicity felt to be dexamethasone-related	Omit dexamethasone from current cycle. If symptoms resolve to grade 1 or less, restart next cycle with dexamethasone dose reduction by one level.

*[1]Please consult NCI CTCAE version 3.0 http://ctep.cancer.gov/reporting/

2.4.5. Maintenance Therapy

To proceed to maintenance patients must have no evidence of disease progression (Section 3.3) and fulfill eligibility criteria described in Section 2.3.5.

Patients will begin maintenance therapy with lenalidomide after the first or second transplant (preferably between 60 to120 days after stem cell infusion, but at least 60 days or less than 180 days post autologous transplant – Treatment Arms A and B) or immediately after consolidation therapy ends (between Day 84 and 180 days or after the 4th cycle of consolidation – Treatment Arm C). Lenalidomide will be administered initially at a dose of 10 mg per day continuously for the first three cycles subsequently increased to 15 mg daily. Cycle duration during maintenance therapy is 28 days. Patients will continue lenalidomide for a total of 3 years or until disease progression.

2.4.5.1. Lenalidomide maintenance dose modifications

Lenalidomide dose escalation from 10 mg to 15 mg will occur after completion of 3 cycles of maintenance therapy. In the presence of lenalidomide-related non-hematologic toxicities (Table 2.4.4a, Column 1), the study drug will be held until the toxicity resolves then restarted at a reduced dose as described in Table 2.4.5.1. Dose modifications for hematologic toxicities are described below. If the patient is on DVT/PE prophylaxis or treatment, discontinuation or modifications of anticoagulation should be considered by the treating physician.

Table 2.4.5.1 – Lenalidomide Dose Reduction Steps <u>During Maintenance Therapy</u>

Lenalidomide Dose Reduction Steps for Non-Hematologic Toxicity	
Dose at Time of Toxicity	**Dose Reduction**
15 mg daily	10 mg daily
10 mg daily	5 mg daily
5 mg daily	5 mg daily for 21 days every 28 days
5 mg daily for 21 days every 28 days	Discontinue lenalidomide

Hematologic Dose Modifications:

- **If on lenalidomide 15 mg per day** and the ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Lenalidomide drug may be re-instituted at 10 mg per day once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL. If, however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.
- **If on lenalidomide 10 mg per day** and the ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Lenalidomide may be re-instituted at 5 mg per day once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL. If however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.

- **If on lenalidomide 5 mg per day** and the ANC is < 1000/μL or the platelet count is < 50,000/μL, then lenalidomide will be held for up to 8 weeks. Once the ANC is ≥ 1000/μL and the platelet count is ≥ 50,000/μL, then lenalidomide may be re-instituted at 5 mg per day for 21 days of a 28-day cycle. If, however, after an 8 week treatment delay, the ANC remains < 1000/μL or the platelet count < 50,000/μL, maintenance therapy will be discontinued.
- **If on lenalidomide 5 mg per day for 21 of 28 days,** the ANC is < 1000/μL or the platelet count is < 50,000/μL, then maintenance therapy will be discontinued.

Lenalidomide Maintenance Dose Re-escalation:
If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75,000/μL, the study drug dose may be re-escalated as shown on Table 2.4.5.1, one step per cycle to a maximum of 15 mg daily.

Patients who stop maintenance therapy due to toxicity will continue to be followed for four years post randomization.

2.5. Supportive Care

2.5.1. Post Autologous Transplantation(s)

All supportive care will be given in keeping with BMT CTN MOP and local institutional practice.

2.5.2. Bisphosphonates

Monthly IV bisphosphonates [either zolendronic acid (Zometa®) or pamidronate according to institutional preference] may be initiated (or re-initiated) after the first (or second) autograft according to local institutional practice.

2.5.3. Prophylaxis against infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peri-transplant period according to the BMT CTN MOP and local institutional practice. Additional specifications/requirements for this study are summarized below. Infectious prophylaxis will include prophylaxis for:

1. Anti-bacterial: In keeping with the BMT CTN MOP and local institutional standards.
2. *Pneumocystis jiroveci*: Prophylaxis against pneumocystis pneumonia is not mandated by protocol and the decision to proceed with this treatment is based on institutional guidelines. The recommendation is to start prophylaxis at time of engraftment or on Day 30 post autologous transplant according to institutional preference.
3. Anti-fungal Therapy: Anti-fungal prophylaxis will be initiated peri-transplant according to local institutional practice and will continue until neutrophil recovery post autologous transplant.

4. HSV/VZV: Prophylaxis will be initiated according to local institutional practice peri-transplant and continue until six months post autologous transplantation. Patients randomized to RVD consolidation therapy should continue HSV/VZV prophylaxis until completion of consolidation. The choice of agent will be as per institution standard practice.

2.5.4. Post-transplant Growth Factors

Patients will receive ~5 micrograms/kg/day of G-CSF subcutaneously per institutional guidelines until ANC $\geq$ 0.5 x 10^9/L for two days or ANC $\geq$ 1 x 10^9/L on a single determination. G-CSF dosing can be rounded based on patient weight and available G-CSF vial sizes to best approximate 5 micrograms/kg/day (e.g., < 70 kg use 300 microgram vial, 70 to 90 kg use 480 microgram vial and > 90 kg use 2 x 300 microgram vials). If the patient is unable to tolerate G-CSF subcutaneously, it may be administered intravenously as per package insert.

2.5.5. Radiation Therapy

Radiation therapy is not permitted to be given in concurrent with melphalan administration. When blood count recovery is adequate (ANC $\geq$ 1 x 10^9/L, platelets $\geq$ 75 x 10^9/L) after autologous transplantation, radiation may be administered for the following indications after consultation with the Medical Monitor or one of the Protocol Chairs and a radiation oncologist:

1. Palliation of pain from bone lesions;
2. Prevention of pathologic fractures;
3. Relief of spinal cord compression or nerve root compression.

The radiation oncologist will determine dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

In addition to blood count recovery, except for emergent indication (e.g. cord compression), patients must also be recovered from autologous transplantation with resolution of mucositis, resolution of fever, discontinuation of antibiotics and receiving adequate oral hydration and nutrition to receive radiation therapy.

2.5.6. Post-transplant Blood Products

Transfusion thresholds for blood product support should be per institutional guidelines. All blood products will be irradiated.

2.5.7. Immunizations Schedule

Immunizations should be administered according to institutional guidelines.

2.5.8. Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Prophylaxis

Patients receiving dexamethasone and thalidomide as remission induction therapy for MM have an increased risk of developing DVT/PE. This risk may be as high as 10%. It is unclear whether the risk is the same in patients receiving lenalidomide as a single agent and as maintenance therapy after autologous transplantation. Treating physicians should be aware of this risk and have heightened vigilance regarding this possible toxicity. Aspirin should be administered per institutional guidelines for at least 14 days each consolidation cycle (Days 1 to 14) and during lenalidomide maintenance therapy unless the patient is treated with alternate prophylaxis of either low molecular weight heparin or coumadin. The incidence of DVT/PE will be monitored by the BMT CTN data safety monitoring board. Aspirin is usually administered in patients without a history of thromboembolic events; low molecular weight heparin or coumadin is usually administered in patients with a history of thromboembolic events or those that cannot tolerate aspirin.

2.6. Participant Risks

Recipients of autologous transplantation incur risks from pre-transplant conditioning and post-transplant therapy, which must be weighed against the risk of the disease for which the transplant is prescribed. Major risks following transplantation include: 1) Infection, which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 2) Graft Failure can occur and is associated with a high-risk of mortality; 3) End Organ Damage of one or more major organs may occur as a result of reactions to drugs (e.g., melphalan, antibiotics, anti-fungal medications, etc.), and as a result of destructive processes (e.g., infection, etc.) and may have a fatal outcome; 4) Progression of MM may occur; 5) Unknown Toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain. Brain damage can result in severe loss of cognitive or neurologic function; and, 6) Death. These risks may or may not be increased by the post-transplant therapies to be evaluated in this protocol.

2.6.1. Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with BMT specific definitions when appropriate.

2.6.2. Dexamethasone

Dexamethasone may cause nausea, vomiting, insomnia, agitation, weight gain, fluid retention, hypertension, metabolic disturbances (increased glucose, increased potassium, decreased bone density), increased risk of infection, gas and heartburn. Sometimes it may aggravate underlying peptic ulcer disease and may cause gastrointestinal bleeding. Dexamethasone may also cause secondary hypertension and hyperglycemia or may aggravate the underlying hypertension and diabetes.

2.6.3. Lenalidomide

Common toxicities described for lenalidomide include:

- Neurologic: Somnolence, dizziness, headache, confusion, tremor, loss of co-ordination, asthenia, paresthesia, numbness, and leukoencephalopathy (radiographic findings).
- Hematologic: anemia, neutropenia, leucopenia, lymphopenia and thrombocytopenia; thromboembolic events (deep vein thrombosis and pulmonary embolism).
- Gastrointestinal: Constipation, dehydration, dry mouth, diarrhea, dyspepsia, nausea, vomiting and stomatitis.
- Constitutional: Weakness, insomnia, rigors, chills, sweating, weight loss and fever.
- Reproductive: teratogenicity and miscarriage.
- Musculoskeletal: arthralgia, back/neck pain, joint pain, muscle cramp and weakness.
- Cardiac: hypotension.
- Dermatologic: rash, dry skin, itching.
- Endocrine: hypothyroidism.
- Infection.
- Pulmonary: cough, dyspnea.
- Metabolic: hypokalemia, liver damage.
- Renal: increased creatinine, renal failure.

Pregnancy reporting:
See Section 4.2.3, Adverse Event Reporting.

Other instructions related to lenalidomide:
Only one cycle of therapy may be dispensed to the patient each month. During maintenance a max of a 28-day supply may be dispensed. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients taking more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. See Section 2.7.2.2, Chapter 4, Appendices D (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and E (Revlimid REMS® program).

2.6.4. Filgrastim (G-CSF)

Common toxicities described for G-CSF include:

- Musculoskeletal: In clinical trials, medullary bone pain was the only consistently observed adverse event attributed to G-CSF and was reported in approximately 24% of patients across all indications. The bone pain was generally mild to moderate in severity and controllable in most patients with non-narcotic analgesia; infrequently, bone pain was severe enough to require narcotic analgesia.
- Cardiovascular: Rarely fluid retention; transient hypotension; pericardial effusion.

- Dermatologic: Local inflammation at the injection site; rarely cutaneous vasculitis.
- Other: Headache, transient, mild to moderate elevations of uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs.
- Rare and uncommon: splenic rupture.

See the FDA-approved package insert for a comprehensive list of adverse events.

2.6.5. 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.

Toxicities described for bortezomib include:

- Hematologic: anemia, neutropenia, thrombocytopenia, leucopenia, lymphopenia.
- Neurologic: asthenia, dizziness, anxiety, syncope, headache, insomnia, fever, rigors, chills, sensory peripheral neuropathy, and leukoencephalopathy, including reversible posterior leukoencephalopathy syndrome.
- Pulmonary: cough, dyspnea, pleural effusion, pneumonitis, shortness of breath, interstitial pneumonia, acute respiratory distress syndrome (ARDS).
- Cardiovascular: hypotension, tachycardia, atrial fibrillation, palpitation, congestive heart failure, bradycardia, atrial flutter, atrioventricular block, arrhythmia, cardiac failure, cardiac arrest, pericardial effusion, pericarditis.
- Infectious: reactivations of herpes zoster, opportunistic infections.
- Gastrointestinal: weight loss, decreased appetite, anorexia, constipation, dehydration, diarrhea, heartburn, dyspepsia, stomatitis, nausea, vomiting, ileus, GI perforation, acute pancreatitis.
- Metabolic: hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia.
- Renal: renal failure.
- Other: arthralgias, back pain, bone pain, joint pain, muscle cramp and myalgias, rash, edema, hemorrhage, blurred vision, deafness, hepatitis, hyperbilirubinemia.

2.6.5.1. Concomitant medications

A list of medications or compounds that potentially may increase bortezomib exposure (Cytochrome P450 3A4 Inhibitors) or decrease exposure (Cytochrome P450 3A4 Inducers) can be found at the site (http://medicine.iupui.edu/Flockhart/table.htm). The table below shows an abbreviate list of these medication or compounds.

Increased Toxicity monitoring is recommended when Cytochrome P450 3A4 Inhibitors are used in conjunction with bortezomib, as the combination may increase bortezomib concentration.

The effectiveness of bortezomib may be reduced when Cytochrome P450 3A4 Inducers are used in conjunction with bortezomib, as the combination may reduce bortezomib concentration.

Cytochrome P450 3A4 Inhibitors
Atazanavir
Chlarithromycin
Fluconazole
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Nefazodone
Nelfinavir
Ritonavir
Saquinavir
Telithomycin
Cytochrome P450 3A4 Inducers
Carbamazepine
Hyperforin (St. Johns Wort)
Phenytoin
Rifampin

2.6.6. High-dose Melphalan

High-dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC infusion and colony stimulating factors. Gastrointestinal toxicity, which includes severe stomatitis, esophagitis and diarrhea, can be severe or life-threatening. Most patients receiving high-dose melphalan will require parental narcotics for mucositis-related pain, IV hydration; may require IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

See the FDA-approved package insert for a comprehensive list of adverse events.

2.7. Study Drug Supply

2.7.1. Melphalan, Dexamethasone, and Filgrastim

Melphalan, dexamethasone, and filgrastim are commercially available agents and will be administered per local institutional guidelines.

2.7.2. Lenalidomide and Bortezomib

Bortezomib will be provided by Millennium Pharmaceutics and distributed by EMINENT Services Corporation directly to transplant centers.

Lenalidomide will be provided by Celgene and distributed by Biologics, Incorporated. **Patients must be registered in the** Revlimid REMS® **program in order to receive lenalidomide through the program (please see Appendix E).**

2.7.2.1. Bortezomib

Drug Supply, Preparation, Handling and Storage:
Bortezomib is supplied by Millennium.

Vials containing lyophilized Bortezomib for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

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.

Drug is available in sterile, single use vials containing 3.5 mg of Bortezomib. The initial shipment of drug will contain two extra vials to be kept at the center in case of emergency (breakage, etc). The vials are not patient specific. Each vial of Bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing. For intravenous infusions, reconsitituion must be with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP with a concentration of 1 mg/mL. For subcutaneous infusion, reconstitution must be with 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, with 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. Reconstituted Bortezomib should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Administration:
Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an out-patient basis, if possible.

The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram. 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 patient experiences a notable change in weight (e.g., loss or gain of ≥ 8 lbs or 3.6 kg) within a cycle, between cycles, or any time since initiation of consolidation as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time.

The appropriate amount of Bortezomib will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

Drug Ordering:
Bortezomib will be ordered from the DCC/EMMES and sent to the transplant center pharmacy. Contact the Protocol Coordinator with questions regarding the drug ordering procedures.

Drug Accountability:
Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing bortezomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

2.7.2.2. Lenalidomide (NSC 703813)

NOTE:
Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the Revlimid REMS® program. BMT CTN 0702 study patients must be counseled through the Revlimid REMS® program. A maximum 28-day supply may be dispensed to a patient at one time.

Chemical Name: 3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione

Other Names: CC-5013, Revlimid™, CDC-501

Classification: Immunomodulatory Agent

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$ **M.W.:** 259.25

Mechanism of Action:
Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition of angiogenesis, inhibition of hematopoietic tumor cell proliferation, modulation of stem cell differentiation and up regulating responses of T cells and NK cells.

Drug Supply and Storage:
Celgene supplies and Biologics, Inc. distributes lenalidomide 5 mg (size 2) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 21 capsules per container.

The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

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 Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 7 days.

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

Any unused lenalidomide supplies distributed through the Revlimid REMS® program must be returned as instructed through the Revlimid REMS® program.

Administration:
Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

Dispensing:
Only enough lenalidomide for one cycle may be dispensed at one time. The drug will be mailed directly to the patient through the Revlimid REMS® program. Patients still must return every 3 months to the transplant center for protocol required evaluations.

Patient Care Implications and Counseling:
Risks Associated with Pregnancy
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.

Definition of female 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 (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug (prescriptions must be filled within 7 days as required by Revlimid REMS®). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling Requirements for Revlimid REMS® program:

- This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling will be provided by Biologics, Inc. prior to drug distribution, please refer to Appendix E (Revlimid REMS® program). Patients will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate and take telephone surveys regarding compliance with the program.

Potential Drug Interactions:
Periodic monitoring of digoxin levels is recommended during co-administration with lenalidomide.

Monitor patients receiving concomitant warfarin per standard practice guidelines.

Lenalidomide is not a substrate of human CYP enzymes, nor is it an inhibitor or inducer.

Drug Ordering and Accountability:
The Revlimid REMS® program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling will be provided by Biologics, Inc. prior to drug distribution. Please refer to Appendix E (Revlimid REMS® program). The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program. All physicians must be registered prescribers of Revlimid® in the Revlimid REMS® program. Physician registration allows access to the Revlimid REMS® software to enroll patients in the Revlimid REMS® program. The prescriber should submit the Registration Form via fax number 919-256-0794 or Revlimid REMS® Online ***(RAO)***for Revlimid) to Celgene Customer Care. Please reference Appendix E (Revlimid REMS® program) and follow the directions for submitting the registration. Biologics, the distributor of the lenalidomide, will not dispense or ship Revlimid® prior to Celgene's receipt of registration. Prescription information MUST BE entered using the Revlimid REMS® study specific electronic prescription form referenced in Appendix E (Revlimid REMS® program). An authorization **number** must be on the prescription form at the time of faxing. Prescriptions for Revlimid® must be sent to Biologics Clinical Trial Division at the following FAX number: 919-256-0794. A maximum of a 28-day supply of Revlimid® may be dispensed per cycle sent to the actual address noted on the Revlimid REMS® electronic prescription form. Biologics will verify the authorization number and complete the patient counseling. Patients will be provided with instructions from Biologics with each new dispense on the procedures for return of any un-used Revlimid® capsules. Refer to Appendix E (Revlimid REMS® program).

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITIONS

3.1. Definition of High-risk vs. Standard-risk Myeloma

Multiple myeloma patients on this study will be stratified for the purposes of statistical analysis into high-risk and standard risk-groups. High-risk multiple myeloma is defined by the presence of high beta-2 microglobulin (> 5.5mg/L) or the presence of cytogenetic abnormalities including t(4;14), t(14;20), t(14;16), deletion (17p) detected by FISH or standard cytogenetics, deletion 13 detected by standard cytogenetics only or aneuploidy.[33] Patients without cytogenetic analysis available and beta-2 microglobulin ≤ 5.5mg/L or with deletion 13 detected by FISH will be classified as standard-risk disease.

3.2. Definition of Disease Status

Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria. Until disease progression, all disease classifications are relative to the patient's disease status prior first autologous transplantation (i.e., study entry).

3.2.1. International Uniform Response Criteria

Stringent Complete Response (sCR):

- sCR requires, in addition to CR (defined below), all of the following:
- Normal free light chain ratio (FLC).
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Complete Response (CR) requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation. The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR;
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed;
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)*; and,
- Disappearance of soft tissue plasmacytomas.

**If not clinically indicated, radiographs are not required to document CR.*

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial

response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Near Complete Response (nCR) represents disease detected only by immunofixation and it is defined as:[43, 44]

- Presence of the original monoclonal paraprotein in serum and urine by immunofixation
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude nCR)

Very Good Partial Response (VGPR) requires, in addition to PR (defined below), all of the following:

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis,
  OR
- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100 mg/24hrs.

Partial Response (PR) requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and/or reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to <200 mg/24 hours in light chain disease.
- If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio.
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%.
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

Stable Disease (SD)

- Patients who do not meet criteria for sCR, CR, VGPR, PR or progressive disease are considered to have stable disease (SD).

3.3. Progressive Disease (PD)

Progression (PD) from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.

- Abnormal FLC levels of >10 mg/dl, only in patients without measurable paraprotein in the serum and urine.
- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Progressive Disease (PD) for patients not in CR or sCR, progressive disease requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- >25% increase 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 bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Scheduled evaluations for disease response are described in Chapter 4.

3.4. Primary Endpoint

3.4.1. Progression-free Survival

The primary endpoint to be compared between all three treatment arms is PFS as a time to event endpoint censored after 38 months of follow-up on each patient. Patients are considered a failure of the primary endpoint if they die or suffer from disease progression. The time to this event is the time from randomization to progression, death, initiation of non-protocol anti myeloma therapy, loss to follow up or end 38 months whichever comes first. Estimates of PFS will be described for each treatment group at 1 and 2 years as well as 38 months post-randomization. PFS beyond 38 months from randomization may be estimated through data reported to the CIBMTR (see Section 4.2.2) or a long-term follow-up protocol.

3.5. Secondary Endpoints

3.5.1. Incidence of Progression

The cumulative incidence of progression will be compared between the three treatment arms. The time to this event is the time from randomization to progression, death, loss to follow-up or the end of 38 months, whichever comes first. Death will be considered a competing risk. Patients alive or lost to follow-up at the time of last observation are considered censored. Estimates of progression will be described for each treatment group at 1 and 2 years as well as 38 months post-randomization. Incidence of progression beyond 38 months from randomization may be estimated through data reported to the CIBMTR (see Section 4.2.2) or a long-term follow-up protocol.

3.5.2. Response to Treatment Endpoints

The trial will assess the rates of VGPR or better (VGPR, nCR, CR and sCR) responses according to the International Uniform Response Criteria (Section 3.2) at specific time points in all arms. Assessment of disease response will be done immediately prior to the second transplant, consolidation and maintenance therapy. Additional disease status assessments will be at one year after randomization and every six months thereafter until disease progression or completion of maintenance therapy. Rates of VGPR or better responses will be compared among the three arms at one and two years after randomization. For patients not in CR upon initiating maintenance therapy, the rate of CR conversion will be assessed at 3 months, 6 months, 1, 2 and 3 years of maintenance therapy or until disease progression.

3.5.3. Overall Survival

The event is death from any cause. The time to this event is the time from randomization to death, loss to follow-up or the end of 38 months, whichever comes first. Patients alive at the time of last observation are considered censored. Estimates of overall survival will be described for each treatment group at 1 and 2 years as well as 38 months post-randomization. Overall survival beyond 38 months from randomization may be estimated through data reported to the CIBMTR (see Section 4.2.2) or a long term follow up protocol.

3.5.4. Incidence of Toxicities Grade ≥ 3 per CTCAE Version 3.0

All Grade ≥ 3 toxicities will be tabulated for treatment arms. The proportion of patients developing Grade ≥ 3 toxicity will be compared between treatment arms within specified time periods corresponding approximately to after the first transplant, after the second transplant or consolidation, and one, two, and three years from randomization or until disease progression.

3.5.5. Incidence of Infections

The incidence of definite and probable viral, fungal[34] and bacterial infections will be tabulated for each patient. The proportion of patients in each treatment arm with these infections will be

compared within specified time periods corresponding approximately to after each autologous transplantation, consolidation and one and two years as well as 38 months from randomization.

3.5.6. Treatment-related Mortality (TRM)

TRM is defined as death occurring in a patient from causes other than disease progression. Disease progression is a competing event for TRM. Patients alive and progression-free at 38 months will be censored. Prior to the completion of the first year from randomization, disease progression and death will be assessed immediately prior to the second transplantation, consolidation and maintenance in all treatment arms. Thus patients randomized to arms A and C will have two assessments in the first year and patients randomized to Arm B will have one assessment. Subsequently, a scheduled assessment of disease and patient status will occur at one year from randomization and every 6 months thereafter for four years; the primary analysis will occur at 38 months post-randomization.. TRM is also monitored using safety guidelines as described in Section 5.7. Beyond 38 months from randomization, TRM may be analyzed with data reported to the CIBMTR (see Section 4.2.2) or a long term follow up protocol.

3.5.7. Rate of Noncompliance with Study Treatment

The proportion of patients who do not proceed to their second or, if applicable, third phase of treatment or who discontinue consolidation or maintenance at any time point due to toxicity, noncompliance or other reasons will be tabulated. The rate of noncompliance will be compared between treatment arms starting at one year from randomization and yearly thereafter until completion of maintenance or evidence of progression. The rate of noncompliance is also monitored using safety guidelines as described in Section 5.8.

3.5.8. Quality of Life

The FACT-BMT[40] version 4.0 instrument is comprised of a general core questionnaire, the FACT-G, which evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The MOS SF-36 [36, 37] instrument is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

HQL will be described and compared between all treatment arms utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool (SF-36). The questionnaires will be scored according to standard procedures. The self report questionnaires will be completed prior to the first and second transplants, consolidation therapy and maintenance therapy, at one year after randomization and yearly thereafter for four years or until disease progression. Comparisons of quality of life will be done between treatment arms at 1, 2, and 3 years post-randomization. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

The BMT CTN 0702 protocol includes an option for patients to provide bone marrow aspirate samples for future research.

Patients can consent for an additional aliquot of the bone marrow aspirate sample to be collected for future research (see Appendix C for details). BMT CTN Core and Affiliate centers that choose to collect the research bone marrow aspirate sample at the same time as the routine bone marrow aspirate and biopsy for disease assessment will use the Screening Consent Form included in Appendix B. BMT CTN Core and Affiliate centers will enter the date the patient signed the consent form in AdvantageEDC Segment 0 (Screening Segment) to obtain a patient study number. Entering a patient in Segment 0 does not guarantee that the patient will be enrolled in BMT CTN 0702; if the patient is determined to be not eligible for BMT CTN 0702, the bone marrow aspirate collected for future research will be discarded.

4.1.1.1. BMT CTN Core and Affiliate Centers

BMT CTN Core and Affiliate Centers will register patients using the Advantage Electronic Data Capture (AdvantageEDC^{SM}) system. The following procedures should be followed:

An authorized user at the clinical center completes a form with demographic and primary eligibility screening questions. The eligibility form includes a question confirming that the patient signed the informed consent form and that they have an adequate autologous graft available to them. Randomization will be done at time of study registration (enrollment into Segment A in AdvantageEDC^{SM}).

Once the patient is randomized to one of the three treatment arms (Eligibility Form, Segment A completed):

1. A visit schedule based on transplant date is available for printing.
2. After recovery from the 1st autologous transplantation (at least 60 days post first transplant), an authorized user at the clinical center completes a checklist confirming that the patient has recovered and is eligible for either consolidation, second autologous transplant or maintenance therapy.
3. If the patient is eligible, the treatment plan is continued.
4. For patients randomized to tandem autologous HCT or consolidation, upon recovery (at least 60 days post second transplant or 84 days after consolidation), an authorized user at the clinical center completes a checklist confirming that the patient has recovered from therapy and is eligible to initiate maintenance.

5. If the patient is eligible, the treatment plan is continued.

4.1.1.2. Revlimid REMS® lenalidomide counseling

Lenalidomide counseling will be provided through the Revlimid REMS® program. Biologics Inc. will supply all counseling prior to drug distribution. Requirements are outlined in the Study Drug Supply Section 2.7.2.2 (Counseling for the Revlimid REMS® program). Refer to Appendix E (Revlimid REMS® program) for procedures.

4.1.1.3. U.S. cooperative group centers participating through the CTSU

U.S. Cooperative Group Centers participating through the Cancer Trials Support Unit (CTSU) should follow the CTSU instructions for site activation and patient registration in Appendix L.

4.2. Study Monitoring

4.2.1. Follow-up Schedule

The follow-up for scheduled study visits are separated into two categories: 1.) endpoint assessments common to all treatment arms; and, 2.) pre- and post-intervention clinical assessments for each treatment arm as outlined in Tables 4.2.1a, 4.2.1b, 4.2.1c, and 4.2.1d. The first category of assessments is based on date of randomization and the second on previous intervention. If the specified date of evaluation based on randomization falls within one month of the scheduled evaluation based on the date of an intervention, all required observations can be done on the same date. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook. The Data Management Handbook, including the Forms Submission Schedule, is available on the homepage of AdvantageEDC℠, the Internet data entry system and the BMT CTN secure website (http://bmtctn.def6.net).

Table 4.2.1a -- Follow-up Schedule –Endpoint Assessments – All Treatment Arms
Assessments based on date of randomization

Endpoints	Days From Randomization* (±14 Days)
1 year	365 days
2 year	730 days
3 year	1095 days
4 year	1460 days

*All visits must be scheduled within a ± 14-day window of the indicated days from randomization.

Table 4.2.1b -- Follow-up Schedule – Clinical Assessments- Treatment Arm A
Tandem Autologous Transplant Patients

Post - Intervention	Target Day[2]
First Autologous HCT[3]	**(Days Post-1st Transplant, ± 7 Days)**
60 day	56
100 days[1]	100
5 month[1]	150
6 month[1]	180
Second Autologous HCT[3]	**(Days Post-2nd Transplant, ± 7 Days)**
60 day	56
100 days[1]	100
5 month[1]	150
6 month[1]	180
Maintenance[3]	**(Days Post Initiation of Maintenance Therapy, ± 7 Days)**
Baseline*	Day 1
1 month	28
2 month	56
3 month	84
6 month	180
9 month	270
12 month	365
15 month	455
18 month	545
21 month	635
24 month	725
27 month	815
30 month	905
33 month	995
36 month	1,085
48 month[4]	1,460

Notes for Table 4.2.1b

[1] Evaluations beyond Day 60 post autologous transplant will only be performed for patients not proceeding to the next intervention. The interval between interventions is preferably 60 to 120 days, but no later than 180 days.

[2] The recommended ±7-day window is increased to a recommended ±14-day window after 6 months of follow-up post-intervention. Note that if an assessment is missed within the recommended window, but precedent or subsequent data are available (which does not fall within the window for another visit), the available data should be reported.

[3] If the endpoint assessment from Table 4.2.1a falls within a ± 7-day window of a clinical assessment visit, the endpoint assessment can satisfy the clinical assessment requirement.

[4] The purpose of this visit is to capture assessments required at 4 years post randomization.

* According to Federal requirements from the Food and Drug Administration, patients taking lenalidomide require evaluations before each 28 day supply of lenalidomide is dispensed. Evaluation of blood counts, pregnancy test and renal function may also be required prior release of lenalidomide. These monthly evaluations will be performed as clinically indicated and may be performed remotely from the transplant center.

Table 4.2.1c -- Follow-up Schedule – Treatment Arm B
Autologous HCT Followed by Maintenance

Post - Intervention	**Target Day[2]**
First Autologous HCT[3]	**(Days Post-1st Transplant, ± 7 Days)**
60 day	56
100 days[1]	100
5 month[1]	150
6 month[1]	180
Maintenance[3]	**(Days Post Initiation of Maintenance Therapy, ± 7 Days)**
Baseline*	Day 1
1 month	28
2 month	56
3 month	84
6 month	180
9 month	270
12 month	365
15 month	455
18 month	545
21 month	635
24 month	725
27 month	815
30 month	905
33 month	995
36 month	1,085
48 month[4]	1,460

Notes for Table 4.2.1c

[1] Evaluations beyond Day 60 post autologous transplant will only be performed for patients not proceeding to the next intervention. The interval between interventions is preferably 60 to 120 days, but no later than 180 days.

[2] The recommended ±7-day window is increased to a recommended ±14-day window after 6 months of follow-up post-intervention. Note that if an assessment is missed within the recommended window, but precedent or subsequent data are available (which does not fall within the window for another visit), the available data should be reported.

[3] If the endpoint assessment from Table 4.2.1a falls within a ± 7-day window of a clinical assessment visit, the endpoint assessment can satisfy the clinical assessment requirement.

[4] The purpose of this visit is to capture assessments required at 4 years post randomization.

* According to Federal requirements from the Food and Drug Administration, patients taking lenalidomide require evaluations before each 28 day supply of lenalidomide is dispensed. Evaluation of blood counts, pregnancy test and renal function may also be required prior release of lenalidomide. These monthly evaluations will be performed as clinically indicated and may be performed remotely from the transplant center.

Table 4.2.1d -- Follow-up Schedule – Treatment Arm C
Autologous HCT followed by RVD Consolidation Therapy

Post - Intervention	**Target Day[2]**	
First Autologous HCT[3]	**(Days Post-1st Transplant, ± 7 Days)**	
60 day	56	
100 days[1]	100	
5 month[1]	150	
6 month[1]	180	
Consolidation[3]	**(Days Post Initiation of Consolidation, ± 7 Days)**	**Consolidation Cycle**
Baseline*	0	1
1 week	8	-
2 week	15	-
3 week	22	2
4 week	29	-
6 week	43	3
9 week	64	4
12 week	85	-
18 week	127	-
6 month	180	-
Maintenance[3]	**(Days Post Initiation of Maintenance Therapy, ± 7 Days)**	
Baseline*	Day 1	
1 month	28	
2 month	56	
3 month	84	
6 month	180	
9 month	270	
12 month	365	
15 month	455	
18 month	545	
21 month	635	
24 month	725	
27 month	815	
30 month	905	
33 month	995	
36 month	1,085	
48 month[4]	1,460	

Notes for Table 4.2.1d

[1] Evaluations beyond Day 60 post autologous transplant will only be performed for patients not proceeding to the next intervention. The interval between interventions is preferably 60 to 120 days, but no later than 180 days.

[2] The recommended ±7-day window is increased to a recommended ±14-day window after 6 months of follow-up post-intervention. Note that if an assessment is missed within the recommended window, but precedent or subsequent data are available (which does not fall within the window for another visit), the available data should be reported.

[3] If the endpoint assessment from Table 4.2.1a falls within a ± 7-day window of a clinical assessment visit, the endpoint assessment can satisfy the clinical assessment requirement.

[4] The purpose of this visit is to capture assessments required at 4 years post randomization.

* According to Federal requirements from the Food and Drug Administration, patients taking lenalidomide require evaluations before each 28 day supply of lenalidomide is dispensed. Evaluation of blood counts, pregnancy test and renal function may also be required prior release of lenalidomide. These monthly evaluations will be performed as clinically indicated and may be performed remotely from the transplant center.

4.2.2. Data Reporting

Criteria for Forms Submission
Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook. Forms that are not entered into the web-based data entry system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the web based data entry system and integrated into the Data and Coordinating Center's (DCC's) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths
Recipient Death Information must be entered into the web-based data entry system within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in the web-based data entry system.

Center for International Blood and Marrow Transplant Research (CIBMTR) Data Reporting
Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment on BMT CTN #0702 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post-transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule. Patients not undergoing HCT are not required to have their information reported to the CIBMTR.

4.2.3. Adverse Event Reporting

Adverse events will be reported according to procedures specified in the BMT CTN MOP. Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system using NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event.

Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using CTCAE version 3.0 at regular intervals as defined on the Form Submission Schedule.
All second primary malignancies (SPM), excluding non-melanoma skin cancers, experienced by patients enrolled on the study will be reported using the Adverse Event forms (AE1-AE6) in AdvantageEDC and must be reported within three business days of knowledge of the event. The Event Description of the Adverse Event forms should include histologic type.

CTCAE term (AE description) and grade: 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). All appropriate treatment areas should have access to a copy of the CTEP version 3.0 (for toxicity) and 4.0(for AE reporting) of the CTCAE.

Additionally, selected events listed in Appendix K (Table K-2) will also be reported through an expedited AE reporting system if they fulfill the criteria for serious adverse events (SAE), according to the Code of Federal Regulations Title 21 (21 CFR 312.32). These selected SAEs must be reported within three business days of the transplant center's knowledge of the event. Other expected events listed in Appendix K (Table K-3) will only require expediting reporting if they occur after the initiation of lenalidomide or bortezomib. See Appendix K for additional details on expedited reporting.

4.2.3.1. Adverse Event Reporting Following Progression

- If a patient meets the protocol defined definition of progression (Chapter 3), Unexpected Grade 3-5 Adverse Events and events listed in Appendix K are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of lenalidomide. However, SPMs should continue to be reported within three business days of the knowledge of the event through the end of the study follow up period.

4.2.3.2. Adverse Event Reporting Following an SPM

Adverse Event reporting following an SPM is dependent on the treatment received for the reported SPM.

- If a patient experiences an SPM resulting in permanent discontinuation of lenalidomide and initiation of non-protocol systemic therapy, Unexpected Grade 3-5 Adverse Events and events listed in Appendix K are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of lenalidomide.
- If a patient experiences an SPM that does *not* result in permanent discontinuation of lenalidomide, Adverse Events will continue to be reported as per section 4.2.3 and appendix K of the protocol.
- Requests to discontinue Adverse Event Reporting for events that do not meet the criteria above will be considered on a case by case basis.

Pregnancy Reporting
Pregnancies occurring while the subject is on lenalidomide and/or bortezomib or within four weeks after the subject's last dose of lenalidomide and/or bortezomib are considered expedited reportable events. If the subject is on lenalidomide and/or bortezomib, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide and/or bortezomib to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must report the outcome of the pregnancy and neonatal status as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures to report the event within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to lenalidomide must be reported within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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 lenalidomide should also be reported.

In the case of a live "normal" birth, the outcome should be reported as soon as the information is available.

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 her healthcare provider immediately.

4.2.4. Patient Assessments

Tables 4.2.4a, 4.2.4b and 4.2.4c summarize patient clinical assessments over the course of the study. All assessments prior to and after transplants and therapies are considered standard of care.

4.2.4.1. Evaluations prior to first autologous HCT (all treatment arms)

The following observations must be determined **≤ 12 weeks prior to initiation of high-dose melphalan.** If these tests are done prior to mobilization therapy and there is clinical suspicion of cardiac or pulmonary toxicity following mobilization therapy, they must be repeated prior to the initiation of high-dose melphalan. See Table 4.2.4a.

1. EKG.
2. LV ejection fraction by MUGA, echocardiogram or MRI according to local institutional practice.
3. DLCO, FEV1 and FVC.

Infectious disease testing including hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), syphilis and HIV should be determined **30 days prior to the initiation of mobilization therapy**. If there is clinical suspicion of new infection, tests must be repeated prior to the initiation of high-dose melphalan.

The following observations are to be determined **≤ 8 weeks prior to the initiation of high-dose melphalan** either before or after initiation of mobilization therapy depending on transplant center standard of practice. See Table 4.2.4a.

1. History, physical examination, height and weight.
2. Measurement of waist and hip circumference (see Appendix M).
3. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
4. Skeletal survey to include cranium, axial skeleton and proximal long bones.
5. Laboratory Disease Response Assessments
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine protein electrophoresis (UPEP).
    d. Immunofixation electrophoresis of serum protein and urine protein regardless of SPEP and UPEP results.
    e. Serum beta 2 microglobulin (B2M serum).
    f. Serum free light chain ratio (FLC ratio).
6. Bone marrow evaluation:
    a. Mandatory evaluation: unilateral bone marrow biopsy and aspirate are indicated to assess disease status prior first transplantation.
    b. Ancillary Study and Future testing: bone marrow aspirate (10 cc) collection for the PRIMeR ancillary study and future research (Appendix C and Appendix N).
7. Four vials (31 cc total) of peripheral blood for future research (Appendix C).

The following observations should be determined **≤ 4 weeks prior to the initiation of high-dose melphalan,** before or after mobilization, depending on transplant center standard of care.

1. Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP).
2. Health quality of life assessment, SF-36 and FACT-BMT (for English and Spanish speaking patients only).
3. The Karnofsky performance score should be determined **≤ 2 weeks prior to the initiation of high-dose melphalan**.

4.2.4.2. Schedule of evaluations for treatment Arm A

The following evaluations are after the first autologous HCT. Evaluations will be done at 8 weeks (~60 days) after the first autologous transplantations (see Table 4.2.4b):*

1. History and physical examination.
2. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
3. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.†
4. Laboratory Disease Response Assessment (see Section 4.2.4.5).‡

The following evaluations will be done ≤ 4 weeks prior to initiation of high-dose melphalan for the second autologous HCT (see Table 4.2.4a):

1. History and physical examination
2. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events§
3. Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP).
4. Karnofsky performance score.
5. CBC with differential, platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.§
6. LV ejection fraction only if clinically significant cardiac symptoms/signs develop after the first autologous transplant.

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* These evaluations will continue at Days 100, 150, 180 or until the patients proceed to the second autologous HCT or, for patients not able to receive their second HCT, to maintenance.

† History, physical exam, toxicity assessment and routine laboratory evaluation performed as scheduled after the first transplant can be used as evaluation prior to second autologous transplant if they are < 4 weeks prior to scheduled high-dose melphalan for second transplant.

‡ Patients will have protocol required evalutations every 6 months during maintenance. However, if patients experience disease progression, between required evaluations the laboratory disease response assessment will be collected at the the time the event occurred.

§ History, physical exam, toxicity assessment and routine laboratory evaluation performed as scheduled after the first transplant can be used as evaluation prior to second autologous transplant if they are < 4 weeks prior to scheduled high-dose melphalan for second transplant.

7. DLCO, FEV1 and FVC only if clinically indicated.
8. Health quality of life assessment (for English and Spanish speaking patients only).

The following evaluations will be done at 8 weeks (~60 days) after the second autologous HCT (see Table 4.2.4b):*

1. History and physical examination.
2. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
3. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.†
4. Laboratory Disease Response Assessment(See Section 4.2.4.5)‡

The following evaluations will be done ≤ 4 weeks prior to initiation of maintenance therapy (see Table 4.2.4a):

1. History and physical exam
2. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.
3. Measurement of waist and hip circumference (see Appendix M).
4. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT*.
5. Required evaluation prior Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for FCBP. Women are required to have 2 pregnancy tests prior to the initiation of lenalidomide as follows (Appendix D):
   a. The first is required within 10 to 14 days prior to beginning lenalidomide,
   b. The second is required within 24 hours of beginning treatment with lenalidomide.
6. Health quality of life assessment, FACT-BMT and SF-36 (for English and Spanish speaking patients only).
7. Bone marrow evaluation:
   a. Ancillary Study Testing: bone marrow aspirate (2 cc) collection for the PRIMeR ancillary study (Appendix N).
8. Four vials (31 cc total) of peripheral blood for future research (Appendix C).

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* These evaluations will continue at Days 100, 150, 180 or until the patients proceed to maintenance.

† History, physical exam, toxicity assessment and routine laboratory evaluation performed as scheduled after the second transplant can be used as pre-maintenance therapy evaluation if they are < 4 weeks prior to scheduled initiation of maintenance.

‡ Patients will have protocol required evalutations every 6 months during maintenance. However, if patients experience disease progression between required evaluations, the laboratory disease response assessment will be collected at the the time the event occurred.

The following evaluations will be done after initiation of maintenance therapy (see Table 4.2.4d):

1. The following evaluations will be done monthly for the first 3 months then every 3 months after initiation of maintenance therapy:
   a. History and physical exam.
   b. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
   c. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.
   d. Neurotoxicity assessment
2. Measurement of waist and hip circumference (see Appendix M).
3. Required evaluation for Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
   a. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix D).
   b. The subject must follow the requirements of the Revlimid REMS® program of the Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.
   c. Patients will require CBC with differential prior to the monthly supply of lenalidomide. These laboratory tests may be done remotely and sent to the transplant center.
4. Laboratory Disease Response Assessment(see Section 4.2.4.5))*
5. Bone marrow evaluation (see Section 4.2.4.5)
   a. Ancillary Study and Future Testing: bone marrow aspirate (10 cc) collection for the PRIMeR ancillary study and future research (Appendix C and Appendix N) at one year post randomization.
   b. Future Testing: bone marrow aspirate (10 cc) collection for future research will be performed yearly post-randomization at years two, three, and four (Appendix C)

* Patients will have protocol required evaluations every 6 months during maintenance. However, if patients experience disease progression, between required evaluations the laboratory disease response assessment will be collected at the the time the event occurred.

6. Four vials (31 cc total) of peripheral blood for future research will be collected yearly post randomization for four years (Appendix C).
7. Health quality of life using FACT-BMT and SF-36 assessment tools (for English and Spanish speaking patients only) will be performed at one year from randomization or six months from initiation of maintenance in this treatment arm and repeated yearly thereafter until disease progression.
8. Long Term Follow Up Protocol Screening for eligibility on the long-term follow-up protocol will be completed at the time of BMT CTN 0702 maintenance completion or BMT CTN 0702 follow up completion..

4.2.4.3. Schedule of evaluations for treatment Arm B

The following evaluations are after the first autologous HCT. Evaluations will be done at 8 weeks (~60 days) after the first autologous transplant (see Table 4.2.4b):*

1. History and physical examination.
2. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
3. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.†
4. Laboratory Disease Response Assessment*: See Section 4.2.4.5

The following evaluations will be done ≤ 4 weeks prior to initiation of maintenance therapy (see Table 4.2.4a):

1. History and physical exam
2. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.
3. Measurement of waist and hip circumference (see Appendix M).
4. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
5. Required evaluation prior Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for FCBP. Women are required to have 2 pregnancy tests prior initiation of lenalidomide as follows (Appendix D):
   a. The first is required within 10 to 14 days prior to beginning lenalidomide,
   b. The second is required within 24 hours of beginning treatment with lenalidomide.
6. Health quality of life assessment, FACT-BMT and SF-36 (for English and Spanish speaking patients only).
7. Four vials (31 cc total) of peripheral blood for future research (Appendix C).

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* These evaluations will continue at Days 100, 150, 180 or until the patients proceed to maintenance.

† History, physical exam, toxicity assessment and routine laboratory evaluation performed as scheduled after the first transplant can be used as evaluation prior to maintenance if they are <4 weeks prior to scheduled initiation of maintenance.

8. Bone marrow evaluation:
    a. Ancillary Study Testing: bone marrow aspirate (2 cc) collection for the PRIMeR ancillary study (Appendix N).

The following evaluations will be done after initiation of maintenance therapy (see Table 4.2.4d):

1. The following evaluations will be done monthly for the first 3 months then every 3 months after initiation of maintenance therapy:
    a. History and physical exam
    b. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT;
    c. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.*
    d. Neurotoxicity assessment
2. Measurement of waist and hip circumference (see Appendix M).
3. Required evaluation for Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
    a. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix D).
    b. The subject must follow the requirements of the Revlimid REMS® program of the Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.
    c. Patients will require CBC with differential prior to the monthly supply of lenalidomide. These laboratory tests may be done remotely and sent to the transplant center.
4. Laboratory Disease Response Assessment(See Section 4.2.4.5)*
5. Bone marrow evaluation: See Section 4.2.4.5

* Patients will have protocol required evalutations every 6 months during maintenance. However, if patients experience disease progression, between required evaluations the laboratory disease response assessment will be collected at the the time the event occurred.

a. Ancillary Study and Future testing: bone marrow aspirate (10 cc) collection for the PRIMeR ancillary study and future research (Appendix C and Appendix N) at one year post randomization.

b. Future testing: bone marrow aspirate (10 cc) collection for future research will be performed yearly post-randomization at years two, three, and four (Appendix C).

6. Four vials (31 cc total) of peripheral blood for future research will be collected yearly post-randomization for four years (Appendix C).
7. Health quality of life using FACT-BMT and SF-36 assessment tools (for English and Spanish speaking patients only) will be performed at one year from randomization or 9 months from initiation of maintenance in this treatment arm and repeated yearly thereafter until disease progression.
8. Long Term Follow Up Protocol Screening for eligibility on the long-term follow-up protocol will be completed at the time of BMT CTN 0702 maintenance completion or BMT CTN 0702 follow up completion.

4.2.4.4. Schedule of evaluations for treatment Arm C

The following evaluations are after the first autologous HCT. Evaluations will be done at 8 weeks (~60 days) after the first autologous transplant (see Table 4.2.4b):*

1. History andphysical examination.
2. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT†.
3. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events†
4. Laboratory Disease Response Assessment(See Section 4.2.4.5)*

The following evaluations will be done ≤ 4 weeks prior to initiation of consolidation therapy (see Table 4.2.4a):

1. History and physical exam (height and weight).
2. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.
3. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT.
4. Required evaluation prior Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for FCBP. Women are required to have 2 pregnancy tests prior initiation of lenalidomide as follows (Appendix D):

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* These evaluations will continueat Days 100, 150, 180 or until the patients proceed to RVD consolidation, or for patients not able to receive RVD consolidation, to maintenance.

† History, physical exam, and toxicity assessment and routine laboratory evaluation performed as scheduled after the first transplant can be used as evaluation prior to consolidation therapy if they are <4 weeks prior to scheduled initiation of consolidation.

a. The first is required within 10 to 14 days prior to beginning lenalidomide,

b. The second is required within 24 hours of beginning treatment with lenalidomide.

5. Health quality of life assessment, FACT-BMT and SF-36 (for English and Spanish speaking patients only).

The following evaluations will be done <u>after the initiation of consolidation therapy (see Table 4.2.4c):</u>

1. Evaluations prior to the initiation of each scheduled consolidation cycle:
   a. History and physical examination.
   b. CBC with differential and platelet count, creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT
   c. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events*
2. Neurotoxicity assessment will be done after each cycle of consolidation therapy.
3. <u>Required evaluation for lenalidomide:</u> Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
   a. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix D).
      b. The subject must follow the requirements of the Revlimid REMS® program of the Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.
4. Laboratory Disease Response Assessment(See Section 4.2.4.5)†

The following evaluations will be done ≤ 4 weeks <u>prior to initiation of maintenance therapy (see Table 4.2.4a):</u>

1. History and physical exam

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* History, physical exam, toxicity assessment and routine laboratory evaluation performed as scheduled after consolidation therapy can be used as evaluation prior to maintenance if they are < 4 weeks prior to scheduled initiation of maintenance.

† Patients will have protocol required evalutations every 6 months during maintenance. However, if patients experience disease progression, between required evaluations the laboratory disease response assessment will be collected at the the time the event occurred.

2. Toxicity assessment: maximum grade and status of ≥ grade 3 adverse events.
3. Measurement of waist and hip circumference (see Appendix M).
4. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT*.
5. Required evaluation prior Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for FCBP. Patients enrolled in treatment Arm C had already undergone initial pregnancy tests as described above, thus FCBP will only require:
    a. One pregnancy test within 24 hours of beginning treatment with lenalidomide.
6. Health quality of life assessment, FACT-BMT and SF-36 (for English and Spanish speaking patients only).
7. Four vials (31 cc total) of peripheral blood for future research (Appendix C).
8. Bone marrow evaluation:
    a. Ancillary Study Testing: bone marrow aspirate (2 cc) collection for the PRIMeR ancillary study (Appendix N).

The following evaluations will be done after the initiation of maintenance therapy (see Table 4.2.4d):

1. The following evaluations will be done monthly for the first 3 months then every 3 months after initiation of maintenance therapy:
    a. History and physical exam
    b. CBC with differential and platelet count, estimated creatinine clearance, creatinine, bilirubin, alkaline phosphatase, ALT;
    c. Toxicity assessment with maximum grade and status of ≥ grade 3 adverse events.
    d. Neurotoxicity assessment
2. Measurement of waist and hip circumference (see Appendix M).
3. Required evaluation for Lenalidomide: Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
    a. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix D).
    b. The subject must follow the requirements of the Revlimid REMS® program of the Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the

pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.

c. Patients will require CBC with differential prior to the monthly supply of lenalidomide. These laboratory tests may be done remotely and sent to the transplant center.

4. Laboratory Disease Response Assessment (see Section 4.2.4.5)*
5. Bone marrow evaluation: see Section 4.2.4.5
    a. Ancillary Study and Future testing: bone marrow aspirate (10 cc) collection for the PRIMeR ancillary study and future research (Appendix C and Appendix N) at one year post randomization.
    b. Future testing: bone marrow aspirate (10 cc) collection for future research will be performed yearly post-randomization at years two, three, and four (Appendix C).
6. Four vials (31 cc total) of peripheral blood for future research will be collected yearly post-randomization for four years (Appendix C).
7. Health quality of life using FACT-BMT and SF-36 assessment tools (for English and Spanish speaking patients only) will be performed at one year from randomization or 3 months from initiation of maintenance in this treatment arm and repeated yearly thereafter until disease progression.
8. Long Term Follow Up Protocol Screening for eligibility on the long-term follow-up protocol will be completed at the time of BMT CTN 0702 maintenance completion or BMT CTN 0702 follow up completion.

4.2.4.5. Laboratory Disease Response Assessment†

The following Laboratory Disease Response Assessments will be completed:

1. Laboratory Disease Response Assessments
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine urine protein electrophoresis (UPEP).
    d. Immunofixation electrophoresis of serum protein and urine protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratio (FLC ratio).

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* Patients will have protocol required evaluations every 6 months during maintenance. However, if patients experience disease progression between protocol required evaluations, the laboratory disease response assessment will be collected for the time the event occurred.

† Patients will have protocol required evaluations every 6 months during maintenance. However, if patients experience disease progression between protocol required evaluations, the laboratory disease response assessment will be collected at the time the event occurred.

2. Mandatory Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are indicated to assess disease status prior first transplantation*.

Laboratory Disease Response Assessments will be performed at the following timepoints:

- **Treatment Arm A**:
  - 8 weeks (~60 days) after the first autologous transplantation†
  - 8 weeks (~60 days) after the second autologous transplantation‡
  - 1 year after randomization, which for treatment Arm A will fall approximately 6 months from initiation of maintenance*
  - Every 6 months during maintenance until the completion of maintenance or until disease progression§
  - 4 years after randomization.
- **Treatment Arm B:**
  - 8 weeks (~60 days) after the first autologous transplantation*
  - 1 year after randomization, which for treatment Arm B will fall approximately 9 months after initiation of maintenance†
  - Every 6 months during maintenance until the completion of maintenance or until disease progression*
  - 4 years after randomization.
- **Treatment Arm C:**
  - 8 weeks (~60 days) after the first autologous transplantation*
  - At completion of consolidation therapy or at least Day 56 from starting consolidation therapy.**
  - 1 year after randomization, which for treatment Arm C will fall approximately 6 months after initiation of maintenance*
  - Every 6 months during maintenance until the completion of maintenance or until disease progression§
  - 4 years after randomization.

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* Unilateral bone marrow aspirate and biopsy performed after first transplantation will be done only to confirm complete remission in patients with negative biochemical evidence of disease.

† Patients will require multiple myeloma disease response assessment at least once between 60 to 120 days after first autologous transplant. Additional disease assessment evaluations will be done if clinically indicated or if the period between the evaluation after the first autologous HCT and initiation of second conditioning regimen exceeds 3 months.

‡ Patients will require multiple myeloma disease response assessment at least once between 60 to 120 days after second autologous transplant. Additional disease assessment evaluations will be done if clinically indicated or if the period between the evaluation after the second autologous HCT and initiation of maintenance exceeds 3 months.

§ It is recommended that all disease evaluations be performed at least every 3 months during treatment of multiple myeloma as standard clinical practice.

** Additional disease assessment evaluations will be done if clinically indicated or if the period between the evaluation after consolidation and initiation of maintenance exceeds 3 months.

Table 4.2.4a – Evaluation prior to First and Second Autologous HCT, Consolidation and Maintenance Therapies

Required Studies / Testing*	Prior to 1st Auto Transplant	Prior to 2nd Auto Transplant[1]	Prior to Consolidation[1]	Prior to Maintenance[1]
History and Physical Examination (Height and Weight)	X	X	X	X[2]
Pregnancy Test[3]	X	X	X[4]	X[4]
Toxicity Assessment		X		
Karnofsky Performance Score	X	X	X	X
CBC with Differential, PLT, Creatinine Clearance, Creatinine, Bilirubin, Alkaline Phosphatase, ALT.	X	X	X	X
Hepatitis Panel (A, B, C), Syphilis	X			
HIV Antibody	X			
EKG	X			
LV Ejection Fraction assessment	X	X[5]	X[5]	X[5]
DLCO/FEV1/FVC	X	X[5]	X[5]	X[5]
Skeletal Survey	X	X[6]	X[6]	X[6]
Bone Marrow Aspirate and Biopsy	X	X[7]	X[7]	X[7]
Serum Immunoglobulin Levels	X	X[8]	X	X
SPEP and Immunofixation	X	X[8]	X	X
24 Hr Urine for UPEP and Immunofixation[9]	X	X[8]	X	X
Serum Free Light Chain Ratio	X	X[8]	X	X
Serum Beta-2 Microglobulin	X			
Health Quality of Life	X	X	X	X
Anthropomorphic Measurements[10]	X			X
Blood sample for future research[11]	X			X
Bone marrow aspirate for future research[11]	X			
Bone marrow for the PRIMeR study[12]	X			X

*All evaluations are standard of care for treatment or transplantation of patients with multiple myeloma. The only evaluations not considered standard of care include collection of nucleated cells and serum for future analysis, health quality of life.

[1] To be performed within 4 weeks of intervention.
[2] Height and weight is not required as prior to maintenance therapy.
[3] For female of childbearing potential: A female of childbearing potential (FCBP) is 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).
[4] Two pregnancy tests are required (1st within 10 to 14 days, 2nd within 24 hours) prior to the initiation of lenalidomide.
[5] If clinically significant cardiac or pulmonary symptoms/signs develop post-autograft.
[6] Skeletal surveys should be repeated only if clinically indicated.
[7] Unilateral bone marrow aspirate and biopsy will be done only to confirm complete remission in patients with negative biochemical evidence of disease.
[8] Baseline disease evaluations are also included in the post-intervention assessment. Patients will need at least one disease status assessment prior to second transplant and maintenance. More than one evaluation will be performed if clinically indicated or if the period from one evaluation and the next intervention (second autologous HCT or maintenance) exceeds 3 months.
[9] If the baseline urine paraprotein level is less than 200mg/24hrs, the UPEP is not required.
[10] Measurements of hip and waist circumference (Appendix M).
[11] Blood and bone marrow aspirate samples collected for future ancillary studies are voluntary.
[12] Bone marrow immunophenotyping in the PRIMeR study coincides with evaluation prior to the first autoHCT described in Appendix N. Bone marrow aspirate samples for the PRIMeR study are voluntary.

Table 4.2.4b – Evaluations after First and Second Autologous Transplant

Study Assessments/ Testing*	Days from First or Second HCT				
	28	**56**	**100[1]**	**150[1]**	**180[1]**
History and Physical Examination[2]		X	X	X	X
CBC with Differential, PLT, Creatinine Clearance, Creatinine, Bilirubin, Alkaline Phosphatase, ALT		X	X	X	X
Toxicity Assessment[2]	X[3]	X			
Serum Immunoglobulin Levels[4]		X			
SPEP and Immunofixation[4]		X			
24 Hour Urine for UPEP, Protein Excretion and Immunofixation[4,5]		X			
Serum free light chain ratio[4]		X			
Bone marrow aspirate and biopsy[6]		X			

*All evaluations are standard of care for treatment or transplantation of patients with multiple myeloma.

[1] Evaluations at days 100, 150 and 180 are only performed in patients who did not proceed to next intervention (second autologous transplant, consolidation or maintenance) before Day 100.

[2]. The maximum grade and the status of ≥ grade 3 adverse events will be collected.

[3] Day 28 toxicity assessment only required post second HCT.

[4] Disease responses will be done once between 60 to 120 days post-transplant (first or second). Disease assessment is also included in the pre-intervention evaluations which should be done ≤4 weeks from the intervention (second autologous, consolidation or maintenance). Thus disease evaluation can be repeated if the next intervention is scheduled to begin beyond Day 100 post first or second transplant.

[5] If the baseline urine paraprotein level is less than 200mg/24hrs, the UPEP is not required.

[6] Bone marrow analyses are only required to confirm complete remission.

Table 4.2.4c – Evaluation after Initiation of RVD Consolidation Therapy

Study Assessments/Testing*	Weeks Post Consolidation Initiation								
	1	**2**	**3**	**4**	**7**	**10**	**13[1]**	**18[1]**	**24[1]**
Consolidation Cycle	**1**			**2**	**3**	**4**			
History and Physical Examination[2]	X			X	X	X	X	X	X
Toxicity Assessment[2]				X	X	X	X	X	X
CBC with Differential, PLT, Creatinine Clearance, Creatinine, Bilirubin, Alkaline Phosphatase, ALT.[2]	X			X	X	X	X	X	
Pregnancy Test[3]	X	X	X	X	X	X			
Serum Immunoglobulin Levels[4]							X	X	X
SPEP and Immunofixation[5]							X	X	X
24 Hour Urine for UPEP, Protein Excretion and Immunofixation[4,5]							X	X	X
Serum free light chain ratio[4]							X	X	X
Neurotoxicity evaluation	X			X	X	X			
BM Aspirate & Biopsy[6]							X	X	X

*All evaluations are standard of care for treatment or transplantation of patients with multiple myeloma.

[1] Evaluations beyond week 12 are only performed in patients who did not proceed to maintenance.
[2] The maximum grade and the status of ≥ grade 3 adverse events will be collected.
[3] For female of childbearing potential: A female of childbearing potential (FCBP) is 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).
[4] Disease responses will be done once after completion of consolidation (at least Day 56 or prior initiation of the 12th week and up to 180 days).
[5] If the baseline urine paraprotein level is less than 200mg/24hrs, the UPEP is not required.
[6] Bone marrow analyses are only required to confirm complete remission.

Table 4.2.4d – Evaluations after Initiation of Maintenance Therapy for <u>All Treatment Arms</u>

NOTE: Disease Response Assessments are to be performed at 1-Year Post Randomization, and then every 6 months thereafter until completion of maintenance or disease progression. The table below indicates that most patients will be at the 1-Year Post Randomization time point approximately 6 months (180 days) after the initiation of Maintenance Therapy, and is consistent with the AdvantageEDC data entry system. However, because of the known variability in calculating the 1-Year Post Randomization time point for patients across the three treatment arms (approximately 6 months for Arms A and C, and approximately 9 months for Arm B), this table is strictly an *estimate* of when these assessments should be performed. Referencing the Segment C Forms Grid for each individual patient is the most accurate way of determining on which date these assessments are due.

Study Assessments/ Testing	**Days Post Maintenance Initiation**														**1 Yr Post Rand**	**2 Yr Post Rand**	**3 Yr Post Rand**	**4 Yr Post Rand[6]**
	28	**56**	**100**	**180**	**270**	**365**	**450**	**540**	**630**	**730**	**810**	**900**	**990**	**1095**				
History and Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
*CBC with Differential, PLT, Creatinine Clearance, Creatinine, Bilirubin, Alkaline Phosphatase, ALT	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Toxicity Assessment[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
*Pregnancy Test [2]	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X				
*Serum Immunoglobulin Levels				X[7]		X[7]		X[7]		X[7]		X[7]		X[7]				X
*SPEP and Immunofixation				X[7]		X[7]		X[7]		X[7]		X[7]		X[7]				X
*24 Hour Urine for UPEP, Protein Excretion and Immunofixation[4]				X[7]		X[7]		X[7]		X[7]		X[7]		X[7]				X
*Serum Free Light Chain Ratio				X[7]		X[7]		X[7]		X[7]		X[7]		X[7]				X
*Bone marrow for aspirate and biopsy[5]				X[7]		X[7]		X[7]		X[7]		X[7]		X[7]				X
Health Quality of Life															X	X	X	X
Neurotoxicity Assessment			X	X		X				X				X				
Anthropomorphic Measurements[8]															X			
Blood Research Sample[9]															X	X	X	X
Bone Marrow Aspirate Research Sample[9]															X	X	X	X
Bone Marrow IP (PRIMeR study)[10]															X			
Long Term Follow Up & Maintenance Screening														X[11]				

*All evaluations are standard of care for treatment or transplantation of patients with multiple myeloma.

[1] The maximum grade and the status of ≥ grade 3 adverse events will be collected.

[2] Requirement for patients taking lenalidomide: Pregnancy tests for FCBP only: a female of childbearing potential (FCBP) is 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). All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks through the Revlimid REMS® program -See Appendix E: Revlimid REMS® program. A maximum supply of lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle. Patients will require CBC with differential prior to the monthly supply of lenalidomide. These laboratory tests may be done remotely and sent to the transplant center.

[3] Patients randomized to treatment Arms A and B will be exposed to lenalidomide for the first time within the context of this trial. These women (FCBP only) will require weekly pregnancy tests for the first 28 days of maintenance therapy, and then prior to the start of every 28-day maintenance cycle thereafter. FCBP with irregular menstrual cycles will have pregnancy tests every 14 days.

[4] If the baseline urine paraprotein level is less than 200mg/24hrs, the UPEP is not required.

[5] Bone marrow analyses are only required to confirm complete remission.

[6] The final evaluation after completion of maintenance will be at 4 years from randomization. The actual date on which these evaluations will be performed will differ from patient to patient, depending on the patient's randomization assignment. Visit 1460, which has a 1 year window, will capture the myeloma and toxicity assessment data that is required at the final study time point. The Health Quality of Life assessments and the final blood and marrow research samples will be recorded at the R4Y visit.

[7] Laboratory Disease Response Assessment to be done 1 year from randomization, then at least every 6 months thereafter until completion of maintenance or disease progression. It is recommended that all disease evaluations be performed at least every 3 months during treatment of multiple myeloma as standard clinical practice.

[8] Measurement of hip and waist circumference (Appendix M).

[9] Blood and bone marrow aspirate samples collected for future ancillary studies are voluntary.

[10] Bone marrow sample for the PRIMeR ancillary study is voluntary.

[11] Long Term Follow Up and Maintenance Screening is due at the time the patient is presented the informed consent form for *Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702.*

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The primary objective of this randomized Phase III trial is to compare three different treatment regimens for multiple myeloma with respect to progression-free survival (PFS) as a time to event endpoint through 38 months of follow-up from randomization. It is expected that 38 months is the earliest time point at which a participant may have completed 3 years of maintenance.

All subjects receive conditioning with melphalan and an autologous transplant. Following that, the first arm receives a second autologous transplant (auto-auto, treatment Arm A), the second arm receives consolidation with lenalidomide, bortezomib, and dexamethasone (D) (auto-RVD, treatment Arm C). All three arms receive maintenance therapy with lenalidomide. The third arm is thus auto followed by lenalidomide (auto-R, treatment Arm B).

Patients are considered a failure with respect to PFS if they die or experience disease progression. The time to this event is the time from randomization to progression, initiation of non-protocol anti-myeloma therapy, or death from any cause. Subjects alive or lost to follow upwithout confirmed disease progression will be censored at the time of last disease evaluation prior to 38 months.

The primary analysis of PFS through 38 months of follow-up from randomization will include all randomized subjects, classified according to their randomized treatment assignment, irrespective of treatment actually received [intent-to-treat]. The treatment arms will be compared with a two-sided log-rank test stratified on risk status. Tests will be performed pair-wise at the .01667 level in order to maintain study-wide type I error at 0.05.

5.2. Accrual, Registration and Follow-up

The targeted sample size is 750 subjects. It is estimated that three years of accrual will be necessary to enroll this number of subjects. BMT CTN Core and Affiliate centers will participate as well as Eastern Cooperative Oncology Group (ECOG) centers, SWOG, Cancer and Leukemia Group B (CALGB) centers, and centers affiliated with other NCI-sponsored Cancer Cooperative Groups that enroll patients through the Cancer Trials Support Unit (CTSU). These collaborators are essential to meet the accrual goal.

The randomization will be stratified by risk status (high versus low), and clinical site. After eligibility is established, subjects will be randomized in equal numbers to the auto-auto, auto-RVD, and auto-R arms using permuted blocks within strata.

All subjects will be "on-study" for four years from time of randomization, during which they will be monitored for the effects of treatment through regular clinic visits and data submitted to the

BMT CTN Data and Coordinating Center. Additional follow-up data beyond four years of progression-free survival will be available through routine CIBMTR mechanismsor a long term follow up protocol

5.3. Sample Size and Power Calculations

As a useful approximation to the power of the analysis of time to progression or death, we consider an analysis of the proportion surviving without progression at three years. The power of a two-sample level two-sided test of binomial proportions was calculated with an arcsine and continuity correction in PASS 2000.

The study design considers PFS at three years post-transplant ranging from 30% to 60%. This range was chosen based on current literature, for example PFS of 60% at three years post-transplant has been reported for multiple myeloma patients randomized to tandem autologous transplant (Cavo et. al. 2007). These results were seen in an intent-to-treat analysis in which one-third of subjects were non-compliant with the regimen.

We will refer to the ranked treatment arms generically as 1, 2 and 3. At the two-sided 0.01667 level, a sample size of 250 subjects per arm suffices for power of 81% to compare a proportion of 0.60 in arm 1 with a proportion of 0.45 in arm 2, power of 84% to compare a proportion of 0.45 in arm 2 with a proportion of 0.30 in arm 3, and power of nearly 100% to compare arm 1 with arm 3.

The actual analysis will be conducted using a stratified log-rank test comparing time-to progression or death, rather than a binomial test of proportions. We provide power calculations based on Monte Carlo simulations of exponentially distributed time to event data in a subsequent section that details our planned interim analyses.

5.4. Planned Group Sequential Analyses for Efficacy and Futility

Planned interim analyses for futility and efficacy for the primary outcome will be conducted one year and two years after the last subject is randomized to the study,. The final comparisons will be analyzed after the last participant has been followed for 38 months. If accrual is completed in three years, the interim analyses will be performed at 48 and 60 months after study initiation. The actual timing of the interim analyses may be modified to coincide with the length of study accrual and dates of data freezes for DSMB meetings.

As an example, Table 5.4.1 shows the critical values, nominal, and cumulative Type I error for a single one of the planned pairwise tests conducted after three information increments, starting in this example when 80% of the information is accrued. To permit necessary flexibility in scheduling interim analyses, the critical values will be recomputed to correspond to the actual available statistical information for each pairwise comparison and interim time using the O'Brien-Fleming "use-function" approach of Lan and DeMets.

TABLE 5.4.1 EXAMPLE OF CRITICAL VALUES

Month of Interim Analysis*	Estimated Information Fraction	Critical Lower Value	Critical Upper Value	Nominal Upper Type I Error	Cumulative Type I Error
48	0.80	-2.73	2.73	0.00318	0.00636
60	0.95	-2.52	2.52	0.00585	0.01359
74	1.00	-2.50	2.50	0.00618	0.01667

*The actual timing of the interim analyses will depend on factors including length of accrual and timing of DSMB meetings.

The rationale for conducting the first sequential analysis for futility and efficacy one year after the completion of accrual is a desire to avoid premature termination of accrual to a study arm based on short term trends that may later reverse. The goal of the trial is to assess long-term PFS and overall survival. The use of a group sequential monitoring boundary will permit annual inspections of the data in the latter years of the trial while controlling the type I error of falsely reporting a treatment difference.

Analyses will be reported to the NHLBI-appointed Data and Safety Monitoring Board (DSMB), whose members meet at six months intervals

The group sequential analyses for efficacy will consist of three stratified log-rank tests comparing each pair of treatment groups. In order to preserve the overall type I error rate at $\alpha = 0.05$, each pair-wise comparison is allocated a type I error of $\alpha/3$. The p-value is further adjusted for group sequential monitoring using O'Brien Fleming boundaries to conserve type I error. The Lan DeMets spending function will be used to permit flexibility in performing analyses to coincide with the DSMB's meeting schedule.

In addition to an early decision in favor of the alternative hypothesis (efficacy), we may also assess futility. For each pairwise comparison, we calculate the conditional power of rejecting the null hypothesis at the final analysis. Conditional power will be calculated assuming that the normalized test statistic follows a Brownian motion process over time, conditioning on the observed value of the test statistic, and assuming that the drift parameter for future data follows the current trend. Futility is declared at an interim look if the maximum of the three conditional power values is less than 10%. In practice, the Data and Coordinating Center will report to the DSMB a sensitivity analysis that considers drift parameters for the future data extending over a range of values bounded by the 95% confidence interval for the current trend in the data. The DSMB may also consider information about the maturation of statistical information on secondary endpoints in reaching a decision to recommend futility.

5.5. Operating Characteristics of the Group Sequential Design

Our calculations of power for the interim efficacy and futility analyses described in the previous section depend on distributional assumptions. As noted above, we assume three-year PFS proportions of 0.60, 0.45 and 0.30 in treatment arms 1, 2 and 3. If time to progression or death

follows an exponential distribution, this corresponds to PFS hazard rates of .0142, .0222, and .0334, respectively, and median PFS of 48.8, 31.2 and 20.7 months, respectively. Further, we assume that 20% of subjects are high risk with a hazard rate 50% above others in their treatment arm, and that subjects will accrue uniformly over a three-year period.

A Monte Carlo simulation with 10,000 replications was used to study the operating characteristics of the group sequential design under the assumption of exponential distribution of PFS with interim analyses for efficacy and futility. As shown in Table 5.5.1 below, under the alternative hypotheses of 60%, 45%, 30% 3-year PFS, there is 88% power 38 months after the close of enrollment to compare treatment 1 with 2, 91% power to compare 2 with 3, and nearly 100% power to compare 1 with 3. Under a null hypothesis of 3-year PFS equal to 45% in all arms, type I error is 4.5% without futility monitoring (result not shown).

The Monte Carlo simulation demonstrates that the study is adequately powered for a primary analysis of PFS two years after the close of accrual, and that type I error is conserved for continuing inspections after that time-point.

Table 5.5.1 - Operating Characteristics of the Sequential Design under Exponential Distribution of Time to Progression or Death

Cumulative Percent of Trials Concluding Benefit or Futility Under the alternative hypothesis 60%, 45%, 30% 3-year PFS			
	12 Months	24 Months	38 Months
1 vs. 2	68.8	84.3	87.8
1 vs. 3	100.0	100.0	100.0
2 vs. 3	77.0	88.2	90.5
Futility	0.0	0.0	0.0
Cumulative Percent of Trials Concluding Benefit or Futility Under the null hypothesis 45%, 45%, 45% 3-year PFS			
	12 Months	24 Months	38 Months
1 vs. 2	0.7	1.3	1.5
1 vs. 3	0.6	1.0	1.2
2 vs. 3	0.7	1.1	1.2
Futility	82.0	90.9	96.6
Cumulative Percent of Trials Concluding Benefit or Futility Under the alternative hypothesis 50%, 40%, 30% 3-year PFS			
	12 Months	24 Months	38 Months
1 vs. 2	28.6	44.6	49.4
1 vs. 3	96.2	97.2	97.3
2 vs. 3	35.2	49.6	53.7
Futility	2.6	2.7	2.7

[1.] O'Brien Fleming use function boundaries for interim efficacy analyses, conditional power calculated under the current trend in the data. Maximum follow-up per subject of 38 months.

5.6. Overview of Statistical Guidelines for Safety and Compliance Monitoring

Statistical guidelines for monitoring treatment-related mortality (TRM) and compliance with treatment are intended to assist the independent DSMB in monitoring the safety of study participants and the risk benefit ratio of the trial. It is presumed that excess toxicity will be manifest as TRM or failure to complete protocol specified therapy. Monitoring will be performed monthly, separately by unblinded treatment arm. If rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised.

The monitoring guidelines serve as a trigger for consultation with the DSMB for additional review, and do NOT mandate automatic closure of study enrollment to that treatment arm. If enrollment to a treatment arm is discontinued, the boundaries and critical values for the interim analyses for efficacy and futility will be appropriately adjusted, e.g. to reflect a two-arm rather than a three-arm comparison.

5.7. Monitoring Guidelines for TRM

TRM includes all deaths from causes other than progression. Monitoring for TRM will be performed monthly beginning after the third month of enrollment until six months after the last subject initiates maintenance therapy. At least three events must be observed in order to trigger review. Monitoring guidelines #1-#6 will monitor the rate of TRM separately by treatment arm, and in each of two different risk periods. The first risk period starts with receipt of the initial auto-transplant and extends until maintenance therapy is initiated, or until the subject is no longer receiving protocol-mandated therapy if maintenance therapy is never initiated. A subject is in the second risk period while receiving maintenance therapy for up to six months. We assume that no more than 5% of subjects will experience TRM during each approximately six-month risk period, and wish to detect rates in excess of 10% with high power.

Table 5.7.1 - Monitoring Guidelines for TRM

				Six Month Event Rate	
	Study Arm	**Endpoint**	**Risk Period**	**Target**	**Excess**
# 1	Auto-Auto	TRM	0 to M*	5%	10%
# 2	Auto-RVD	TRM	0 to M	5%	10%
# 3	Auto-R	TRM	0 to M	5%	10%
# 4	Auto-Auto	TRM	M to M+180	5%	10%
# 5	Auto-RVD	TRM	M to M+180	5%	10%
# 6	Auto-R	TRM	M to M+180	5%	10%

M* = start of maintenance therapy

An extension of the Sequential Probability Ratio Test (SPRT) will be used to test event rates, with the null and alternative hypotheses for the test tabulated above. The SPRT permits continuous testing while preserving the study-wide type I error of the procedure. The SPRT contrasts an event rate of 5% versus an event rate of 10%, assuming a censored exponential distribution for the time to TRM. Refer to Appendix H for the motivation and derivation of the

SPRT for censored exponential time to event data. The intercept and slope of the lower boundary for the SPRT, shown in Table 5.7.2 below, were calculated using large sample theory, with the nominal type I and type II errors set at 0.05 and 0.10 in order to obtain the desired empirical type I and II errors of 0.10 and 0.10 with the truncated test with no lower boundary.

The censored exponential SPRT for each guideline can be represented graphically. At each monthly interim analysis, the sufficient statistics are plotted against each other, with the total number of observed events on the y-axis, and the total time on risk on the x-axis. The continuation region of the test is defined by two parallel lines. Only the upper boundary will be used to protect against an excessive six-month TRM rate. If the graph rises above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more TRM events than predicted by the observed time at risk. Otherwise, the SPRT continues until the last subject has exited the risk period for that cohort.

Table 5.7.2 shows the operating characteristics of the TRM monitoring guidelines to be used in this study. The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. While the boundary values were calculated using large sample theory for a test with no restrictions on the sample size, a simulation study was used to calculate the operating characteristics of the truncated test.

The expected sample size, as measured in enrolled subjects, and time to reach the stopping boundary, are based on the an assumption of uniform accrual over a three year period, and the timing of interventions after enrollment. The protocol specifies a 60-120 day recovery period after each auto-transplant, and that consolidation takes between 84-180 days, with maintenance starting immediately afterwards. Therefore, we assume that the first auto-transplant is coincident with randomization (time zero), and that the initiation of maintenance therapy occurs on average, at Day 180, Day 222, and Day 90, in the auto-auto, auto-RVD and auto-R arms, respectively.

Table 5.7.2 - Operating Characteristics of the Sequential Testing Procedures for Monitoring TRM

	SPRT Parameters		**Rejection Probability**		**Mean Counts under HA**		
	Intercept	**Slope**	**H0**	**HA**	**Month Stopped**	**Number Events**	**Subjects Enrolled**
# 1	4.02	0.150	.094	.902	20.2	11.7	135.6
# 2	4.02	0.150	.103	.944	18.3	12.2	124.2
# 3	4.02	0.150	.048	.648	28.9	8.9	183.4
# 4	4.02	0.150	.090	.891	25.4	11.6	135.0
# 5	4.02	0.150	.086	.884	26.7	11.5	134.7
# 6	4.02	0.150	.093	.902	22.8	11.7	135.1

The testing procedure for TRM in the auto-auto arm during the first risk period between the first auto-transplant and the initiation of maintenance rejects the null hypothesis in favor of the alternative 9% of the time when the true one-year rate is 5%, and 90% of the time when the rate is 10%. This corresponds to a type I error rate of $\alpha = 0.09$ and a type II error rate of $\beta = 0.10$.

On average, the DSMB will be consulted 20.2 months after the trial has opened, when 11.7 events have been observed in 135.6 subjects enrolled to the auto-auto arm.

5.8. Monitoring Guidelines for Compliance

Protocol adherence will be monitored in real-time in order to facilitate study management and operational oversight of this complex trial. Failure to comply with study therapy would first trigger an intervention to improve compliance, with closure of the treatment arm a last resort. A subject is non-compliant with therapy if they do not receive the initial autologous transplant or do not initiate maintenance therapy with Lenalidomide. Additionally, in the auto-auto arm, a subject who does not receive a second autologous transplant is non-compliant. Similarly, in the auto-VRD arm, a subject who is unable to complete two cycles within 3 months or 4 cycles within 6 months of VRD consolidation therapy is non-compliant. Note that a subject who does not receive the first auto-transplant is non-compliant for all subsequent interventions, and subjects who do not receive a second transplant or complete VRD are non-compliant for starting maintenance therapy.

Monitoring for non-compliance will be performed monthly beginning after the third month of enrollment until six months after the last subject initiates maintenance therapy. At least three events must be observed in order to trigger review. Monitoring guidelines #7-#11 will monitor the rate of non-compliance separately by treatment arm, and at specific evaluation time points: receipt of 2nd transplant for auto-auto subjects, completion of RVD for auto-RVD subjects, and initiation of maintenance therapy for subjects in each treatment arm. We assume that no more than 30% of subjects will fail to receive the 2nd transplant or finish RVD, and wish to detect rates of 40% with high power. We also assume that no more than 20% of subjects will fail to start maintenance, and with to detect rates in excess of 30% with high power.

Table 5.8.1- Monitoring Guidelines for Compliance

			Evaluation	**Failure Proportion**	
			Time Point	**Target**	**Excess**
# 7	Auto-Auto	Compliance	Get 2nd Transplant	30%	40%
# 8	Auto-RVD	Compliance	Finish RVD	30%	40%
# 9	Auto-Auto	Compliance	Start Maintenance	20%	30%
# 10	Auto-RVD	Compliance	Start Maintenance	20%	30%
# 11	Auto-R	Compliance	Start Maintenance	20%	30%

An extension of the Sequential Probability Ratio Test (SPRT) will be used to test event rates, with the null and alternative hypotheses for the test tabulated above. The SPRT permits continuous testing while preserving the study-wide type I error of the procedure. The SPRT contrasts an event rate of 30% versus an event rate of 40%, (or 20% versus 30%) assuming a binomial distribution for the proportion of non-compliant subjects. The intercept and slope of the upper boundary for the SPRT, shown in Table 5.8.2 below, were calculated using large sample theory, with the nominal type I and type II errors set at 0.05 and 0.10 in order to obtain the desired empirical type I and II errors of 0.10 and 0.10 with the truncated test.

The binomial SPRT for each guideline can be represented graphically. At each monthly interim analysis, the sufficient statistics are plotted against each other, with total number of subjects on the y-axis and the total number of observed events on the x-axis. The continuation region of the test is defined by two parallel lines. Only the upper boundary will be used to protect against an excess proportion of non-compliant subjects. If the graph rises above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more non-compliant subjects than predicted by the total number of subjects who have reached the evaluation time point. Otherwise, the SPRT continues until the last subject has reached the evaluation time point for that guideline.

Table 5.8.2 shows the operating characteristics of the compliance monitoring guidelines to be used in this study. The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. While the boundary values were calculated using large sample theory for a test with no restrictions on the sample size, a simulation study was used to calculate the operating characteristics of the truncated test.

The expected sample size, as measured in enrolled subjects, and time to reach the stopping boundary, are based on the an assumption of uniform accrual over a three year period, and the timing of interventions after enrollment. The protocol specifies a 60-120 day recovery period after each auto-transplant, and that consolidation takes between 84-180 days, with maintenance starting immediately afterwards. Therefore, we assume that the first auto-transplant is coincident with randomization (time zero), that receipt of the second transplant occurs on average at Day 90, and that completion of consolidation occurs on average at Day 222. Initiation of maintenance therapy is assumed to occur on average at Day 180, Day 222, and Day 90, in the auto-auto, auto-RVD and auto-R arms, respectively.

Table 5.8.2 - Operating Characteristics of the Sequential Testing Procedures for Monitoring Compliance

	SPRT Parameters		**Rejection Probability**		**Mean Counts under HA**		
	Intercept	**Slope**	**H0**	**HA**	**Month Stopped**	**Number Events**	**Subjects Enrolled**
# 7	6.54	0.349	.124	.937	18.8	43.5	108.7
# 8	6.54	0.349	.123	.935	22.9	43.4	108.5
# 9	5.36	0.248	.128	.963	19.2	27.6	92.0
# 10	5.36	0.248	.127	.962	20.5	27.5	91.8
# 11	5.36	0.248	.128	.963	16.3	27.5	91.9

The testing procedure for non-compliance in the auto-auto arm with receipt of the second transplant rejects the null hypothesis in favor of the alternative 12% of the time when the true one-year rate is 30%, and 94% of the time when the rate is 40%. This corresponds to a type I error rate of $\alpha = 0.12$ and a type II error rate of $\beta = 0.06$. On average, the DSMB will be consulted 18.8 months after the trial has opened, when 43.5 events have been observed in 108.7 subjects enrolled to the auto-auto arm.

5.9. Analysis of the Primary Endpoint

The primary analysis will include all randomized subjects, classified according to their randomized treatment allocation, irrespective of treatment actually received [intent-to-treat]. Analyses of PFS through 38 months of follow-up are planned at intervals as described in Section 5.4 Patients are considered a failure of the primary endpoint if they die or suffer from disease progression. The time to this event is the time from randomization to progression, death, initiation of non-protocol anti-myeloma therapy, loss to follow-up, or end of 38 months, whichever comes first. The treatment arms will be compared with a log rank test stratified on risk status, and using a two-sided level significance level of 0.0167 adjusted for sequential monitoring. Note that the large number of clinical sites and other logistical issues precludes stratification by center. At each interim analysis, if the DSMB has judged that the chance of observing a significant pairwise treatment comparison is inadequate, or if the DSMB has judged that non-compliance with protocol therapy is systemic and has failed to respond to remediation efforts, the trial as a whole may be declared futile. In reaching a futility recommendation, the DSMB may apply the guidelines in this protocol, or revise them as necessary given the context of data from this and other trials. The Kaplan Meier estimates of PFS will be provided with confidence intervals for each treatment group at 1, 2, and 38 months post-randomization. The confidence intervals at 38 months will be adjusted for the pair-wise comparisons and sequential monitoring.

5.10. Analysis of the Secondary Endpoints

Cumlative Incidence of Progression
The cumulative incidence of progression will be compared between the three treatment arms using Gray's test. The time to this event is the time from randomization to progression, death, loss to follow-up or the end of 38 months, whichever comes first. Death will be considered a competing risk. Patients alive or lost to follow-up at the time of last observation are considered censored. Estimates of progression will be described for each treatment group at 1 and 2 years as well as 38 months post-randomization. Incidence of progression beyond 38 months from randomization may be estimated through data reported to the CIBMTR (see Section 4.2.2) or a long-term follow-up protocol.

Response to Treatment
The rates of very good partial remission (VGPR) or better (nCR, CR, and sCR) according to the International Uniform Response Criteria (Section 3.2) will be calculated at one and two years after randomization. Subjects starting maintenance therapy without CR will be considered for the CR conversion endpoint. The proportion of subjects who achieve CR on maintenance will be assessed and compared. The rate of CR conversion will be compared at 1 and 2 years as well as 38 months post-randomization.

Overall Survival
The event is death from any cause. The time to this event is the time from randomization to death, loss to follow-up or the end of 38 months, whichever comes first. Patients alive or lost to follow up at the time of last observation prior to 38 months are considered censored. The Kaplan-Meier estimate of survival will be estimated separately for each treatment-group at 1

and2 years and 38 months posts-randomization. Overall survival will be compared using a log-rank test stratified on risk status, conducted at a two-sided significance level of .0167 analogous to the analysis of PFS described above.

Safety Monitoring Endpoints
The incidence of toxicities of grade 3 or higher toxicities (CTCAE version 3.0), the incidence of probable viral fungal and bacterial infections, and the incidence of treatment-related morality, i.e., from causes other than progression, will be recorded for each patient at set intervals over the course of the study. Safety data will be described in a variety of ways, both graphical and tabular, and incidence will be compared across time points and treatment arms. The DSMB will be presented with a comprehensive semi-annual report that will contain both solicited and unsolicited adverse event reports.

Incidence of Toxicities Grade ≥ 3 per CTCAE Version 3.0
All Grade ≥ 3 toxicities will be tabulated for treatment arms. The proportion of patients developing Grade ≥ 3 toxicity will be compared between treatment arms within specified time periods corresponding approximately to after the first transplant, after the second transplant or consolidation, and one, two, and three years from randomization or until disease progression. Individual organ system toxicities will be compared as secondary toxicity endpoints.

Incidence of Infections
The incidence of definite and probable viral, fungal[34] and bacterial infections will be tabulated for each patient. The proportion of patients in each treatment arm with these infections will be compared within specified time periods corresponding approximately to after each autologous transplantation, consolidation and one year, two years, and 38 months from randomization.

Treatment-related Mortality (TRM)
TRM is defined as death occurring in a patient from causes other than disease progression. Disease progression is a competing event for TRM. The time to this event is the time from randomization to death, disease progression, loss to follow-up or the end of 38 months, whichever comes first. Patients alive or lost to follow-up without disease progression at the time of last observation prior to 38 months are considered censored. The cumulative incidence of TRM at 1 and 2 years and at 38 months from randomization will be estimated separately for each treatment-group. Overall TRM through 38 months of follow-up will be compared using Gray's test.

Rate of Noncompliance to Study Treatment
The proportion of patients who, for any reason, do not proceed to second transplant, discontinue consolidation therapy, or do not initiate maintenance, will be monitored as part of a feasibility stopping rule for the study (refer to Section 5.5) reported at the semi-annual meetings of the D SMB. The proportion of subjects who discontinue maintenance therapy, while not part of the formal stopping rule, will also be monitored over the course of the study and presented to the DSMB. Additionally, the proportion of patients who do not proceed to their second or, if applicable, third phase of treatment or who discontinue consolidation or maintenance at any time point due to toxicity, noncompliance or other reasons will be tabulated. The rate of

noncompliance will be compared between treatment arms starting at one year from randomization and yearly thereafter until completion of maintenance or evidence of progression.

Health Quality of Life
Health quality of life will be compared between all treatment groups utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial. The HQL assessments will be performed prior to transplant, prior to consolidation, prior to initiation of maintenance, and at one, two, three and four years after randomization or until disease progression. Comparisons of quality of life will be done between treatment arms at 1, 2, and 3 years post-randomization.

5.11. Data Reporting

Based on the interim analyses for efficacy and futility and other considerations (for example, secondary endpoints, safety issues, etc.) described above, the DSMB will make recommendations to the NHLBI regarding release of data to investigators and the general public.

5.12. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. All reported serious adverse events potentially associated with study drug will be carefully examined with respect to the severity and relationship to study drug. The type and severity of adverse events will be described.

5.13. Sub-group Analysis

Primary and secondary endpoints will be further described by baseline disease risk status as a pre-specified sub-group analysis. Treatment group comparisons will be made with the standard risk and high risk groups to assess the treatment effect within each disease risk status. Analyses will follow as described in sections 5.9 and 5.10.

5.14. Analysis of 4-year endpoints

All patients on BMT CTN protocols will have long-term follow-up data reported through the CIBMTR mechanism and would facilitate the future analyses after the 38 month time point post-randomization. Additionally, long-term follow-up may be performed via a long-term follow-up protocol which will also facilitate future analyses after the 38 month time point post-randomization.

APPENDIX A

CRITERIA FOR SYMPTOMATIC MULTIPLE MYELOMA

APPENDIX A

CRITERIA FOR SYMPTOMATIC MULTIPLE MYELOMA

All three required:

1. Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma
2. Monoclonal protein present in the serum and/or urine[a]
3. Myeloma-related organ dysfunction (1 or more)[b]

   [C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal)

   [R] Renal insufficiency (serum creatinine > 2mg/dl)

   [A] Anemia (hemoglobin <10 g/dL)

   [B] Lytic bone lesions or osteoporosis[c]

*Note: These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[a] If no monoclonal protein is detected (nonsecretory disease), then ≥30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[b] A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

[c] 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.

*Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. The Hematology Journal (2003) 4, 379–398

APPENDIX B

CONSENT FORMS

SCREENING CONSENT
AND
PATIENT INFORMED CONSENT

SCREENING CONSENT

BMT CTN 0702
A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma

Study Sponsor: This study is sponsored the National Institutes of Health (NIH): the National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI) by providing financial support for this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Principal Investigator: (site specific PI)

24-Hour Phone: <Insert 24-hour contact information>

This is a clinical trial, which is a research study to answer specific medical questions. Your doctor (the person in charge of the research) will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with family and friends. You can also discuss this with your health care team. If you have any question, you can ask the study doctor for more information.

INTRODUCTION

This is a screening informed consent for a clinical trial in multiple myeloma. This trial includes the option to patients to provide samples for important research on multiple myeloma and transplant. At this stage we are asking you consent to provide a bone marrow sample for research. This is not the informed consent for the clinical trial.

Some transplant centers perform routine bone marrow biopsy and aspirate prior to decide to offer patients clinical trials. In order to avoid repeating the bone marrow examination after patients are registered to participate in the clinical trial, we are asking consent for collection of an additional volume of bone marrow for research related to this clinical trial. In case you are not eligible for the clinical trial or decide against participating, this sample of your bone marrow will be discarded.

If you sign this screening consent, your bone marrow sample will be utilized by the BMT CTN for future research.

CLINICAL TRIAL SUMMARY

This screening process is for the research protocol entitled: "A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma" or STaMINA (Stem Cell Transplant in Myeloma Incorporating Novel Agents) trial. You are being asked to take part in this research study because you have multiple myeloma (MM), a cancer of the bone marrow. The study is designed to test different treatments for patients with multiple myeloma.

A separate consent form will be provided to you describing the full research study in detail. You will have the opportunity to have all of your questions answered prior to deciding to participate.

By agreeing to take part in the screening tests, the investigators cannot promise that you will be able to take part in the research study. Also, by agreeing to take part in the screening, you will allow your physician to collect an additional volume of bone marrow aspirate for research. No additional bone marrow aspirates prior to your transplant will be required. The sample for research will be collected in addition to the amount collected by your doctor for routine tests to assess if there are cancer cells in your bone marrow. You can still decide not to participate in the research study, in which case this additional volume of bone marrow will be discarded.

If after completion of the screening, you are found to be eligible for participation in the research protocol, you will be asked to consider participation in the full treatment research protocol. Prior to you agreeing to participate and signing the consent form for the treatment research protocol, you will have the opportunity to discuss the study with your transplant physician. Signing either this screening consent form or the treatment research consent form does not in any way obligate you to participate in this research protocol. Participation in this screening process does not guarantee inclusion in the treatment research protocol.

YOUR PARTICIPATION IS VOLUNTARY

Once you understand the screening process and agree to take part, you will be asked to sign this consent form. You will be given a copy of this consent form to take with you for your records. It is important that you understand that ***your participation is completely voluntary,*** and that ***you may decide to drop out of the study at any time*** without losing the benefits of your regular medical care.

RISKS AND/OR DISCOMFORTS

Below is a summary of known risks with the invasive screening procedures. The risks and discomforts of the procedures will be explained by the doctor who does the procedures and another consent form must be signed for any invasive tests. Listed below are specific invasive procedures that are done at screening and may be repeated later if necessary.

Bone Marrow Aspiration and Biopsy: A bone marrow aspiration is a procedure in which an area of the hip (buttock area) is numbed with local anesthetic, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle. When the local anesthesia is given, you may initially feel a

burning sensation in your skin and bone surface for several seconds. During the actual procedure itself, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely an infection can develop.

POTENTIAL BENEFITS
Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may lead to the improvement or "temporary" disappearance of your myeloma and prolongation of your life. However, no benefit is guaranteed.

COSTS TO THE SUBJECT (YOU)
There are no additional costs to you to provide bone marrow sample for future research.

RESEARCH-RELATED INJURY
If you should be injured as a result of your participation in this study, emergency medical care is available to you at the usual charge. The hospitals and/or treating physicians reserve the right to bill you and/or your insurance provider(s) for services you receive for the injury. There is no provision for free medical care or monetary compensation from the study sponsor, The National Institutes of Health.

PAYMENTS (REIMBURSEMENT)
You will not be paid for taking part in this study. You will be reimbursed for travel expenses related to study-related evaluations and/or treatments only as explained above under the COSTS TO THE SUBJECT (YOU) section.

CONFIDENTIALITY
We will try to keep your personal information as private as we can. There is no guarantee of absolute privacy. Your personal information may be disclosed if required by law. We will keep track of your medical information after you return home. Organizations that are listed below may inspect or copy your research records for quality assurance and data analysis. Your research records will identify you by name and will include things such as your medical history, results of your blood tests and exams, reports from your surgery and treatment, and reports of your office visits.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

SCREENING DESCRIPTION/PROCEDURES
Researchers are trying to learn more about multiple myeloma and other health problems. Much of this research is done using human tissue or blood. These samples are collected during the clinical trial and stored for future use.

You are being asked to let us store some of your bone marrow for possible use in future research and/or for the PRIMeR ancillary study (Prognostic Immunophenotyping in Myeloma Response). The samples collected for future research and the samples collected for the PRIMeR ancillary study can be done at the same time.

Future Research Samples

Your bone marrow samples for future research will be collected at your transplant center during the period you are participating in this study and kept at a central place, called the BMT CTN Research Sample Repository (this will be called the "Repository" in the rest of the consent form). A Repository is a place that protects, stores and sends out samples for approved research studies.

Future research bone marrow samples will be collected prior to first autologous transplant and yearly thereafter (4 more times). The bone marrow samples will be collected as part of the scheduled evaluations in the STaMINA clinical trial and routine assessment of your disease.

PRIMeR Ancillary Study Samples

The PRIMeR ancillary study will be conducted along with the STaMINA clinical trial. All patients who participated in the STaMINA clinical trial are eligible to participate in the PRIMeR ancillary study. This study will use a technique called flow cytometry to look for small quantities of myeloma cancer cells in your bone marrow. This method has been shown in previous studies to help doctors predict which patients will have a longer period without their myeloma coming back. We are investigating whether treatment in the STaMINA clinical trial increases the chance of having no myeloma cancer cells detected by this method.

The results of the PRIMeR ancillary study will help investigators understand the results of the STaMINA clinical trial; and in the future will help in selecting the best treatment for patients with myeloma.

Your participation in the PRIMeR Ancillary Study will involve collection of three bone marrow samples in the course of one year (Figure 1). These samples will be kept at the BMT CTN Research Sample Repository. The first and third bone marrow samples will be collected as part of the scheduled evaluations in the STaMINA clinical trial and routine assessment of your disease. One additional bone marrow aspiration procedure will be done as part of the PRIMeR ancillary study. This additional procedure will be done prior to initiation of maintenance therapy in the STaMINA trial (see bold arrows in Figure 1 for when all PRIMeR bone marrow collections will happen).

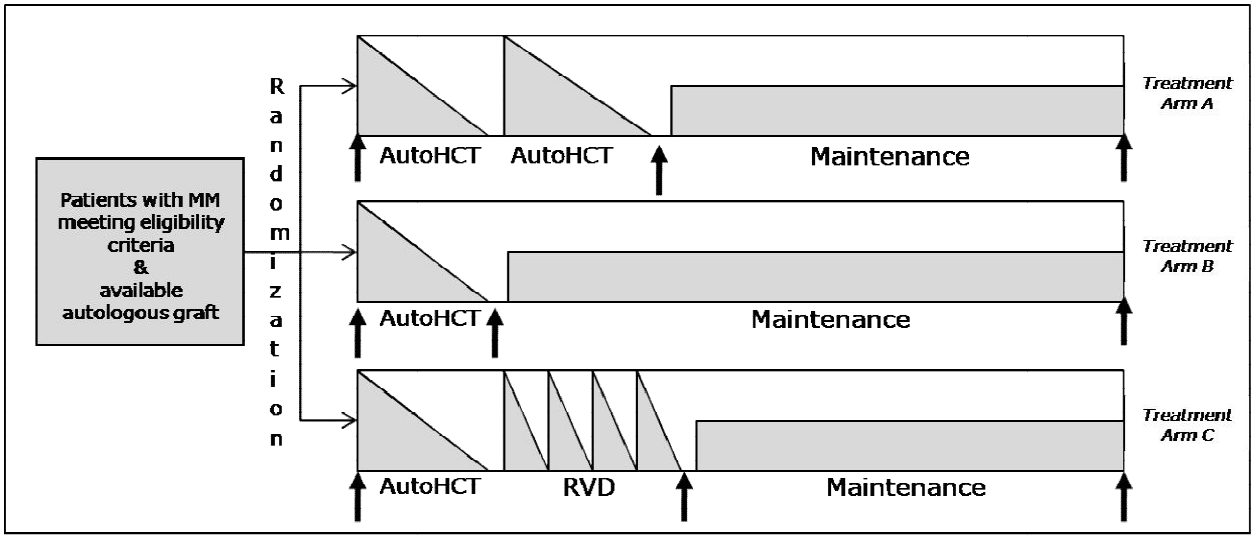


Figure 1 -- Outline of the STaMINA clinical trial. The arrows represent times that a bone marrow is collected as part of the PRIMeR study.

Some general things you should know about letting us store your bone marrow samples for research are:

- We will only store samples from people who give us permission. You should feel free to talk over your decision with your family, friends, doctor, and health care team. If you decide to not let us store research samples now or in the future, it will not affect your medical care.
- Research is meant to gain knowledge that may help people in the future. You will not get any direct benefit from taking part. Taking part may also involve some risks.
- All testing done on your blood and tissue samples are for research purposes. You or your doctor will not be given results and they will not be added to your medical record.
- You will not get paid for any samples or for any products that may be developed from current or future research.

If you agree to provide bone marrow samples, here is what will happen:

a.) Bone Marrow Aspirate Samples: if you have multiple myeloma, it is likely that you have already had a bone marrow biopsy and aspirate as part of your evaluations. Bone marrow tests are done as part of your routine medical care in case the multiple myeloma is not detected in blood or urine, in order to make sure your disease is in remission. Also, all patients in this study will have a bone marrow examination done prior to the first transplant. We are asking that an additional sample of the liquid bone marrow (2 teaspoons) be collected for research purposes. A small volume of liquid marrow (1/2 teaspoon) will be set aside for the PRIMeR ancillary study for three bone marrow aspirates collected in the first year of the study (PRIMeR Study Figure 1 above). After the first bone marrow examination, a maximum of 5 bone marrow examinations will be performed for research purposes, three in the first year and once a year thereafter (3 more times). Most, but not all, of these samples will be collected at the time that a bone marrow examination would be done anyway as part of your routine clinical care.

b.) All research samples will be given a unique bar code designation that cannot be linked to you by the researcher testing your samples.

c.) Researchers can apply to study the materials stored in the Repository.

d.) Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the remaining research samples and clinical data will be made available outside of this network. Researchers from other universities, the government, and drug or health-related companies can apply to use the samples and information. Only skilled researchers will be allowed to use the samples and information.

e.) The BMT CTN Steering Committee or the BMT CTN Biomarkers Committee must approve each study application before they will share samples or information with researchers. This kind of review is to make sure that the investigators requesting the samples are qualified, and that the research they propose has a high potential of success and for contribution of scientific knowledge.

f.) DNA from your stored bone marrow samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH).

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease.

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans must not request your genetic information that we get from this research. This means that they may not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

What if I am not eligible for the full research protocol?

If the Principal Investigator determines that you are not eligible for the research protocol your samples will not be used and will be discarded.

What if I change my mind?

You can change your mind about allowing us to use your samples and health information for research at any time. We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. If you withdraw yourself from this protocol, even if you allowed your samples to be used for research, your samples will not be used from that point and they will be discarded. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

HIPAA[27] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of collecting bone marrow samples and information regarding the research study entitled *A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work-up and after transplantation (e.g., bone marrow tests, blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from (*list hospitals, clinics or providers from which health care information can be requested*).

_____

_____

_____

27 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item "c." above and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. George Somlo, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. Edward Stadtmauer, Study Chairperson and staff/laboratories at University of Pennsylvania Cancer Center.
- National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data and coordinating center
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- The NCI-sponsored Cancer Cooperative Groups that enroll patients on this trial through the CTSU
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Celgene (the manufacturer of lenalidomide)
- Biologics, Inc. (the distributor of lenalidomide)
- Millennium Pharmaceutics (the manufacturer of Bortezomib)

e. Right to Refuse to sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

PROBLEMS OR QUESTIONS

If you have questions about this study or experience a research-related injury, you should contact Dr. _____ at *insert phone number*. If you have any questions about your rights as a research participant, please contact _____ at *insert phone number*, or if you prefer, you can direct your questions to _____ at the following address: *insert address here*.

SIGNATURE PAGE

Statement of consent

The purpose of storing bone marrow samples for future research and/or for the PRIMeR study, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my bone marrow samples for future research nor for the PRIMeR ancillary study. If I decide to not let you store future research and/or PRIMeR bone marrow samples, it will not affect my medical care in any way.

I voluntarily agree that my bone marrow samples and information can be stored indefinitely by the BMT CTN Repository for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my pre-transplant bone marrow samples to be stored and used for future research.
- ❑ I do not agree to allow my pre-transplant bone marrow samples to be stored nor used for future research.
- ❑ I agree to allow my pre-transplant bone marrow samples to be stored and used for the PRIMeR study.
- ❑ I do not agree to allow my pre-transplant bone marrow samples to be stored nor used for the PRIMeR study.

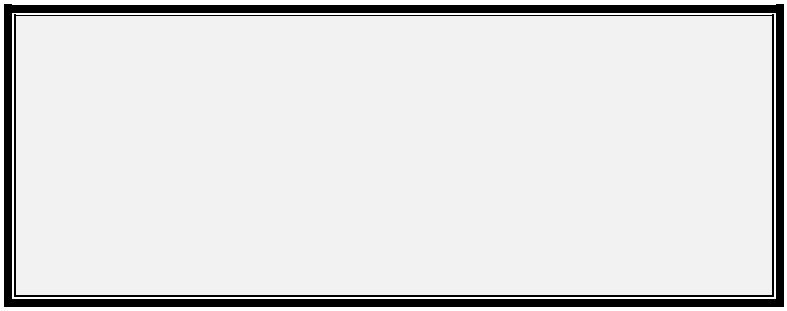
_____	_____	_____
Research Subject's Name *(Typed or printed)* **OR**	**Research Subject's Signature**	**Date**
_____	_____	_____
Research Subject's Legal Guardian/Representative *(Typed or printed)*	**Legal Guardian's Signature**	**Date**
_____	_____	_____
Witness's Name and Title *(A witness to the research subject's signature is required.)*	**Witness's Signature**	**Date**

Signature of person explaining and obtaining the consent:

_____	_____	_____
Name and title *(Typed or printed)*	**Signature**	**Date**

(Note: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)

Informed Consent to Participate in Research



You are being asked to take part in a large clinical trials research study. About 750 patients will take part in this study at many centers around the country. Your participation in this study is expected to last an average of 4 years.

This consent form tells you about the study. The Principal Investigator (the person in charge of this research) or a co-worker of the Principal Investigator will also describe this study to you and answer all of your questions. Furthermore, throughout your treatment your care will be discussed with you and questions answered as needed. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Taking part in this study is entirely your choice.

1. Name of the Subject ("Study Subject")

2. Title of Research Study

A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma

3a. Principal Investigator Contact Information

Insert name, affiliation and contact information.

3b. Contact information for emergencies after hours or on weekends or holidays

Call (###) ###-####, the in-patient Bone Marrow Transplant Unit. Ask to speak to the Charge Nurse.

4. Sponsor and Source of Funding or Other Material Support

The sponsor of this study, The National Institutes of Health (NIH), is providing financial support for the coordination of this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

5. What is the purpose of this study?

You are being asked to take part in this research study because you have multiple myeloma (MM), a cancer of the bone marrow. The study described in this consent form is designed to test different treatment strategies for patients with multiple myeloma. Multiple myeloma is considered incurable. The standard therapy sometimes produces remission (absence of disease) in some individuals, but the disease recurs in all patients.

Past studies have shown that high-dose chemotherapy (drugs that kill cancer) can improve the survival of myeloma patients. However, this intensive therapy damages the special cells in the bone marrow called blood stem cells. Blood stem cells are cells found in the bone marrow and blood stream that produce all of the body's blood cells. Without healthy blood stem cells, a person cannot produce white blood cells (which fight infection), red blood cells (which transport oxygen to organs) or platelets (which help blood clot). Blood stem cells can be collected from the patient before high-dose chemotherapy. Then, after the patient receives high-dose chemotherapy these blood stem cells are returned intravenously (through a vein) to the patient. This procedure is called autologous **stem cell transplantation** (SCT). Autologous transplantation is accepted standard therapy for patients with multiple myeloma. Although high-dose chemotherapy with autologous SCT has significantly improved the survival of myeloma patients, it does not cure them and the potential to further improve treatment remains. One approach has been to kill myeloma cells left after the first autologous SCT with another course of high-dose therapy and a second autologous SCT. Studies have shown that receiving two autologous transplants a few months apart (tandem autologous SCT) improves survival for patients with multiple myeloma. Unfortunately, this approach still does not cure myeloma. It is not known if additional drugs given after the second autologous SCTs will further improve survival of patients with multiple myeloma. This study will test whether adding lower doses of drugs that are active against myeloma will prolong the survival by preventing the cancer cells to grow again. There are new drugs that have demonstrated significant activity against myeloma, they include lenalidomide and bortezomib. The study will assess whether adding these medications after the autologous SCT will improve the period the cancer stays inactive. There are two ways in which these drugs can be used after SCT. One approach is consolidation treatment and that has the same aim as a second autologous transplant that is to kill any leftover myeloma cells that remained after the first autologous transplantation. This study will evaluate whether this approach is superior to two (tandem) autologous SCT. The other approach is to assess whether maintenance therapy with low doses of continuous lenalidomide after an autologous SCT is better than the other two treatments described above (see picture). Maintenance treatment is designed to help the treatment succeed and is given to patients with cancer in remission to prevent progression. In summary, there are three main groups to be compared in this study: tandem autologous SCT + maintenance, one autologous SCT +

consolidation + maintenance and one autologous SCT + maintenance. The different treatments will be tested by randomizing patients to one of the three treatments before their first autologous SCT. Randomizing means assigning to a treatment by chance, like the flip of a coin.

In more detail, the consolidation treatment will include the combination of three drugs: lenalidomide, bortezomib and dexamethasone (or RVD) given for four cycles, each cycle being 21 days long. The maintenance uses lenalidomide alone continuously for a period of three years or until there is evidence that the cancer is becoming more active. This study will compare the time it takes for the disease to become active (progression-free survival) between the two single transplant arms and each single transplant arm to the tandem transplant arm. Additionally, this study will compare how the disease responds to each treatment given to you, specifically how the cancer responded after one year from entering the trial and yearly thereafter. For individuals who have not achieved maximum response (complete response) by the time they start maintenance, the rate of achieving maximum response during maintenance will be assessed and compared between treatment arms. Additional comparisons and assessment in this study include, overall survival, if a particular treatment prolongs more the survival than other treatments, assessment of the side effects of treatment, quality of life and incidence of infections in all three study treatments.

The study may find that patients who have different treatments for MM have similar results.

6. What will be done if you take part in this research study?

If you decide to take part in this study and have signed the informed consent, you will be evaluated to reduce the risk of having adverse events while participating in this study. Before starting treatment in this study, your doctor will check your general health.

You will have the following tests and evaluations to find out if you can participate:

- Medical history and physical examination, including height and weight.
- Blood tests (approximately 4 – 5 tablespoons).
- Urine tests.
- Electrocardiogram (ECG or EKG), a picture of the electrical action of the heart.
- Echocardiogram (a picture of the heart in motion made using ultrasound or sound waves) or MUGA scan (a picture of your heart after a small amount of radioactive material is injected into the bloodstream through a vein) to evaluate your heart function.
- Pulmonary Function Test (PFT), which is a breathing test that tells how your lungs are working, measures the amount of air taken into your lungs and exhaled as you breathe.
- Bone marrow biopsies and aspirates. A bone marrow aspiration is a procedure in which an area of the hipbone is numbed, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle.

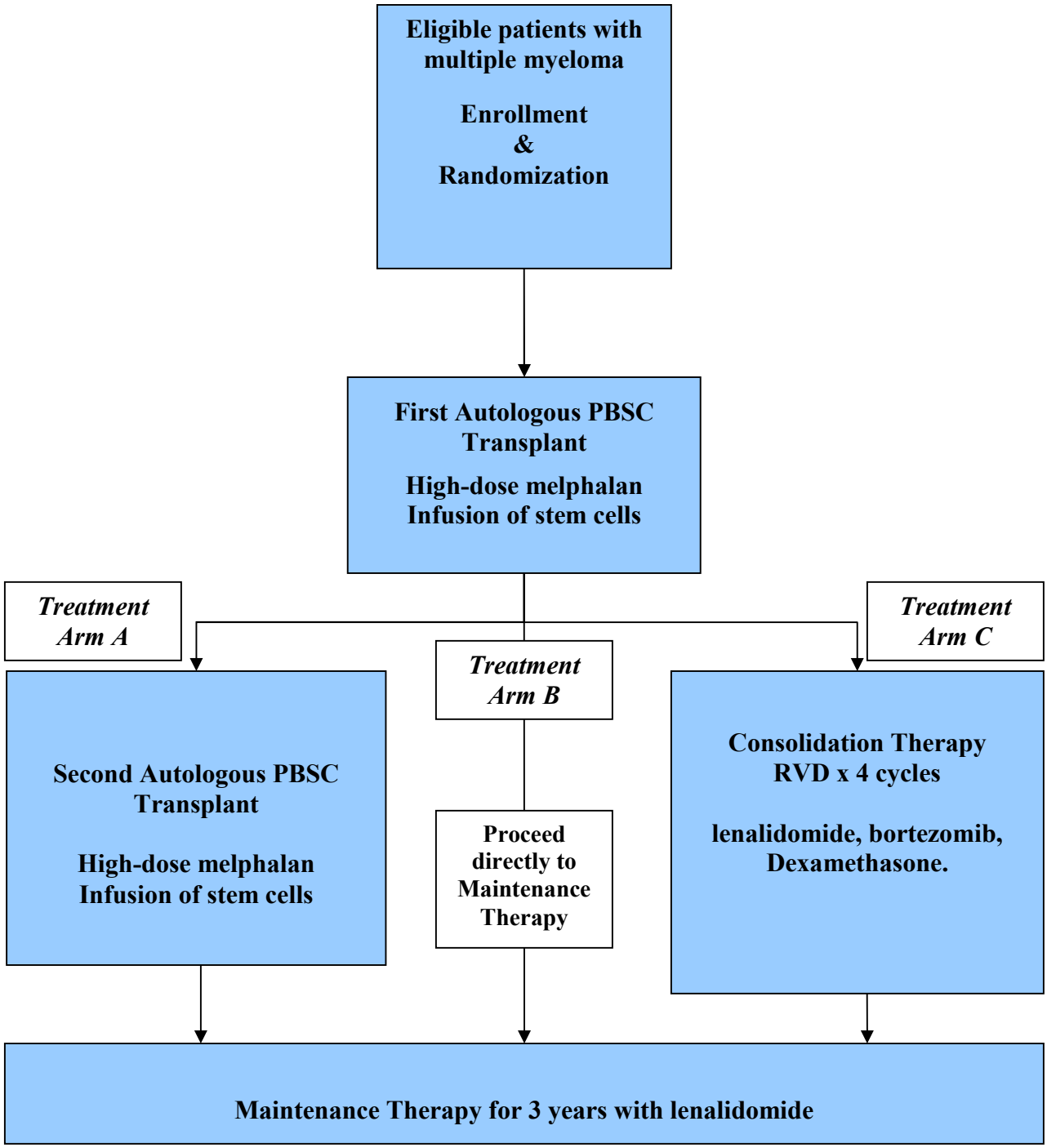
- If you are a woman able to have children, a serum pregnancy test will also be performed. If you are pregnant, you will not be able to take part in this study. Pregnancy tests will be repeated prior to and while you are taking lenalidomide. You must also commit to either continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide.
- If you are a man who has sexual relations with women who can become pregnant, you will be required to use a latex condom during sexual relations while taking lenalidomide.

Some additional x-rays will be done to evaluate your disease. These tests will help your doctor determine the amount of disease you have at the start of treatment and to follow the status of your disease throughout your treatment.

This study is divided into three phases and is explained in detail below. All patients will undergo the Phase I treatment portion of this study, using high-dose chemotherapy (melphalan) followed by an autologous SCT. Phase I is considered standard of care for patients with multiple myeloma, the research aspect of the study is the randomization in Phase II. Under the Phase II treatment portion of this study, you will be randomized (like the tossing of a coin) to one of three treatment arms. Patients randomized to receive a second autologous SCT (referred to as Treatment Arm A) will receive the same high-dose chemotherapy (melphalan) as described above followed by maintenance therapy with lenalidomide. Patients randomized to maintenance (Treatment Arm B) will receive maintenance therapy with lenalidomide after the first autologous transplantation. Patients randomized to consolidation and maintenance (Treatment Arm C) will receive consolidation therapy (bortezomib, lenalidomide and dexamethasone) followed by maintenance therapy with lenalidomide. Regardless of the treatment arm you are assigned, you will receive three years of maintenance lenalidomide. Your doctor will tell you your Treatment Arm placement.

One of the objectives of this study is to evaluate how the treatment affects the quality of the patient's life and whether there is a difference between the three treatment arms. Therefore, all English and Spanish speaking patients will be asked to complete questionnaires asking about their quality of life before the first and second transplants, prior to consolidation maintenance therapy and at one year from enrollment to the trial and yearly thereafter until four years from your enrollment in the study or until your disease returns or becomes active whichever comes first. It will take you approximately half an hour to complete the questionnaires.

Outline of Treatment Plan



Patient Initials _____

First Phase of the Study (All Study Participants)

Central Venous Catheter: You will need to have a central venous catheter (CVC) placed to participate in the study. A central venous catheter is a flexible sterile tube that will be placed into a large vein that runs under your collarbone so that blood can be withdrawn and medications given to you more easily and with less discomfort. This tube is usually placed under local anesthesia. There is a lot of experience with the use of these catheters. Complications include blood clots and infection. Clotting may require removal of the catheter or treatment of the clot by instilling a medicine that dissolves blood clots into the line. If you develop an infection you will require treatment with antibiotics and your catheter may need to be replaced. Other uncommon side effects may include swelling of the face and arm and/or lung collapse. If the lung collapses, it may be necessary to place a tube between the ribs to allow the lung to re-expand.

Mobilization and Leukapheresis (collection of stem cells from your peripheral blood), also called apheresis: There are several ways to collect stem cells for the SCT and the one selected depends on your doctor's preferences or the practice most commonly performed at your transplant center. This is not dictated as part of this protocol and it is routinely performed for all SCT. Briefly, the methods may involve administration of chemotherapy plus bone marrow stimulating medication, bone marrow stimulating cells alone or with other medications that help the release of stem cells from the bone marrow into the blood circulation (mobilization). This allows for collection of stem cells for the transplant through a central venous catheter (mentioned above) or a vein from your arm. If you receive chemotherapy as part of the mobilization, your doctor will explain the side effects, benefits and types of chemotherapy you may receive to mobilize your blood stem cells. Following chemotherapy for stem cell mobilization, you will receive a bone marrow stimulating medication called granulocyte-colony stimulating factor (G-CSF) by injection under your skin daily for approximately 10 days. G-CSF will help to move your stem cells out of the bone marrow into the bloodstream. You or someone who agrees to be responsible may be taught how to give you the G-CSF, so you can receive it at home. Once the number of stem cells in your blood stream is high enough, they will be collected over 2-5 days, while you are still receiving the G-CSF injections. A procedure called Leukapheresis will be done to collect your stem cells. During this procedure, your blood will be collected either through your central venous catheter or from a vein in one arm, processed through a machine to remove the white blood cells (stem cells), and then the rest of the blood will be returned to you through your catheter or a vein in the other arm. The leukapheresis procedure will last approximately several hours each time. **You will be asked to sign a separate consent form for the leukapheresis procedure.** Enough stem cells will be collected from you for two autologous SCTs. Your stem cells will be frozen (cryopreserved) until the time when they will be given back to you. Other methods to mobilize stem cells include only G-CSF, which follows the same description as above but without the chemotherapy. New medications have been approved for routine mobilization of stem cells, which if used will be explained to you by your doctor.

Measurements of Waist and Hip: During this study, your doctor or nurse will make measurements of your waist and hip. These measurements will be done at most three times during the study. This information will be collected and will be used along with your height and weight to study if they are related to the development of complications after the transplant.

Autologous Stem Cell Transplant: Approximately a couple of weeks after your stem cells have been collected, you will undergo an autologous SCT using high-dose chemotherapy with a drug called melphalan given through your central venous line. Since this high-dose treatment destroys the normal bone marrow in addition to the myeloma cells, your blood stem cells (blood cells able to mature and grow into useful part of your bone marrow such as red cells, white cells and platelets) must be given back to you. Your previously collected stem cells will be unfrozen and given back to you through your central venous catheter, similar to a blood transfusion, one or two days after you received the melphalan. Starting on the fifth day after you received your stem cells, you will be given the drug G-CSF, subcutaneously (under the skin) or intravenously (through a vein). G-CSF is called a growth factor and helps to stimulate the bone marrow to produce cells and will continue until your white blood count returns to normal.

Table 1 -- High-Dose Melphalan / Autologous SCT

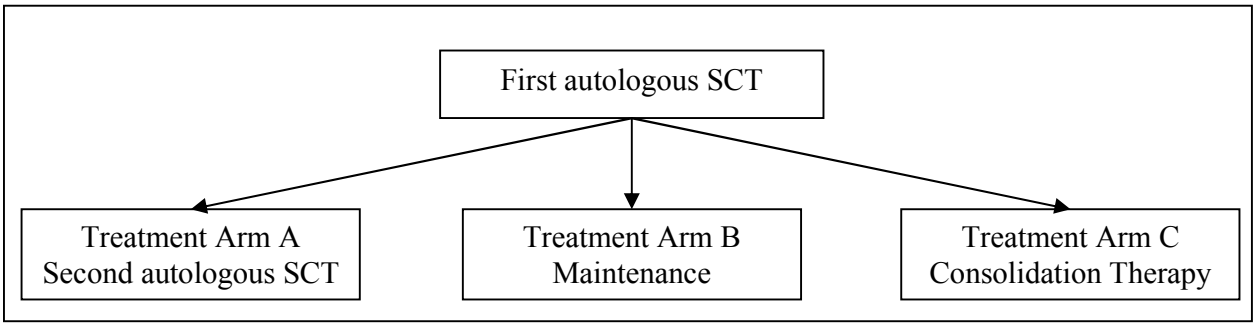
	-2 OR -1	**0**	**+5 or per Institutional Guidelines to Engraftment**
Melphalan	X		
PBSC Infusion		X	
G-CSF (5 μg/kg/day) SQ until ANC recovery (defined as an ANC ≥ 500/mm^3 x 2 days)			X

After your stem cells have been infused, it will take about two weeks before adequate numbers of blood cells are made. During this time you may not be making any of your own useful blood cells and therefore may require several red blood cell and platelet transfusions. Because your immune system is very weak, you may develop serious infections. You will be watched closely and receive antibiotics at the earliest sign of infection. During the time that your blood counts will be low, you may have mouth sores and feel very tired. You will receive medications to lessen these symptoms as much as possible. You will probably have a poor appetite during this time and may need to be given feedings through the central venous catheter. You may also receive pain medications as needed to minimize and control discomfort and pain. Once you begin to make new blood cells, the risk of serious infections will gradually be reduced. You should gradually come to the point where you will no longer require red cell and platelet transfusions. You should gradually regain your appetite. Although it is possible that the entire process may be done in the outpatient setting, it is also possible that a hospital stay of approximately 3 to 4 weeks will be necessary.

After completion of the transplant process, you will be followed in the outpatient clinic facility at least weekly, or as clinically indicated, until you are ready for your second intervention.

Second Phase Treatment Arms

Approximately 60 to 120 days after your initial autologous SCT, you will receive one of three therapies: a second autologous SCT, consolidation therapy, or maintenance.



Treatment Arm A (Second Autologous SCT)

If you are placed on Treatment Arm A, you will receive a second autologous transplant between 2 to 4 months from the initial transplant (this is usually the length of time it takes you to recover from your initial transplant). You will then receive maintenance therapy with lenalidomide (an anti-myeloma medication) at a dose of 10 mg daily for three months then the dose will be increased to 15 mg every day for a total of three years. Maintenance will starts 2 to 4 months after the second autologous transplant. You will also receive aspirin per your institution's guidelines during the lenalidomide maintenance.

You will be seen frequently in the clinic for evaluation. During the recovery from the first and second transplant you may be seen in clinic at least weekly. During maintenance you will be required to come to clinic once a month for the first three months and then every three thereafter. Evaluations may include physical exam, interview with a physician, blood and urine test, x-rays and if necessary a bone marrow biopsy in case there is no evidence of cancer elsewhere. You will require a blood test prior to the monthly supply of lenalidomide. These tests may be done remotely and sent to the transplant center.

Additional assessments: If you are a woman able to become pregnant you will undergo pregnancy counseling and test as long as you are taking lenalidomide. The test will be performed 10-14 days prior to starting lenalidomide, again within 24 hours of starting lenalidomide, weekly for the first four weeks of taking lenalidomide, and then every four weeks thereafter. If your periods are irregular, you will have additional serum pregnancy test performed at two weeks. An additional pregnancy test will be done 28 days after stop taking lenalidomide.

Treatment Arm B (Maintenance)

If you are placed on Treatment Arm B, you will start maintenance therapy with the drug, lenalidomide (an anti-myeloma medication) 2 to 4 months after the first and only transplant (this is usually the length of time it takes you to recover from your initial transplant). You will receive maintenance for a total of three years. The dose will start at a dose of 10 mg of lenalidomide every day for the first three months and it will be increased to 15 mg every day for a total of three years. You will also receive aspirin per your institution's guidelines during the lenalidomide maintenance.

You will be seen in the clinic at least weekly after the transplant. During maintenance you will be required to come to clinic once a month for the first three months and then every three thereafter. Evaluations may include physical exam, interview with a physician, blood and urine test, x-rays and if necessary a bone marrow biopsy in case there is no evidence of cancer elsewhere. You will require a blood test prior to the monthly supply of lenalidomide. These tests may be done remotely and sent to the transplant center.

Additional assessments: If you are a woman able to become pregnant you will undergo pregnancy counseling and test as long as you are taking lenalidomide. The test will be performed 10-14 days prior to starting lenalidomide, again within 24 hours of starting lenalidomide, weekly for the first four weeks of taking lenalidomide, and then every four weeks thereafter. If your periods are irregular, you will have additional serum pregnancy test performed at two weeks. An additional pregnancy test will be done 28 days after stop taking lenalidomide.

Treatment Arm C (Consolidation Therapy)

If you are placed on Treatment Arm C, you will receive consolidation therapy between 2 to 6 months after the initial transplant (this is usually the length of time it takes you to recover from your initial transplant). Consolidation therapy will consist of dexamethasone, lenalidomide, and bortezomib and this combination is also referred as RVD. You will be given consolidation therapy for a total of 4 cycles (where each cycle is 21 days long) with the combination bortezomib (1.3 mg/m^2 on Days 1, 4, 8 and 11 of each cycle), dexamethasone (40 mg total dose per day given on Days 1, 8, and 15 of each cycle) and lenalidomide (15 mg orally on Days 1-14 of each cycle). Bortezomib is administered either subcutaneously (under the skin) or intravenously (through the vein) as a rapid injection. The drugs used in consolidation treatment have the ability to cause blood clots, called deep vein thrombosis (DVT) if in the legs and pulmonary embolus (PE) if in the lungs. To try and prevent this from occurring you will be offered aspirin per your institution's guidelines during consolidation therapy unless you are treated with alternate prophylaxis of either heparin products or warfarin (Coumadin®).

Table 2 -- RVD Treatment Schedule

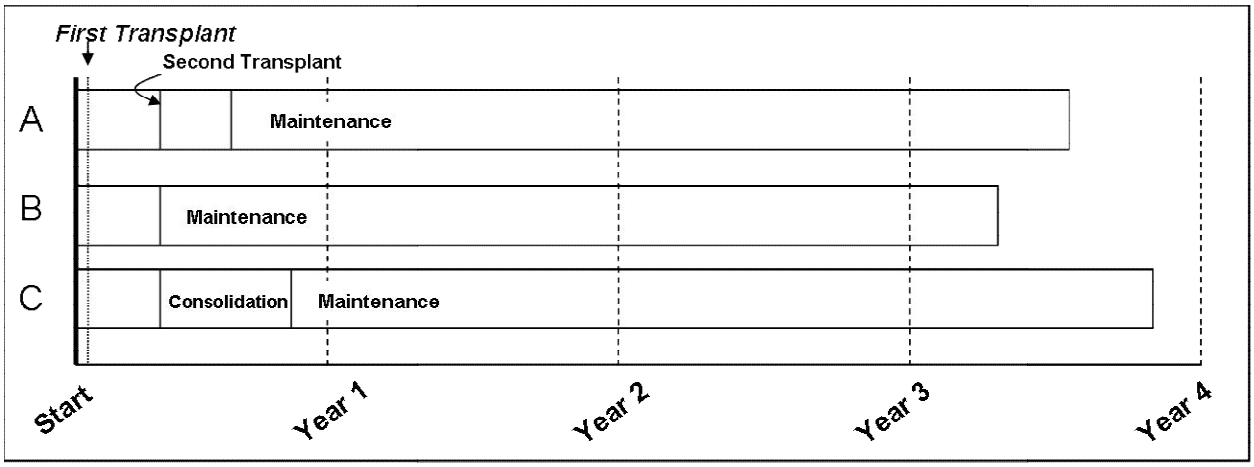
Dexamethasone	**40 mg Days 1, 8, 15**
Lenalidomide	**15 mg/day Days 1 to 14**
Bortezomib	**1.3 mg/m2 Days 1, 4, 8, 11**

You will receive maintenance therapy with the drug, lenalidomide (an anti-myeloma medication) 2 and a half to 6 months after the start date of consolidation therapy. The drug will be administered as 10 mg per day continuously for 3 months then increased to 15 mg daily. You will continue on lenalidomide maintenance for three years. You will also receive aspirin per your institution's guidelines during the lenalidomide maintenance.

You will be seen in the clinic at least weekly after the transplant. During maintenance you will be required to come to clinic once a month for the first three months and then every three thereafter. Evaluations may include physical exam, interview with a physician, blood and urine test, x-rays and if necessary a bone marrow biopsy in case there is no evidence of cancer elsewhere. You will require a blood test prior to the monthly supply of lenalidomide. These tests may be done remotely and sent to the transplant center.

Additional assessments: If you are a woman able to become pregnant you will undergo pregnancy counseling and test as long as you are taking lenalidomide. The test will be performed 10-14 days prior to starting lenalidomide, again within 24 hours of starting lenalidomide, weekly for the first four weeks of taking lenalidomide, and then every four weeks thereafter. If your periods are irregular, you will have additional serum pregnancy test performed at two weeks. An additional pregnancy test will be done 28 days after stop taking lenalidomide.

Outline of treatment arms A, B and C from enrollment (Start) to four years, demonstrating the length of each treatment arm.



7. Will You Provide Blood and Bone Marrow Samples for Research?

Researchers are trying to learn more about multiple myeloma and other health problems. Much of this research is done using human tissue or blood. These samples are collected during the clinical trial and stored for future use.

You are being asked to let us store some of your blood and bone marrow samples for use in future research and/or the PRIMeR (Prognostic Immunophenotyping in Myeloma Response) ancillary study. The collection for future research samples and the PRIMeR ancillary study samples can be doe at the same time.

Future Research Samples

Your blood and bone marrow samples for future research will be collected at your transplant center during the period you are participating in this study and kept at a central place called the BMT CTN Research Sample Repository (this will be called the "Repository" in the rest of the consent form). A Repository is a place that protects, stores and sends out samples for approved research studies.

Future research blood samples will be collected prior to the first autologous transplant, and prior to the initiation of maintenance therapy in all study arms. After initiation of maintenance, blood samples will be collected yearly throughout the course of the study (4 more times).

Future research bone marrow samples will be collected prior to first autologous transplant and yearly thereafter (4 more times). The bone marrow samples will be collected as part of the scheduled evaluations in the STaMINA clinical trial and routine assessment of your disease.

PRIMeR Ancillary Study Samples

The PRIMeR ancillary study will be conducted along with the STaMINA clinical trial. All patients who participated in the STaMINA clinical trial are eligible to participate in the PRIMeR ancillary study. This study will use a technique called flow cytometry to look for small

quantities of myeloma cancer cells in your bone marrow. This method has been shown in previous studies to help doctors predict which patients will have a longer period without their myeloma coming back. We are investigating whether treatment in the STaMINA clinical trial increases the chance of having no myeloma cancer cells detected by this method.

The results of the PRIMeR ancillary study will help investigators understand the results of the STaMINA clinical trial; and in the future will help in selecting the best treatment for patients with myeloma.

Your participation in the PRIMeR ancillary study will involve collection of three bone marrow samples in the course of one year (Figure 1). These samples will be kept at the BMT CTN Repository. The first and third bone marrow samples will be collected as part of the scheduled evaluations in the STaMINA clinical trial and routine assessment of your disease. One additional bone marrow aspiration procedure will be done as part of the PRIMeR ancillary study. This additional procedure will be done prior to initiation of maintenance therapy in the STaMINA trial (see bold arrows in Figure 1 for when all PRIMeR bone marrow aspirates will happen).

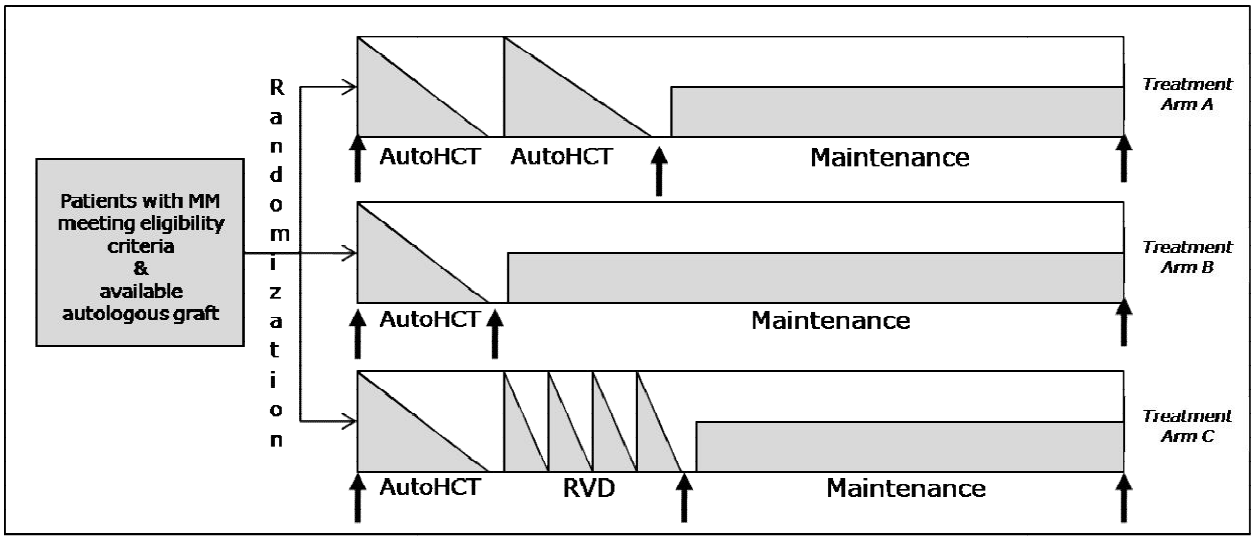


Figure 1 -- Outline of the STaMINA clinical trial. The arrows represent times that a bone marrow is collected as part of the PRIMeR study.

Some general things you should know about letting us store your blood and bone marrow samples for research are:

- We will only store samples from people who give us permission. You should feel free to talk over your decision with your family, friends, doctor, and health care team. If you decide to not let us store research samples now or in the future, it will not affect your medical care.

- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Taking part may also involve some risks.
- All testing done on your blood and tissue samples are for research purposes. You or your doctor will not be given results and they will not be added to your medical record.
- You will not get paid for any samples or for any products that may be developed from current or future research.

If you agree to provide blood and bone marrow samples, here is what will happen:

a) Blood Samples: a maximum of 20 samples of your blood (maximum of 6 teaspoons at each time) will be collected during the course of the study and stored solely for research purposes. The collections will be performed at the same time as the routine blood collections during the study.

b) Bone Marrow Aspirate Samples: if you have multiple myeloma, it is likely that you have already had a bone marrow biopsy and aspirate as part of your evaluations. Bone marrow tests are done as part of your routine medical care in case the multiple myeloma is not detected in blood or urine, in order to make sure your disease is in remission. Also, all patients in this study will have a bone marrow examination done prior to the first transplant. We are asking that an additional sample of the liquid bone marrow (2 teaspoons) be collected for research purposes. A small volume of liquid marrow (1/2 teaspoon) will be set aside for the PRIMeR ancillary study for three bone marrow aspirates collected in the first year of the study (PRIMeR Study Figure 1 above). After the first bone marrow examination, a maximum of 5 bone marrow examinations will be performed for research purposes, three in the first year and once a year thereafter (3 more times). Most, but not all, of these samples will be collected at the time that a bone marrow examination would be done anyway as part of your routine clinical care.

c) All research samples will be given a unique bar code designation that cannot be linked to you by the researcher testing your samples.

d) Researchers can apply to study the materials stored in the Repository.

e) Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the remaining research samples and clinical data will be made available outside of this network. Researchers from other universities, the government, and drug or health-related companies can apply to use the samples and information. Only skilled researchers will be allowed to use the samples and information.

f) The BMT CTN Steering Committee or the BMT CTN Biomarkers Committee must approve each study application before they will share samples or information with researchers. This kind of review is to make sure that the investigators requesting the samples are qualified, and that the research they propose has a high potential of success and for contribution of scientific knowledge.

g) DNA from your stored blood or bone marrow samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH).

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease.

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans must not request your genetic information that we get from this research. This means that they may not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

What if I change my mind?

You can change your mind at any time about allowing us to use your samples and health information for research. We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. If you withdraw yourself from this protocol, even if you allowed your samples to be used for research, your samples will not be used from that point and they will be discarded. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Statement of consent

The purpose of storing blood samples for future research, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

The purpose of storing bone marrow samples for future research and/or the PRIMeR study, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood and/or bone marrow samples for future research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I understand that I do not have to allow the use of my bone marrow samples for the PRIMeR ancillary study. If I decide to not let you store bone marrow samples for the PRIMeR study, it will not affect my medical care in any way.

I voluntarily agree that my blood and/or bone marrow and information can be stored indefinitely by the BMT CTN Repository for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my blood to be stored for future research.
- ❑ I do not agree to allow my blood to be stored for future research.
- ❑ I agree to allow my bone marrow to be stored for future research.
- ❑ I do not agree to allow my bone marrow to be stored for future research.
- ❑ I agree to allow my bone marrow to be stored for the PRIMeR study.
- ❑ I do not agree to allow my bone marrow to be stored for the PRIMeR study.

_____ _____

Signature Date

8. What are the possible discomforts and risks?

The treatment used in this study may cause all, some, or none of the side effects listed below. Also, there is always the chance of unexpected new side effects.

ALL PATIENTS

G-CSF: G-CSF may cause local pain and burning at the injection site and some patients experience pain in their bone when treated with this drug. The bone pain is generally mild to moderate in severity and controllable in most patients with oral medication. The growth factor may cause your white count to become very high, which could affect your blood flow. Your white blood cell count will be measured, and if it becomes too high, the dose of the growth factor will be reduced or stopped. G-CSF may cause fluid retention and low blood pressure. Less common possible side effects include headaches, body aches, upset stomach, skin rash, fatigue and trouble sleeping. Other possible side effects are increases in uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs. Local inflammation and rarely an infection at the G-CSF injection site may also occur. Rarely your spleen can burst (called splenic rupture). Please let your doctor or healthcare provider know immediately if you experience any pain in the left upper stomach area or left shoulder tip. This may be a sign of enlarged or burst spleen.

Leukapheresis (collection of stem cells from your peripheral blood), also called apheresis: If you have a central venous catheter, this procedure will be done through the catheter and not through a vein. If done through a vein, the needle insertion used for the leukapheresis procedure may cause local bruising and infection in the vein or on the skin around the vein. The bruising resolves on its own and has no additional risks. The infection in the vein or of the skin around the vein would be treated with antibiotics.

Your blood will be thinned with citrate during the leukapheresis procedure. Citrate decreases the calcium in the blood sometimes causing temporary numbness or tingling of the fingertips or around the mouth. Should you experience any numbness, you must tell the nurse operating the machine. You will be given a dose of calcium to reverse this side effect, before the problem becomes severe. Other possible side effects of the collection procedure include lightheadedness, nausea or more rarely, fainting due to temporary lowering of the blood pressure. Stopping the procedure and giving additional intravenous fluids can correct this. Occasionally, the filtering process also removes platelets (the cells that help the blood to clot). If your platelet count falls low enough to place you in danger of bleeding, any further collection will be postponed until a replacement transfusion is given.

Blood Drawing: The risks of drawing blood from a vein include discomfort at the site of puncture (where the needle is placed in the vein); possible bruising and swelling around the puncture site; rarely, an infection; and uncommonly, faintness from the procedure. If you have a central line or catheter, these risks will not apply to you and the risks of the central line were explained to you at the time you had the line or catheter placed. Occasionally even if you have a central catheter, you may require blood draws from a vein requiring a needle stick.

Bone Marrow Aspiration and Biopsy: A bone marrow aspiration is a procedure in which an area of the hip (buttock area) is numbed with local anesthetic, and a small sample of bone marrow is withdrawn. A bone marrow biopsy is similar to a bone marrow aspiration, except a sample of bone is removed through the needle. When the local anesthesia is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the actual procedure itself, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely an infection can develop.

Bone marrow aspirates and biopsies will be used to check how your disease is responding to the study treatments.

Unexpected Organ Damage and Other Side Effects: Although your major organs function well, it is possible that unexpected heart, lung, kidney, or liver damage may occur as a result of this therapy, which is rarely life-threatening and usually reversible with treatment. You will be informed if problems arise and the measures being taken to help you. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal despite intensive medical management. Other unpredictable side effects can occur and will be explained to you and treated by your physicians should unforeseeable problems arise.

Late Effects: These may include gland problems resulting in poor growth and sterility. There may be poor function of the thyroid gland, requiring thyroid hormone supplementation. There is also a risk of second cancers as a result of the chemotherapy and/or underlying disease. The risk of developing and dying from a secondary cancer is far less than the risk of dying from your disease without treatment. The long-term effects upon heart, lung, and brain are unknown.

Risk to the Unborn: The treatments in this study have not been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some effective method of birth control. Effective birth control would be defined as the following: 1) refraining from all acts of vaginal intercourse (ABSTINENCE); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera, Norplant); 4) tubal sterilization or male partner who has undergone a vasectomy; must still use latex condom; 5) placement of an IUD (intrauterine device); and, 6) use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.

Both men and women will be included in this study. Because the drugs in this study may affect an unborn baby, you should not become pregnant or father a baby while in this study. You must use a highly effective birth control method or a combination of 2 additionally effective birth control methods while in this study. The effect of bortezomib and lenalidomide on reproduction and its safety in pregnancy are unknown. If you are a woman capable of becoming pregnant [women that have not undergone a hysterectomy (removal of the womb), have not had both ovaries removed or have not been post-menopausal (stopped menstrual periods) for more than 24 months in a row], you must have a negative pregnancy test before beginning treatment. In addition, you must not be breastfeeding a baby during this study.

If you think that you have become pregnant or may have fathered a child while taking part in this study you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. You should also notify the doctor managing your pregnancy that the mother/father received a study drug (name of study drug or drugs).

If you are a female study subject and you become pregnant during your participation in this study, your treatment with study drug will be stopped and you may be withdrawn from some of the study procedures but not from follow-up by your study doctor. The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.

If you are a male study subject and your partner becomes pregnant, the study doctor will ask for your partner's permission to collect information about her pregnancy and the health of the baby.

Laboratory tests show that bortezomib and lenalidomide may damage DNA. Based on this information, it is possible that bortezomib and lenalidomide may cause infertility in men and women (not being able to become pregnant or father a child).

Sterility and Future Childbearing Potential for Men and Women: Chemotherapy and /or irradiation may affect fertility. Male patients may become sterile (unable to produce sperm). Female patients may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control. Damage to reproductive tissue may result in birth defects or permanent inability to father a child or become pregnant. You should discuss these risks and options in detail with your doctor before entering this study.

Therapy Toxicities: Unknown Toxicities may occur in any individual patient due to multiple events and cumulative effects, which may involve any and all organs, including the brain.

AUTOLOGOUS STEM CELL TRANSPLANT

Melphalan: The most common side effect in patients who have received melphalan has been nausea and vomiting (mild to moderate), loss of appetite (mild), diarrhea and skin rash. Your doctor will prescribe drugs to prevent and lessen these side effects should they occur. Melphalan will irritate your skin if it leaks outside of the vein while being given. Let your doctor or nurse know if you feel any burning, stinging or pain while you are receiving this drug. Notify your doctor right away if the area around the injection becomes red or swollen after you receive the drug. Side effects that occur several days or a week later include low blood count, mouth sores, temporary hair loss, fatigue and poor appetite. You may need blood and platelet transfusions while your counts are low and/or antibiotics to fight infections. Mouth sores which sometimes extend into the throat or esophagus can be painful, and some patients may require 7 to 10 days of morphine or a similar medication to control the discomfort. Mouth sores can also make eating difficult. If this occurs, patients will receive their nutrition intravenously until the problem resolves. In rare instances, melphalan can cause lung damage or a secondary cancer (a cancer caused by prior cancer treatment). Secondary cancers are often very difficult to treat and can be fatal.

Infusion of Autologous Stem Cells: The stem cell infusion is given similar to a blood transfusion. It is given through your central venous catheter. You will be given pre-medications just prior to the infusion to decrease the risk of a reaction. There is a very slight risk of infection due to contamination of the stem cell products during their storage or drawing. Some patients react to the preservative called DMSO, which is used in the freezing process of your stem cells. You may notice a garlic taste or smell from the DMSO. Common, less serious reactions for patients receiving an autologous SCT include mild wheezing, mild shortness of breath, back or chest pain or lightheadedness. In rare instances, a severe allergic reaction called anaphylaxis can occur leading to a drop in blood pressure or extreme difficulty in breathing. You will be monitored very closely during the infusion and afterwards to look for these reactions and given medications and/or intravenous fluids to correct these side effects. These complications are reversible with treatment.

Risk of Infection and Other Complications of Low Blood Counts: After any of the therapies in this study, but before the stem cells have begun to make new blood cells, your ability to fight infections will be very low. During that time you will be very susceptible to serious infections and will need to take extra precautions to limit your exposure to infectious agents. Bacteria, fungi and viruses that can easily be destroyed by a healthy person's immune system can cause a serious, and sometimes fatal, infection in patients with low white blood cell counts. You will be given medications to prevent infections and to treat them if you develop one as determined by your doctor.

After transplantation you may not be able to make red blood cells or platelets for approximately two to three weeks until the stem cells start growing in your bone marrow. If your red blood cell count is very low, you may have severe fatigue or shortness of breath. If your platelet count is low, there is a small chance of serious bleeding. Therefore, you may need red blood cell and platelet transfusions.

The risk of dying from the complications of an autologous transplant is less than 5%. This means that for every hundred patients who have an autologous transplant for multiple myeloma, up to 5 of them may die from complications of the treatment. It is not possible to know before your transplant if you will die from complications of treatment.

CONSOLIDATION THERAPY

Dexamethasone: This medication may temporarily increase blood pressure and blood sugar levels. Some patients require medication to control their blood sugar. Steroid medications have also been known to cause insomnia (difficulty sleeping), personality changes and depression. Dexamethasone may also cause nausea, vomiting, increased appetite, stretch marks, weight gain, fluid retention, swelling, gas and heartburn. These symptoms usually go away once the medication is stopped. Gas and heartburn can be treated with medications. Call your doctor if you experience these symptoms. Dexamethasone can also cause inflammation of the pancreas, pain, thinning and weakening of the bones, and the potential for a hip replacement.

Bortezomib: Bortezomib is also called **Velcade®.** Bortezomib should not be taken if you have ever had a serious allergic reaction to bortezomib, boron, or mannitol. You face some risks or

discomforts when you are treated with the study drug, bortezomib. You are at risk of having all, some, or none of these symptoms and they may vary in severity. The severity may be mild, moderate or severe, up to and including death. Any symptoms or conditions that you have before you start study drug may get worse. Also, there is always a chance that a risk that is rare or not yet known may occur. If any of these symptoms occur, you must tell your doctor who may give you other drugs to ease discomforts you have. Your doctor may lower or withhold the dose of bortezomib. Also, if you have a very bad reaction to the study drug, your doctor may permanently stop the study treatment for good.

Certain drugs or compounds may change the effectiveness of bortezomib, including grapefruit juice, green tea, vitamin C, and St. John's Wort. Call your doctor if you have questions about drug interactions.

Likely Side Effects (may occur in 20% of patients or more)	**Less Likely Side Effects (may occur in <20% of patients or less)**	**Rare Side Effects (can occur in less than 3% of patients)**
• Decrease in a red blood cell protein that carries oxygen in the body • Decreased number of blood cells that help to clot the blood • Infection which occurs due to a decreased number of a type of white blood cell • Fatigue • Fever in the absence on neutropenia • Anorexia • Loss of appetite • Constipation • Diarrhea • Nausea • Vomiting • Swelling of the arms and legs • Nerve damage causing numbness, tingling, burning	• Decreased total number of white blood cell • Decreased number of a type of white blood cell • Low blood pressure • Difficulty sleeping or falling asleep • Rigors/Chills, Rash/desquamation • Dehydration • Low blood pressure • Abnormal heart beat • Irritation or sores in the lining of the mouth or throat • Sore throat • Heartburn, dyspepsia • Ileus (functional obstruction of the bowel, i.e., neuroconstipation) • Mucositis/stomatitis • Hemorrhage (GI, pulmonary/upper respiratory) • Fever with dangerously low white blood cell count • Infection with low white blood cell count • Pneumonia • Opportunistic infection • Dizziness • Confusion • Anxiety • Changes in the way things taste • Abnormal liver tests • numbness, tingling, burning • Fainting • Blurred vision • Inflammation of the eye	• A hole in the digestive tract • Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings • Kidney failure • Reversible posterior leukoencephalopathy syndrome (affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures)

Likely Side Effects (may occur in more than 20% of patients)	Less Likely Side Effects (may occur in 20% of patients or less)	Rare Side Effects (can occur in less than 3% of patients)
	• Muscle weakness • Nerve damage • Fainting • Blurred vision • Belly pain • Back pain • Bone pain • Leg pain • Head pain • Joint pain • Muscle pain • Nerve pain • Cough • Shortness of breath • Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs	

Lenalidomide: This medication may cause skin rash, drowsiness or sleepiness, dizziness, confusion, tremor, loss of coordination, weakness, and numbness. Lenalidomide may also cause constipation, nausea, diarrhea, vomiting and inflammation of the mucosa of the mouth. General symptoms from taking this drug are weakness, weight loss, and fever. Lenalidomide can cause a significant increased risk of blood clot in multiple myeloma patients. Also this drug can cause a significant decrease in white blood cells (neutrophils) and platelets in the blood. Call your doctor if you experience these symptoms (see below under maintenance additional information about lenalidomide).

Reproductive Risks: Lenalidomide is known to be very harmful to fetuses and can produce miscarriages in pregnant women. It can cause severe life-threatening human birth defects or fetal death. Therefore it is very important not to be pregnant or become pregnant while on lenalidomide. All women of childbearing ages will receive pregnancy tests 10-14 days and 24 hours before starting this drug. Also pregnancy tests will be frequently administered while taking this drug and at the discontinuation of your therapy of this drug.

Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking lenalidomide.

You should discuss with your doctor what the best methods of birth control are for you. Remember, however, than no method of birth control besides complete abstinence provides 100% protection from pregnancy.

If you are a female patient taking lenalidomide, you must either abstain from all reproductive sexual intercourse or use two methods of birth control or at least one highly active method (e.g., intrauterine device [IUD], hormonal [birth control pills, injections or implants], tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), for at least 28 days before starting lenalidomide therapy, during therapy, and for at least 28 days after discontinuing lenalidomide therapy even when there has been a history of infertility, unless due to hysterectomy or because you have been post-menopausal or have had no menses (that is no menstrual period) for at least 24 continuous months.

Patients with multiple myeloma who take lenalidomide and dexamethasone have a greater chance of having blood clots. Because of this, it is recommended patients not take birth control pills or hormone replacement therapy before discussing with the doctor and considering the risks and benefits of these choices.

If you are a male patient, you will be counseled that lenalidomide may be present in your semen. You must use a latex condom every time you have sexual intercourse with a woman during therapy and for four weeks after discontinuing lenalidomide, even if you have had a successful vasectomy. You should request that female partners use a second method of birth control in addition to using a male condom.

Patients should not donate blood during study treatment or for 28 days following discontinuation of lenalidomide.

You will be counseled at least every 28 days either by counselors at the site or through the Revlimid REMS® program during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (or other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

MAINTENANCE THERAPY

Lenalidomide: Lenalidomide is also called **Revlimid®.** This medication may cause skin rashes, drowsiness or sleepiness, dizziness, confusion, tremor, loss of coordination, weakness, and numbness. Lenalidomide may also cause constipation, nausea, diarrhea, vomiting and inflammation of the mucosa of the mouth. General symptoms from taking this drug are weakness, weight loss, and fever. Lenalidomide can cause a significant increased risk of blood clot in multiple myeloma patients. Also this drug can cause a significant decrease in white blood cells (neutrophils) and platelets in the blood. Call your doctor if you experience these symptoms.

Sometimes a second cancer arises after patients have undergone cancer therapy, including chemotherapy used prior to autologous transplants. Recently, in clinical trials of patients with multiple myeloma, a higher number of second cancers has also been reported in patients treated with chemotherapy and/or autologous transplant followed by maintenance lenalidomide compared to those who did not receive lenalidomide.

We do not know at this time whether prolonged lenalidomide therapy in this clinical setting actually increases the risk of second cancers. No increase in second cancers has been observed in patients receiving lenalidomide therapy for other indications or for relapsed multiple myeloma.

We are carefully monitoring these events (second cancers) in all on-going studies of lenalidomide therapy. You will be given any new information regarding second cancers that might affect your decision to stay in the study.

Likely Side Effects (may occur in more than 20% of patients)	**Less Likely Side Effects (may occur in 20% of patients or less)**	**Rare Side Effects (can occur in less than 3% of patients)**
• Decreased number of a type of white blood cells (neutrophil/ granulocyte) • Decreased number of blood cells (platelets) that help to clot blood • Fatigue or tiredness • Anemia or decrease in a red blood cell protein (hemoglobin) that carries oxygen in the body • Constipation • Diarrhea •	• Decrease of the total number of white blood cells (leukocytes) • Decreased number of a type of white blood cell (lymphocyte) • Fever • Difficulty sleeping or falling asleep • Chills, shivering • Excessive sweating • Weight loss • A chronic, inflammatory skin condition with sores covering the skin • Abnormally low level of thyroid gland hormone • Loss of appetite • Irritation or sores in the lining of the anus • Irritation or sores in the lining of the mouth • Irritation or sores in the lining of the rectum • Irritation or sores of the lining of the small bowel • Vomiting	• Inflammation (swelling and redness) of the pancreas • Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness • Increased blood level of fat-digesting enzyme (lipase) • Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood calcium, potassium, uric acid, phosphate, and kidney failure • Temporary growth in tumor or worsening of tumor related problems • Progressive necrosis (tissue death) of a part (the

Likely Side Effects (may occur in more than 20% of patients)	Less Likely Side Effects (may occur in 20% of patients or less)	Rare Side Effects (can occur in less than 3% of patients)
	• Infection(s) somewhere in the body • Swelling of the arms and legs • Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking) • Belly pain • Back pain • Head pain or headache • Joint pain • Muscle pain • Cough • Shortness of breath • Formation or presence of a blood clot that breaks loose and is carried by the blood stream to plug another blood vessel • Itching • Rash with the presence of macules (flat discolored area) and papules (raised bump)/flaking or shedding of outer layer of skin • Nausea; the urge to vomit	white matter) of the brain without inflammation (swelling and redness) • Sudden or traumatic injury to the kidney • Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue • Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer) • Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking lenalidomide.

You should discuss with your doctor what the best methods of birth control are for you. Remember, however, than no method of birth control besides complete abstinence provides 100% protection from pregnancy.

If you are a female patient taking lenalidomide, you must either abstain from all reproductive sexual intercourse or use two methods of birth control or at least one highly active method (e.g., intrauterine device [IUD], hormonal [birth control pills, injections or implants], tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), for at least 28 days before starting lenalidomide therapy, during therapy, and for at least 28 days after discontinuing lenalidomide therapy even when there has been a history of

infertility, unless due to hysterectomy or because you have been post-menopausal or have had no menses (that is no menstrual period) for at least 24 continuous months.

Patients with multiple myeloma who take lenalidomide and dexamethasone have a greater chance of having blood clots. Because of this, it is recommended patients not take birth control pills or hormone replacement therapy before discussing with the doctor and considering the risks and benefits of these choices.

If you are a male patient, you will be counseled that lenalidomide may be present in your semen. You must use a latex condom every time you have sexual intercourse with a woman during therapy and for 28 days after discontinuing lenalidomide, even if you have had a successful vasectomy. You should request that female partners use a second method of birth control in addition to using a male condom.

Patients should not donate blood during study treatment or for 28 days following discontinuation of lenalidomide.
Lenalidomide will be provided to you free of charge. Lenalidomide distribution for this trial will change from obtaining the drug directly through the transplant center to mail distribution directly to your address. The way you will be counseled will change due to the change in drug distribution.

You will be counseled at least every 28 days either by counselors at the site or through the Revlimid REMS® program during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (or other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

If you have ever received lenalidomide before, you are already registered in the Revlimid REMS® and there is no additional registration required for this clinical trial. If you have never received lenalidomide before, you will need to be registered in the Revlimid REMS®. This program is a controlled prescription mechanism to dispense lenalidomide for any indication. The registration involves a separate consent process, which outlines the reproductive risks related to this medication, and identifies you as a participant with this clinical trial. Information that will be required for consent includes your name, address, phone number, date of birth, and social security number. This information will be provided to Celgene Corporation and Biologics Incorporated to identify your registration in participating in this trial. RevAssist is the mandatory mechanism by the US Food and Drug Administration for dispending lenalidomide.

Any unused lenalidomide should be returned as instructed though the Revlimid REMS® program.

Additional Instruction for Taking Lenalidomide

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.

If you miss a dose of lenalidomide, take it as soon as you remember on the same day. If you miss taking your dose for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose).

If you take more than the prescribed dose of lenalidomide you should seek emergency medical care if needed and contact study staff immediately.

Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves.

Only one cycle of therapy will be provided to you each month through the Revlimid REMS® program. During maintenance a maximum of a 28-day supply will be dispensed.

Pregnancy:

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Preliminary findings from a monkey study appear to indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Because of this risk, all patients taking lenalidomide must read the following statements that apply to them according to gender and menopausal status.

FOR FEMALES WHO *ARE ABLE* TO BECOME PREGNANT*

*(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 for at least 24 consecutive months)

Please read thoroughly and initial each space provided if you understand each statement

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that my unborn baby may have birth defects and can even die, if I am pregnant or become pregnant while I am taking lenalidomide.

_____: I understand that I must NOT take lenalidomide if I am pregnant, breast-feeding a baby or able to get pregnant and not using 2 reliable methods of birth control.

_____: If I am having sexual relations with a man, my uterus and/or both ovaries have not been removed, I have had at least one menstrual period in the past 24 months and/or my menses stopped due to treatment of my disease, I understand that I am able to become pregnant. I must use one highly effective method of birth control plus one additional effective method of birth control (contraception) at the SAME TIME.

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

_____: These birth control methods must be used during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide therapy; 2) while participating in the study; during interruptions in therapy; and, 3) for at least 28 days after lenalidomide has been stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormone (birth control pill, injection, patch or implant) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

_____: I know I must have a pregnancy test done by my doctor within 10 – 14 days and again within 24 hours prior to starting lenalidomide therapy, even if I have not had my menses due to treatment of my disease or had as little as one menstrual period in the past 24 months. If I have regular or no menstrual cycles, I will then have pregnancy tests every week for the first 28 days, then every 28 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy and then 28 days after I have stopped taking lenalidomide. If I have irregular menstrual cycles, I will have pregnancy tests every week for the first 28 days, then every 14 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy, and then 14 days and 28 days after I have stopped taking lenalidomide.

_____: I know I must immediately stop taking lenalidomide and inform my doctor, if I become pregnant while taking the drug, if I miss my menstrual period or have unusual menstrual bleeding, if I stop using two reliable forms of birth control, or if I think for any reason that I may be pregnant. I must talk to my doctor before changing any birth control methods.

_____: I am not now pregnant, nor will I try to become pregnant for at least 28 days after I have completely finished taking lenalidomide.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.

_____: I agree any unused drug supply will be returned as instructed through the Revlimid REMS® Program.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

Study patients who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

FOR ALL MALES

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I have been told by my doctor that I must NEVER have unprotected sexual contact with a female who can become pregnant. Because it is not known whether lenalidomide is present in semen, my doctor has explained that I must completely abstain from sexual contact with females who are pregnant or able to become pregnant, or I must use a latex condom every time I engage in any sexual contact with females who are pregnant or may become pregnant AND insist that my partners use highly effective contraception. I must do this while I am taking lenalidomide and for 28 days after I stop taking lenalidomide, even if I have had a successful vasectomy.

_____: I know I must inform my doctor if I have unprotected sexual contact with a female who is pregnant or can become pregnant or if I think, for ANY REASON, that my sexual partner may be pregnant. Female partners of male patients taking lenalidomide should be advised to call their own physician immediately if they get pregnant.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are able to have children.

_____: I agree any unused drug supply will be returned as instructed through the Revlimid REMS® Program.

_____: I know that I cannot donate blood, sperm or semen while taking lenalidomide and for 28 days after stopping lenalidomide.

FOR FEMALES THAT ARE ***NOT*** ABLE TO BECOME PREGNANT

Please read thoroughly and initial each space provided if you understand each statement.

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if a female is pregnant or becomes pregnant while taking lenalidomide.

_____: I certify that I am not now pregnant, nor am I of child bearing potential as I have been in a natural menopause for at least 24 months (been through the change in life without even 1 menstrual period for the past 24 months); or I had my uterus removed (hysterectomy) or had both my ovaries removed (bilateral oophorectomy).

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to females who are pregnant or able to have children.

_____: I agree any unused drug supply will be returned as instructed through the Revlimid REMS® Program.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

All Patients Taking Lenalidomide

You will be counseled at least every 28 days either by counselors at the site or through the Revlimid REMS® program during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules. You will be provided with the "Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies" with each new supply of lenalidomide as a reminder of these safety issues.

Other Information:

There may be some unknown or unanticipated discomforts or risks associated with this treatment in addition to those specified above, but every precaution will be taken to assure your personal safety and to minimize discomforts.

Throughout the study, the researchers will tell you of new information that might affect your decision to remain in the study.

If you wish to discuss the information above or any other discomforts you may experience, you may ask questions now or call your doctor _____, the Principal Investigator or contact person listed on the front page of this form.

9a. What are the possible benefits to you for taking part in this study?

Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may lead to the improvement or "temporary" disappearance of your myeloma and prolongation of your life. However, no benefit is guaranteed.

9b. What are the possible benefits to others?

A possible advantage of this study is that benefit to others may result from the knowledge gained from your participation in this research study.

10. If you choose to take part in this study, will it cost you anything?

You are responsible for the costs of treatment for your disease on this protocol. Your insurance provider may not cover all or part of these costs. You are not required to pay for tests or research samples that are being performed or collected only for research purposes. Two drugs from consolidation treatment (lenalidomide and bortezomib) and maintenance (3 years of lenalidomide) are being provided by the manufacturers free of charge. If you have concerns or questions regarding coverage or potential charges, you should contact (contact person's name) at (###) ###-####, or the Principal Investigator of the study, to review the situation.

11. Will you receive payment for taking part in this research study?

No, you will not receive payment for taking part in this research study. Your participation in this study may result in discoveries or products. The discoveries and products may have commercial value, and if there is commercial value, you will not receive any compensation from the discoveries or products.

12. What if you are injured because of the study?

It is important that you tell your study doctor or study staff if you feel that you have been hurt or injured because of taking part in this study. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. This study will not pay for medical treatment. In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form. If you have any questions about injuries, you may call [insert name] at (###) ###-####.

13. What other options or treatments are available if you do not want to be in this study?

Participation in this study is entirely voluntary. You are free to refuse to be in the study, and your refusal will not affect current or future health care you receive at this institution. You and your doctor will discuss any other treatment options available to you.

Current therapies for multiple myeloma include:

- Chemotherapy using single or combinations of drugs
- Single autologous transplants with or without additional drugs to prevent relapse after transplantation
- Double autologous transplants with or without additional drugs to prevent relapse after transplantation
- Allogeneic transplantation using a related or unrelated donor

You may also be eligible to receive other investigational treatment or you may decide not to receive any treatment. Your doctor will discuss these and other possible treatment approaches with you.

13a. How can you withdraw from this research study?

If you agree to be in this study, you are free to change your mind. At any time you may withdraw your consent to be in this study and for us to use your data. If you withdraw from the study, you will continue to have access to health care at [participating clinical facility]. If you decide to withdraw, we ask that you tell the [Principal Investigator] in writing; his/her mailing address is on the first page of this form. If you do withdraw your consent, there will be no penalty and you will not lose any benefits to which you are otherwise entitled.

Due to the nature of your illness and the study treatments, it is important to continue to receive medical follow-up even if you withdraw from the research study. If you have any questions about your rights as a study subject, you may call the Institutional Review Board (IRB) office at (###) ###-####.

13b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we ask that you agree that we can continue using all information about you that has already been collected as part of the study prior to your withdrawal, and to continue to allow your doctor to tell us about your progress until 12 months after your transplant. You may, of course, say no.

13c. Can the Principal Investigator withdraw you from this research study?

You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant as the study treatment could be harmful to the fetus.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the study treatment you are taking has been found to be unsafe.
- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).
- Your myeloma returns.

14. How will your privacy and the confidentiality of your research records be protected?

Study records that have your name will be kept private as required by law. You will not be identified by name in the central study records. Your records will be given a unique code number. The key to the code will be kept in a locked file in the offices of the Coordinating Center for the study. Authorized persons from the [participating clinical facility], the hospital or clinic (if any) involved in this research, and the Institutional Review Board have the legal right to review your research records and will protect their confidentiality to the extent permitted by law. This research study is sponsored by and conducted with funds from the National Institutes of Health; therefore, the sponsor, the sponsor's agent, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the investigators conducting this study, Southwest Oncology Group, the Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials, the NCI-sponsored Cancer Cooperative Groups that enroll patients on this trial through the CTSU, and the FDA also have the legal right to review your research records. Otherwise, your research records will not be shown to anyone without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your name will not be disclosed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

15. Expiration date for retention of records

The study results will stay in your research record at [insert Institution] for at least six years or until after the study is completed, whichever is longer. At that time either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

16. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals. In addition, the sponsor is providing funds to the Principal Investigator to facilitate the conduct of this study.

17. HIPAA[28] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *A Trial of Single Autologous Transplant with or without Consolidation Therapy versus Tandem Autologous Transplant with Lenalidomide Maintenance for Patients with Multiple Myeloma.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work-up and after transplantation (e.g., bone marrow tests, blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from (*list hospitals, clinics or providers from which health care information can be requested*).

_____

_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item "c." above and information

28 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. Amrita Krishnan, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. George Somlo, Study Chairperson and staff/laboratories at City of Hope National Medical Center
- Dr. Edward Stadtmauer, Study Chairperson and staff/laboratories at University of Pennsylvania Cancer Center.
- National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data and coordinating center, including the Center for International Blood and Marrow Transplant Research (CIBMTR), The National Marrow Donor Program (NMDP), and The EMMES Corporation.
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- The NCI-sponsored Cancer Cooperative Groups that enroll patients on this trial through the CTSU
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments
- Celgene (the manufacturer of lenalidomide)
- Biologics, Inc (the distributor of lenalidomide)
- Millennium Pharmaceutics (the manufacturer of Bortezomib)

e. Right to Refuse to sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

18. Further Information

If you have further questions concerning this project at any time, you are free to ask them of Dr. _____, who will be available to answer them. His/her telephone number is located on the first page of the consent.

19. Consent Instructions

<u>To voluntarily become a participant in this research study I must confirm the following and sign below.</u>

* I have read all of the information in the Informed Consent and I have had time to think about it.
* All of my questions have been answered to my satisfaction. If I did not understand any of the words or parts of this study, I asked the study doctor or the research staff to explain what I did not understand.
* I voluntarily agree to be part of this research study and to follow the study procedures as directed. I agree to keep the research staff informed of my current contact information.
* I have been informed that I may discontinue my participation in this study at any time.
* Signing this consent form is not a waiver of my legal rights.
* I have received a signed copy of this Informed Consent to keep for my reference.

Subject Name (please print)

Subject Signature or Legal Representative (relationship) Date & Time

Name of Individual Conducting Informed Consent Discussion
(please print)

Signature of Individual Conducting Informed Consent Discussion Date

Signature of Witness (where Applicable) Date

I have fully explained the research study to the subject and answered all of the subject's questions.

Name of Principal Investigator or Authorized Representative
(please print)

Signature of Principal Investigator or Authorized Representative Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. Collection of Samples for Future Ancillary Studies

Bone marrow aspirate and blood will be collected from patients who signed consent related to providing samples for future research. Sample collection will be done at the transplant center and will require minimum processing. Once the samples are collected at specified time points they will be shipped to the BMT CTN Central Processing Laboratory for final processing and storage at the BMT CTN Research Biologic Repository. These samples will be tracked through GlobalTrace.

2. Bone Marrow Aspirate Samples

Patients who consented for marrow sample collection for future research studies will have 10 cc of bone marrow aspirate collected at baseline (preferably in one single procedure along with standard of care aspirate collection) and yearly subsequently for four years or until disease progression. Samples will be collected in heparin anticoagulant coated tubes and shipped at ambient temperature to the BMT CTN Central Processing Laboratory for further processing and storage. These samples will be tracked through GlobalTrace.

2.1. Bone Marrow Aspirate Samples and Shipping Requirements for the PRIMeR Ancillary Study

Patients who consented for the PRIMeR ancillary study will have an aliquot of 2 mL of marrow samples collected prior to study entry and at one year post-randomization as part of the parent clinical trial. One additional bone marrow aspirate will be collected prior to initiation of maintenance lenalidomide therapy. Samples will be identified with bar-coded labels provided by the BMT CTN to each center. Samples will be placed in a leak-proof container inside a transport box and shipped at room temperature to the Roswell Park Cancer Institute (RPCI) Flow Cytometry Laboratory overnight and tracked through GlobalTrace[SM].

Paul K. Wallace, Ph.D.
Roswell Park Cancer Institute
Department of Flow and Image Cytometry
Elm & Carlton Streets
Buffalo, NY 14263

Telephone: (716) 845-3528
Fax: (716) 845-8806

2.2 Sample Handling and Analysis

Bone marrow specimens for IP should be drawn into one sodium heparin (green top) tube. All samples must be received by the Laboratory within 24-48 hours of collection. Samples older than 48 hours or with a viability of less than 85% will not be processed because they cannot be reliably analyzed. Upon arrival, an automated WBC and lymphocyte count will be performed on each specimen using the standard RPCI IP stain/lyse/wash/fix procedure for routine flow cytometric analysis.(40) Cells stained with the monoclonal antibodies (mAbs) in Panel 2 (see Appendix N, Section 3.1.1., Table 3.1.1a) will first be stained with CD38, CD138, CD45, and CD19 (part A), then lysed, washed, briefly fixed and then stained in a permeabilization buffer with anti-kappa and anti- lambda reagents (part B) to detect cytoplasmic light chains. Collection on the FACSCanto II is routinely performed within 24 hours (or at most 48 hours) after staining. To detect rare populations, data on the flow cytometer are collected using a forward scatter threshold to eliminate cellular debris for up to 3 minutes or 250,000 events, whichever occurs first. Data are subsequently analyzed using a viable, mononuclear cell gate based on forward and side scatter.(41) This is a region that encompasses lymphocytes, monocytes and most abnormal cell populations and excludes dead cells based on a viability dye. The results are reported as the percent positive cells falling within this region, the percent of total cells and as the absolute number of cells/µl of bone marrow.

3. Peripheral Blood Research Specimens

Peripheral blood samples (31 mL total) will be collected for future research testing in patients who consented to provide samples for research purposes. The time points for collection will be prior to the first autologous transplant (baseline) for all patients, and prior to the initiation of maintenance therapy in all study arms. After initiation of maintenance, peripheral blood research samples will be collected yearly after randomization for four years or until disease progression.

SCHEDULE OF LABORATORY EVALUATIONS

	Type of Sample	Type of Processing	Dates Samples Obtained	Shipping Specifications	Storage Location
Patient Research Bone Marrow Aspirate	10 mL bone marrow aspirate	Collect bone marrow aspirate sample and place in a 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant. No additional sample processing is required.	Prior to the 1st autologous transplant and yearly post-randomization subsequently for four years or until disease progression.	Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of marrow aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository is detailed in the 0702 Laboratory Sample Guide.	BMT CTN Research Repository
Patient Research Bone Marrow Aspirate (PD-1 Ancillary Study)	2 mL bone marrow aspirate (Aliquot of 2 mL from the initial bone marrow aspirate collected, as above)	Processed as part of the original 10mL bone marrow aspirate as described above.	Prior to the 1st autologous transplant, and at one year post randomization.	Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection, to the **Department of Flow and Image Cytometry** at Roswell Park Cancer Institute by priority overnight FED EX delivery for immunophenotyping.	BMT CTN Research Repository

	Type of Sample	Type of Processing	Dates Samples Obtained	Shipping Specifications	Storage Location
Bone Marrow Aspirate for Immunopheno-typing (PRIMeR Ancillary study)	2 mL bone marrow aspirate (Aliquot of 2 mL from the initial bone marrow aspirate collected, as above)	Processed as part of the original 10 mL bone marrow aspirate as described above.	Prior to the 1st autologous transplant, prior to maintenance and one year post randomization to BMT CTN 0702.	Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection, to the **Department of Flow and Image Cytometry** at Roswell Park Cancer Institute by priority overnight FED EX delivery for immunophenotyping.	BMT CTN Research Repository
Patient Research Peripheral Blood Specimen (Serum)	6 mL peripheral blood	Collect blood sample in a Red/Gray Top BD SST™ Tube with Silica Clot Activator & Polymer Gel. Let sample sit upright in rack for 30 minutes. Centrifuge for 10 minutes. Gel barrier will form separating the serum specimen from clot. Prepare tube for transport along with other research samples.	Prior to first autologous transplant, and prior to initiation of maintenance therapy. Then yearly post-randomization subsequently for four years or until disease progression.	Serum blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository are detailed in the 0702 Laboratory Sample Guide	BMT CTN Research Repository

	Type of Sample	Type of Processing	Dates Samples Obtained	Shipping Specifications	Storage Location
Patient Research Peripheral Blood Specimen (Plasma)	5 mL peripheral blood	Collect blood sample in a 5 mL fill, white top plastic Greiner Vacuette ® PST tube. Gently mix sample with EDTA by inverting the tube 8-10 times. Centrifuge for 10 minutes. Gel barrier will form separating the plasma specimen from cells. Prepare tube for transport along with other research samples.	Prior to first autologous transplant, and prior to initiation of maintenance therapy. Then yearly post-randomization subsequently for four years or until disease progression.	Plasma blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/ Research Repository is detailed in the 0702 Laboratory Sample Guide	BMT CTN Research Repository
Patient Research Peripheral Blood Specimen (PBMC)	20 mL peripheral blood	Collect peripheral blood sample in two 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant. No additional sample processing is required.	Prior to first autologous transplant, and prior to initiation of maintenance therapy. Then yearly post-randomization subsequently for four years or until disease progression.	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of isolated viable PBMC aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository is detailed in the 0702 Laboratory Sample Guide	BMT CTN Research Repository

APPENDIX D

LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

APPENDIX D

LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

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.

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. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

Females of childbearing potential (FCBP)[†] 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 study drug; 2) while participating in the study; and, 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

<u>Criteria for females of childbearing potential (FCBP)</u>

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 (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

[†] A female of childbearing potential is 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).

Counseling
All counseling will be conducted through the Revlimid REMS® program.

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

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 contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and, 4) for at least 28 days after study treatment 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. T he 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 to 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 study drug

Female Patients:

FCBP must have two negative pregnancy tests (minimum sensitivity of 50mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug (prescriptions must be filled within 7 days as required by the Revlimid REMS® program). The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug 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. Study treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- 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.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.
- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

APPENDIX E

Revlimid REMS® PROGRAM

APPENDIX E

Revlimid Overview

Revlimid REMS® for Study Participants

Revlimid REMS® description:
A program that allows patients enrolled in authorized clinical trials access to free Revlimid® through the Revlimid REMS® program.

Access to the RASP Program:

1. **All physicians must be registered prescribers of Revlimid® in the Revlimid REMS® Program All clinical sites must have access to the Revlimid REMS® software to enroll patients in the Revlimid REMS® program**
   1) Prescriber submits Registration Form via fax or RevAssist® Online ***(RAO*** for Revlimid) to Celgene Customer Care.
   2) Prescriber is registered within 15 minutes.
   3) Registration confirmation fax is sent to prescriber's office via fax. (For RAO, the confirmation notification is displayed on the screen immediately)
   4) Starter Kit is sent to prescriber's office (overnight). The starter kit will contain the following:
      - Instructions For Prescribers
      - Patient Resource Packs
      - Guide to English and Non-English Materials
      - Computer software used to generate Patient-Physician Agreement Forms (PPAF)

2. **All studies must have an FDA letter of IND exemption or an active IND, active IRB approval and Celgene required regulatory documents.**

3. **Patients must sign the research specific IRB-approved informed consent and be enrolled in a Celgene-approved Medical Affairs clinical trial using Revlimid®**

4. Celgene Customer Care Center must be contacted to confirm if a patient needs to be registered by calling 1-888-423-5436.

Patients must also sign the appropriate PPAF form and follow all the procedures of the Revlimid REMS® Program

1) Patient and Prescriber complete the PPAF together.
2) The form is faxed to Celgene Customer Care or submitted electronically through ***RAO***.
3) Patient is registered within 15 minutes.
4) Confirmation fax is sent to prescribing office notifying them that the patient is now registered. For RAO, the confirmation notification is displayed on the screen immediately.

6. **Patients and prescribers must take the phone surveys as required by the Revlimid REMS® Program (The PPAF generated for the patient determines which phone survey questions will be asked.) An authorization number is provided at the completion of the phone survey, the authorization number should be noted on the prescription form.**

   Patient Survey requirements:

   - For men: Do not need to call Celgene the first month but must call monthly starting the second month.
   - For females of non - child bearing potential: Must call for the first month and then call every 6 months after.
   - For females of child bearing potential: Must call for the first month and then every month after.

Prescribing Revlimid REMS® program

- Celgene Medical Affairs Operations will activate the study with Biologics upon receipt of all required regulatory documents.
- Biologics will not dispense or ship Revlimid® prior to Celgene's notification of activation.
- Prescription information MUST BE entered using **the BMT CTN 0702 Revlimid REMS® study specific electronic prescription form**. This form can be found on the BMT CTN SharePoint website (https://bmtctnsp.net)
- **An authorization number** must be on the prescription form at the time of faxing.
- Prescriptions for Revlimid® must be sent to Biologics Clinical Trial Division at the following FAX number: 919-256-0794
- Only a 28-day supply of Revlimid® may be provided per cycle sent to the actual address noted on the **Revlimid REMS® electronic prescription form.**
- **Biologics will verify the authorization number** and complete the patient counseling.

Protocol compliance and drug return

- Patients will be provided with instructions from Biologics with each new dispense on the procedures for return of any un-used Revlimid® capsules. (Patients will be instructed to call the 1-800 number to request a prepaid return envelope as per the commercial drug return procedures)
- Sites may request that patients maintain a diary and/or to bring their bottles in for a pill count at each visit in order to review "**patient compliance**." However, they are not responsible for "**drug accountability**."

IMPORTANT INFORMATION ABOUT Revlimid REMS®

- To avoid fetal exposure REVLIMID®(lenalidomide) is only available under a special restricted distribution program called Revlimid REMS®
- Only prescribers registered with Revlimid REMS®can prescribe REVLIMID®(lenalidomide)
- Only Revlimid REMS®contract pharmacies can dispense REVLIMID®(lenalidomide)
- In order to receive REVLIMID® (lenalidomide), patients must enroll in RevAssist®and agree to comply with the requirements of the Revlimid REMS®program
- Information about REVLIM® (lenalidomide) and the Revlimid REMS®program can be obtained by calling the Celgene Customer Care Center toll-free at 1-888-423-5436, or at www. REVLIMID.com

How to Fill a REVLIMID® (lenalidomide) Prescription

1. Healthcare provider (HCP) instructs patient to complete patient survey
2. HCP completes survey
3. HCP completes patient prescription form
4. HCP obtains Revlimid REMS®authorization number
5. HCP provides authorization number on patient prescription form
6. HCP faxes form, including prescription
7. HCP advises patient that a representative from a RevAssist® contract pharmacy will contact them
8. Revlimid REMS® contract pharmacy conducts patient education
9. Revlimid REMS® contract pharmacy calls for confirmation number
10. Revlimid REMS® contract pharmacy ships REVLIMID® to patient with the FDA-approved MEDICATION GUIDE

APPENDIX F

LENALIDOMIDE INFORMATION SHEET

APPENDIX F

LENALIDOMIDE INFORMATION SHEET

This information sheet is current as of June 24, 2009. A current information sheet will be given with your supply of lenalidomide. **FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES**

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. 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 thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects.

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

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during dose interruptions of lenalidomide
     - for 28 days after stopping lenalidomide
   - **Stop taking lenalidomide if you become pregnant during lenalidomide treatment**
   - **Do not breastfeed while taking lenalidomide**
   - **You must have pregnancy testing done at the following times**
     - within 10 – 14 days and again 24 hours prior to the first dose of lenalidomide
     - 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 lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide

- during dose interruptions of lenalidomide
- and for 28 days after stopping lenalidomide

- Female partners of males taking lenalidomide should be advised to call their own physician right away if they get pregnant.
- Study doctors, healthcare providers and patients should report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation at 1-888-423-5436.

If you are a male:
It is not known if lenalidomide passes into semen.

- Male patients, including those who have had a vasectomy, must use a latex condom during sexual intercourse with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - for 28 days after you stop taking lenalidomide
- **Male patients should not donate sperm or semen** while taking lenalidomide and for 28 days after stopping lenalidomide.

2. **Lenalidomide may cause a reduction in the number of white blood cells and platelets.** This can lead to increased risk of infection and bleeding. You may need a blood transfusion or certain medicines if your blood counts drop too low. You will have blood tests done as part of the clinical research trial in which you are participating. This is discussed in the informed consent document.

3. **Lenalidomide may cause an increased chance for blood clots in the veins and in the lungs.** Call your study doctor or get emergency medical care right away if you get the following signs or symptoms:
   - shortness of breath
   - chest pain
   - arm or leg swelling

4. **Lenalidomide restrictions in sharing lenalidomide and donating blood:**
    - **Do not share lenalidomide with other people**
    - **Do not give blood** while you take lenalidomide and for 28 days after stopping lenalidomide
    - You will get no more than a 28-day supply of lenalidomide at one time

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

APPENDIX G

HUMAN SUBJECTS

APPENDIX G

HUMAN SUBJECTS

Subject Consent

A conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principle investigator or other designated physician. All potential risks associated with the use of high-dose melphalan, TBI, and immunosuppressive drugs should be discussed as objectively as possible. It should be explained that patients offered this protocol have advanced MM with life expectancy of no more than several years with conventional treatments. Furthermore, it should be explained that the patient would be likely to benefit in terms of disease control and prolongation of survival from an autologous transplant alone, but would likely relapse from the disease. In addition, the risk of conventional allogeneic transplant for MM should be described.

The procedure for collecting peripheral blood mononuclear cells and toxicities of G-CSF will be explained to the donor. The donor should be counseled as to the risks of treatment with G-CSF and be informed that leukapheresis at several time points will be necessary. Informed consent from the donor and patient will be obtained using a form approved the Institutional Review Board of the institution enrolling the patient.

1. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

2. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of MM in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

3. Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The

investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

4. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

5. Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. 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).

6. Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

7. Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

APPENDIX H

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

APPENDIX H

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0:\theta=\theta_o$ versus $H_1:\theta=\theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1)/f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B < 1 < A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta=\theta_0$, and of accepting H_0 when $\theta=\theta_1$, respectively, and the expected sample size $E(N\mid\theta_j)\equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject}H_0)\le\alpha$ and $\Pr_1(\text{reject}H_0)\le\beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2,...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1(>\theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A=(1-\beta)/\alpha$ and $B=\beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1)=(A^{h(\theta)}-1)/(A^{h(\theta)}-B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int(f(x;\theta_1)/f(x,\theta_2))^{h(\theta)}f(x;\theta)dx=1$.

The formula $E(N;\theta)=[[(1-O(\theta)]\log A+O(\theta)\log B]/E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N)\approx[E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of TRM at 180 days is less than or equal to 5% versus the alternative hypothesis that it is greater than or equal to 5%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 10%, and that the test provide 90% power to reject the null hypothesis under a specified alternative that the true rate is 10%. A maximum sample size of 250 patients will be permitted.

Let us assume that the survival times, $T_1, T_2, ..., T_n$, are completely observed (uncensored) and are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 180-day survival rate of 95% translates into a mean survival of 9.747 years ($\theta_0 = .1026$), and 90% translates into a mean survival of 4.746 years ($\theta_1 = .2107$).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0 : \theta = \theta_o = .1026$ versus $H_1 : \theta = \theta_1 = .2107$. However, since the log-likelihood ratio for the exponential, $\log\prod_i^n f(x_i;\theta_1) - \log\prod_i^n f(x_i,\theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ. Thus the SPRT is a one-sided level .10 test of a composite null ($H_0 : \theta \le \theta_o = .1026$) versus a composite alternative ($H_1 : \theta \ge \theta_o = .2107$), with power of $1-\beta = .90$ at the selected alternative $\theta = \theta_1 = .2107$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0) = 0.150$, and intercepts $\log A/(\log\theta_1 - \log\theta_0) =$ 3.05 and $\log B/(\log\theta_1 - \log\theta_0) =$ -3.05 for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the current sample size, *n*, is plotted against the cumulative sum of failure times. When this graph crosses the upper boundary, the null hypothesis is rejected.

The maximum sample size of 250 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 250 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 250 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for TRM is constant over the first 180 days post-transplant, and we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a

clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 180 day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, $T_1, T_2, ..., T_n$, with censored failures times, $x_1, x_2, ..., x_n$, and the current sample size, n, with the number of observed failures, d.

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 250 patients to the study, and that the final analysis takes place 180 days after the last patient is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s, ranging from 0 to 3 years 180 days, the number of observed failures, *d(s)*, is plotted against the sum of observed time on study, $\sum_i^n X_i(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the upper boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 180-day TRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in TRM-free survival at Day 180 from 95% to 90%, with type I and II errors of 10% and 10%. Since only the upper boundary is used for monitoring, the continuation region of the test was bounded above by a line with a slope of 0.150 and intercept of 3.05. In our example, the sample size is large enough that the reduction in power due to truncation of the test is negligible compared to the increase in power because the modified SPRT, lacking a lower boundary, cannot stop early to "accept" the null hypothesis. In order to maintain type I error, we raise the upper boundary to make it harder to cross. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of 4.02, corresponding to setting parameters α and β to 10% and 10%, result in empirical type I and II error rates of 10% and 10%.

Table H-1 Operating Characteristics of Sequential Testing Procedures from a Simulation Study with 100,000 Replications

True 180-Day Rate	**5%**	**10%**
Probability Reject Null	0.095	0.903
Mean Month Stopped	41.0	20.2
Mean # Endpoints in 180 days	11.8	11.6
Mean # Patients Enrolled	240.8	135.4

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of TRM on or before Day 180 was 5%, the test crossed the lower boundary in 9484 of 100,000 replications, for an estimated type I error rate of 9.5%. When the true rate of TRM on or before Day 180 was 10%, the test failed to cross the boundary in the in 9742 of 100,000 replications, for an estimated type II error rate of 9.7%. In this setting, on average, the boundary will be crossed at 20.2 months.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 180 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 180 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 180 days were high, the exponential test would reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.

APPENDIX I

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DESIGN

APPENDIX I

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease.

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

APPENDIX J

FACT/GOG NEUROTOXICITY QUESTIONNAIRE

APPENDIX J

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

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

APPENDIX K

ADVERSE EVENTS

APPENDIX K

ADVERSE EVENTS

Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms. The calendar-driven forms are the Toxicity, Neurotoxicity Assessment Tool and Hem/Chem Forms. Event-driven forms include hospitalization, death, infection, thromboembolism forms and adverse event forms, also referred to as Individual Case Safety Report (ICSR). Selected expected serious AEs and grade 3-4 unexpected AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 require expediting reporting with an ICSR. Additionally for selected AEs collected in calendar-driven form (Table K-3) will require expedited reporting through an ICSR, if they fulfill criteria for serious AE and occur after the administration of bortezomib or lenalidomide. Refer to Chapter 4 regarding reporting of SPMs and other reporting requirements.

TABLE K-1: EXPECTED AEs FOR BMT CTN 0702 BY ORGAN SYSTEM

Adverse Event	Collection Form
ALLERGY/INFUSION[1]	
Allergic Reaction	Toxicity Form
Angioedema	Toxicity Form
Cardiac Arrhythmia	Toxicity Form
Chest Pain	RVD Consolidation Regimen and Toxicity Forms
Chills/Rigors	Toxicity Form
Fever	Toxicity Form
Injection site irritation, pain or phlebitis	RVD Consolidation Regimen and Toxicity Forms
Hypoxia	Toxicity Form
Vomiting	Toxicity Form
AUDITORY	
Hearing loss	Toxicity Form
Tinnitus	Toxicity Form
BLOOD	
Anemia	Hem/Chem Form
Eosinophilia	Hem/Chem Form
Lymphopenia	Hem/Chem Form
Neutropenia	Hem/Chem Form
Thrombocytopenia	Hem/Chem Form
CARDIAC	
Atrial Fibrillation	Toxicity Form
Atrial Flutter	Toxicity Form
Cardiac Arrhythmia	Toxicity Form

Adverse Event	Collection Form
Chest Pain	Toxicity Form
Hypertension	Toxicity Form
Hypotension	Toxicity Form
Peripheral edema	Toxicity Form
CONSTITUTIONAL	
Asthenia (fatigue, lethargy or malaise)	Toxicity Form
Fever (without neutropenia)	Toxicity Form
Insomnia	Toxicity Form
DERMATOLOGY	
Pruritus	Toxicity Form
Rash	Toxicity Form
Urticaria (hives, welts, wheals)	Toxicity Form
ENDOCRINE	
Hypothyroidism	Toxicity Form
GASTROINTESTINAL	
Abdominal pain	Toxicity Form
Constipation	Toxicity Form
Diarrhea	Toxicity Form
Dysphagia	Toxicity Form
Heartburn/dyspepsia	Toxicity Form
Mucositis/stomatitis (functional/symptomatic)	Toxicity Form
Nausea	Toxicity Form
Taste alteration (dysgeusia)	Toxicity Form
Vomiting	Toxicity Form
HEMORRHAGE	
Hemorrhage (GI, GU, respiratory, any site except CNS)	Toxicity Form
METABOLIC/LABORATORY	
Hyperglycemia	Hem/Chem Form
Hyperkalemia	Hem/Chem Form
Hypercalcemia	Hem/Chem Form
Hypoglycemia	Hem/Chem Form
Hypokalemia	Hem/Chem Form
Hyponatremia	Hem/Chem Form
MUSCULOSKELETAL/SOFT TISSUE	
Arthralgia	Toxicity Form
Bone Pain	Toxicity Form
Muscle cramps/spasms	Toxicity Form
Muscle weakness, generalized or specific area (not due to neuropathy) - Whole body/generalized	Toxicity Form
Myalgia	Toxicity Form

Adverse Event	Collection Form
NEUROLOGY	
Dizziness	Toxicity Form
Neuropathy: sensory /motor	Neurotoxicity Assessment Tool and Toxicity Form
Somnolence/depressed level of consciousness	Toxicity Form
Syncope (fainting)	Toxicity Form
OCULAR/VISUAL	
Vision-blurred vision	Toxicity Form
Conjunctivitis	Toxicity Form
Conjunctival hemorrhage	Toxicity Form
PULMONARY/UPPER RESPIRATORY	
Cough	Toxicity Form
Dyspnea	Toxicity Form
Hemoptysis	Toxicity Form
Hypoxia	Toxicity Form

[1] Infusion event related to stem cell infusion or allergies to oral drugs are collected on the Toxicity Form; Infusion events related to bortezomib administration will be collected on the RVD Consolidation Regimen and Toxicity Form .

TABLE K-2: SERIOUS ADVERSE EVENTS THAT REQUIRE EXPEDITED REPORTING BY INDIVIDUAL CASE SAFETY REPORTS (ICSR)[1]

Adverse Event	Seriousness or Capture Method[1]	Collection Form
ALLERGY/IMMUNOLOGY		
Anaphylactic reaction	SAE	ICSR
CARDIAC		
Asystole	SAE	ICSR
Atrial Ventricular Block	SAE	ICSR
Congestive Heart Failure	SAE	ICSR
Myocardial Infarction	SAE	ICSR
Pericarditis	SAE	ICSR
Pericardial disease	SAE	ICSR
Pericardial effusion (including tamponade)	SAE	ICSR
Prolongation of QTc interval	SAE	ICSR
Sinus Bradycardia	SAE	ICSR
Supraventricular Tachycardia	SAE	ICSR
Ventricular Tachycardia	SAE	ICSR
Pulmonary hypertension	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
COAGULATION		
Disseminate intravascular coagulation (DIC)	SAE	ICSR
DERMATOLOGY		
Erythema multiforme (toxic epidermal necrolysis)	SAE	ICSR
Sweet's Syndrome (acute neutrophilic dermatosis)	SAE	ICSR
Pyoderma gandrenosum	SAE	ICSR
Vasculitis	SAE	ICSR
ENDOCRINE		
Hyperthyroidism	SAE	ICSR
GASTROINTESTINAL		
Ileus (functional obstruction of bowel, i.e., neuroconstipation)	SAE	ICSR
GI Perforation	SAE	ICSR
Diverticulitis	SAE	ICSR
Ischemic bowel	SAE	ICSR
HEMORRHAGE		
Central Nervous system	SAE	ICSR
HEPATOBILIARY/PANCREAS		
Liver dysfunction/failure (Clinical - CTCAE)	SAE	ICSR
Pancreatitis	SAE	ICSR
NEUROLOGY		
Neurology – Peripheral neuropathy [4]	SAE	ICSR
Neuropathy: Motor [4]	SAE	ICSR
Neuropathy: Sensory [4]	SAE	ICSR
Syncope (fainting)[2]	SAE	ICSR
CNS ischemia	SAE	ICSR
Coma	SAE	ICSR
Cranial palsy	SAE	ICSR
Seizure	SAE	ICSR
Spinal cord compression	SAE	ICSR
Brain Edema	SAE	ICSR
Encephalopathy	SAE	ICSR
Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) or (Leukoencephalopathy radiographic findings)	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
PULMONARY/UPPER RESPIRATORY		
Acute Respiratory Distress Syndrome	SAE	ICSR
Alveolar Hemorrhage	SAE	ICSR
Pleural effusion (non-malignant)	SAE	ICSR
Pneumonitis/Pulmonary Infiltrates (absence of infection)	SAE	ICSR
Pulmonary Hypertension	SAE	ICSR
RENAL/GENITOURINARY		
Renal failure	SAE	ICSR
SYNDROMES		
Tumor flare	SAE	ICSR
Tumor lysis syndrome	SAE	ICSR
VASCULAR		
Acute vascular leak syndrome	SAE	ICSR
DEATH		
Sudden death	SAE	ICSR
OTHER		
Second malignancies	SAE	ICSR

[1] Serious Adverse events are defined by the 21 CFR (312.32a): AE that results in death, requires hospitalization, persistent or significant disability or incapacity, congenital anomaly, that is life threatening or considered as medically important.

TABLE K-3: EXPECTED ADVERSE EVENTS THAT ARE CAPTURED ON CALENDAR OR EVENT DRIVEN FORMS AND WILL REQUIRE EXPEDITED REPORTING IF THEY MEET SERIOUS ADVERSE EVENT CRITERIA AND OCCUR AFTER THE INITIATION OF BORTEZOMIB OR LENALIDOMIDE

Adverse Event	Seriousness or Capture Method[1]	Collection Form
AUDITORY/EAR		
Hearing loss[2]	SAE	ICSR
CARDIAC		
Atrial fibrillation [2]	SAE	ICSR
Atrial flutter[2]	SAE	ICSR
COAGULATION		
Deep vein thrombosis[3]	SAE	ICSR
Pulmonary emboli[3]	SAE	ICSR
HEMORRHAGE		
Hemorrhage, Gastrointestinal	SAE	ICSR
Hemorrhage, Pulmonary	SAE	ICSR

Adverse Event	Seriousness or Capture Method[1]	Collection Form
METABOLIC/LABORATORY		
Elevation of ALT ≥ 2.5x ULN[2]	SAE	ICSR
Elevation of AST ≥2.5x ULN[2]	SAE	ICSR
Elevation of Bilirubin ≥ 3x ULN[2]	SAE	ICSR
MUSCULOSCELETAL/SOFT TISSUE		
Muscular weakness [2]	SAE	ICSR
NEUROLOGY		
Neurology – Peripheral neuropathy [4]	SAE	ICSR
Neuropathy: Motor [4]	SAE	ICSR
Neuropathy: Sensory [4]	SAE	ICSR
Syncope (fainting)[2]	SAE	ICSR
OCULAR/VISUAL		
Vision – Blurred vision[2]	SAE	ICSR
PAIN		
Pain – Neuralgia [4]	SAE	ICSR
INFECTION		
Febrile neutropenia[5]	SAE	ICSR
DEATH		
Sudden death	SAE	ICSR
OTHER		
Second malignancies	SAE	ICSR

[1] Serious Adverse events as defined by the 21 CFR (312.32a): AE that results in death, requires hospitalization, persistent or significant disability or incapacity, congenital anomaly, that is life threatening or considered as medically important.

[2] AEs also captured in Toxicity or Hem/Chem forms and collected on a protocol-defined schedule. If these specific AEs fulfill the 21 CRF criteria for SAE and occur during administration of bortezomib or lenalidomide, an ICSR will be required.

[3] Deep vein thrombosis and pulmonary emboli will be collected on event-driven forms. If these thromboembolic events fulfill the 21 CFR criteria for SAE and occur during administration of bortezomib or lenalidomide, an ICSR will be required.

[4] Peripheral neuropathy (including neuropathy motor and neuropathy sensory) and neuropathic pain (neuralgia) will be collected on a separate calendar-driven form during lenalidomide and bortezomib administration. If these specific neurologic AEs fulfill the 21 CFR criteria for SAE and occur during administration of bortezomib or lenalidomide, an ICSR will be required.

[5] Febrile neutropenia will be collected on the event-driven Infection Form. If febrile neutropenia fulfills the 21 CFR criteria for SAE and occurs during administration of bortezomib or lenalidomide, an ICSR will be required.

APPENDIX L

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

APPENDIX L

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

BMT CTN Core and Affiliate Centers should refer to Chapter 4 of the protocol for patient enrollment procedures.

Flow Document for U.S. Cooperative Group Centers Participating on the BMT CTN 0702 Protocol

Step 1: Document Access

1. Download protocol and regulatory documents (including BMT CTN 0702 Affiliate Center Application Form) from CTSU website https://www.ctsu.org/

Step 2: Pre-Approval (see Table L-1 at the end of this appendix)

1. Fax the Affiliate Center Application Form to the BMT CTN Data and Coordinating Center (DCC)/EMMES at 240-306-0963.

2. Receive email from the BMT CTN 0702 Protocol Coordinator confirming receipt of Application Form.

3. Fax the draft 0702 consent form to the BMT CTN 0702 Protocol Coordinator for review prior to submitting the protocol to your local IRB.

4. Note: The BMT CTN 0702 Protocol Coordinator will inform you of your site's pre-approval. The CTSU Regulatory Office will be copied on this correspondence.

Step 3: Regulatory Document Submission (See Table L-2 at the end of this appendix)

1. Complete and submit documents in Table L-2 to the CTSU Regulatory Office.

2. Note: The CTSU Regulatory Office will notify the BMT CTN DCC once your site has fulfilled all requirements in Table L-2. However, your site's approval will remain pending in the CTSU Regulatory Support System (RSS) until completion of BMT CTN DCC requirements in Table L-3.

Step 4: BMT CTN DCC Requirements (see Table L-3 at the end of this appendix)

1. BMT CTN requirements for site approval are listed in Table L-3.

2. Your site will be given information for the AdvantageEDC and GlobalTrace on-line training. Your site will also be contacted to schedule a Pre-Study Initiation Conference Call.

3. The BMT CTN DCC will notify the CTSU Regulatory Office when all requirements are fulfilled and your site status will be updated to 'approved' in RSS. Your site will then be able to enroll patients.

Step 5: Patient Enrollment

1. Sites will contact the CTSU Patient Registration Desk to facilitate enrollment of patients through the CTSU Oncology Patient Enrollment Network (OPEN).

Step 6: Data Submission

1. Sites will submit case report forms using the BMT CTN AdvantageEDC system.

CTSU Procedures for Participation in Protocol BMT CTN 0702

INVESTIGATOR / RESEARCH ASSOCIATE REGISTRATION

1. Obtaining a CTEP-IAM account (Investigators and Associates)

All participating investigators and research staff must be registered members of the CTSU. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system. To register:

- Go to the CTSU public web page at www.ctsu.org and click on the Register tab on the upper right of your screen and follow links to the CTEP-IAM application, OR, go directly to https://eapps-ctep.nci.nih.gov/iam/ and click on the "New Registration" link on the left hand side of your screen and click on "Request New Account".
- Complete CTEP-IAM application instructions.
- You will receive an email from the CTSU providing the status of your application within 2 to 3 business days. Once you receive your email from the CTSU, you may use your new CTEP-IAM username and password to access the CTSU Members website.

2. Obtaining an NCI Investigator number (Investigators Only)

Before the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV [signed and dated], Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU public website (logon to www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

SITE REGISTRATION

The CTSU Regulatory Office and BMT CTN DCC will share documentation and information regarding the status of all registering sites and their progress towards site regulatory approval.

Check your site's registration status by querying the RSS site registration status page of the CTSU website.

- Go to www.ctsu.org
- Enter your CTEP IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Step 1: Document Access

Using your CTEP-IAM account username and password, download protocol and regulatory documents from the CTSU website:

- Go to https://www.ctsu.org/
- Enter your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- The protocol browser uses a "tree-based navigation" structure that allows users to browse through the available protocols within the CTSU by using the drill-down capability of the tree.
- Drill down By Lead Organization (BMT CTN) or By Cancer Type (Multiple Myeloma) or By Study Type (Cancer Treatment or Phase III) and select trial #0702

Step 2: Site Pre-Approval by BMT CTN (see Table L-1 at the end of this appendix)

Before submitting this study to your local IRB, your site must first be pre-approved for participation by the BMT CTN:

1. Download the BMT CTN Protocol #0702 Affiliate Center Application form from the site registration forms section of the BMT CTN 0702 page of the CTSU website. Contact the BMT CTN 0702 Protocol Coordinator at EMMES with questions related to study-specific documents.

2. Complete the Affiliate Center Application and fax, as indicated on the form, to the BMT CTN Data and Coordinating Center (DCC)/EMMES.

3. Once you receive notification from the BMT CTN 0702 Protocol Coordinator that your center has been pre-approved, fax or email the 0702 draft informed consent form to the BMT CTN 0702 Protocol Coordinator at EMMES. The BMT CTN DCC will also inform the CTSU Regulatory Office when your site is pre-approved.

4. The BMT CTN DCC will notify you when you are able to proceed with Site Registration.

Step 3: Regulatory Document Submission (see Table L-2 at the end of this appendix for requirements)

1. Download forms listed in Table L-2 from the site registration forms section of the BMT CTN 0702 page on the CTSU website.

2. Mail, FAX, or E-mail completed forms **along with the other required items listed in Table L-2** to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone - 1-866-651-2878
FAX – 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org

3. The CTSU Regulatory Office will notify the BMT CTN DCC when your site has fulfilled all requirements in Table L-2. However, your site's approval will remain pending in the CTSU Regulatory Support System (RSS) until completion of BMT CTN DCC requirements in Table L-3.

Step 4: BMT CTN DCC Additional Trainings and Requirements (Table L-3)

1. BMT CTN requirements for site approval are listed in Table L-3.

2. Your site will be given information for the AdvantageEDC and GlobalTrace online training. Your site will also be contacted to schedule a Pre-Study Initiation Conference Call.

3. The BMT CTN DCC will notify the CTSU Regulatory Office when all requirements are fulfilled and your site status will be updated to 'approved' in RSS.

PATIENT REGISTRATION

Contact the CTSU Patient Registration Office at 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. Registration hours are between 9:00 a.m. and 5:00 p.m. Eastern Time, Monday-Friday. Registrations received after 5:00 p.m. Eastern Time will be handled the next business day. For immediate registration needs (e.g. enrollments that must be completed within approximately one hour or other extenuating circumstances) call the Registrar's cell phone at 1-301-704-2376.

Complete the following forms:
- CTSU Patient Enrollment Transmittal Form
- Eligibility Form

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039. Registration hours are between 9:00 a.m. and 5:00 p.m. Eastern Time, Monday-Friday. Registrations received after 5:00 p.m. Eastern Time will be handled the next business day. The CTSU Patient Registrar will confirm that the investigator and the site information and enrollment documents provided comply with all regulatory requirements. The registrar will contact the study site to resolve any discrepancies. The CTSU Patient Registrar will conduct the enrollment using the Oncology Patient Enrollment Network (OPEN) Portal System and will convey the patient ID and randomization assignment back to the enrolling site.

DATA SUBMISSION AND QUALITY ASSURANCE

The BMT CTN DCC will grant user rights to the AdvantageEDC^{SM} system for performing data submission and adverse event reporting. (Note: users must be certified by the DCC prior to assignment of rights. Refer to the AdvantageEDC webcast and practicum information in Table L-3 for certification requirements).

The study protocol and supporting materials are posted on the 0702 page of the CTSU website (www.ctsu.org). CTEP-IAM username and password are required for document access. All study data must be entered using the BMT CTN AdvantageEDC system. Hard copies of study data forms will not be

accepted by the BMT CTN DCC. Data validation and quality assurance will also be managed via AdvantageEDC.

ADVERSE EVENT REPORTING

Sites will assess adverse events in accordance with the guidelines outlined in the protocol. Adverse event reporting will be conducted through an expedited AE reporting system within AdvantageEDC.

Sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Table L-1: Documents Collected by BMT CTN Data and Coordinating Center (DCC)/EMMES for Site Pre-Approval

1. Affiliate Application	**For Site Pre-Approval:** Application for participation as an Affiliate Center in the BMT CTN. The Affiliate Application may be downloaded from the site registration documents section of the 0702 page of the CTSU members' website. The Affiliate Application must be approved prior to centers submitting any other documentation for protocol 0702
2. Preview of consent form	A copy of the consent form for review/approval prior to IRB submission

Table L-2: Documents Collected by CTSU Regulatory Office for Site Registration

1. Evidence of approved autologous transplant center status	One of the following is required: -FACT credentialed **autologous** transplant center -NMDP-approved **autologous** transplant center -Cooperative Group-approved **autologous** transplant center
2. BMT CTN Financial Disclosure Form	Signed Financial Disclosure for Principal Investigator for protocol 0702
3. Lab Normals	High and low normal lab values valid at the time of initial center approval.
4. CLIA and/or CAP certification	Valid at the time of initial center approval
5. CTSU IRB/Regulatory Approval Transmittal Form	Standard CTSU cover sheet
6. CTSU IRB Certification Form	Standard form to document local IRB approval
7. Final Approved Consent Form	A copy of the IRB-approved Informed Consent Form for protocol 0702
8. FDA 1572 Form	Signed FDA Form 1572 for Principal Investigator
9. PI CV	CV for 0702 Principal Investigator
10. Study Roster	A listing of names, phone numbers and email addresses of staff participating on protocol 0702, including PI, Clinic Coordinator, Data Coordinator, Lab Coordinator and Pharmacist
11. EMINENT Clinical Site Contact Form	A copy of the EMINENT Services Clinical Site Contact Information Form

Table L-3: BMT CTN DCC Additional Requirements for Site Approval

1. AdvantageEDC Webcast Training	AdvantageEDC (electronic data capture system) online training is required by each staff member responsible for enrolling patients and completing supplementary follow-up forms. Email bmtedc@emmes.com for training materials.
2. AdvantageEDC Practicum	Mandatory completion of one AdvantageEDC Practicum by each staff member that completed on-line training
3. GlobalTrace Webcast Training	GlobalTrace (specimen shipping system) online training is required by each staff member responsible for shipping samples. Email bmtedc@emmes.com for training materials.
4. Pre-Study Site Initiation Conference Call/Visit	Mandatory pre-study site initiation call/visit to discuss protocol 0702

APPENDIX M

OBESITY AND MULTIPLE MYELOMA ANCILLARY STUDY

APPENDIX M

OBESITY AND MULTIPLE MYELOMA ANCILLARY STUDY

MM is increasingly being recognized as an obesity-related disease, with several recent studies documenting increased risk of developing monoclonal gammopathy and MM in overweight and obese patients. Obesity by itself can be a serious morbidity, resulting in numerous adverse health effects. Additionally, obesity is associated with a pro-inflammatory state and increase circulating levels of cytokines, including interleukin-6 (IL6), crucial to the pathogenesis of MM. While knowledge of the adverse health effects of obesity raises concern that high-dose therapy and autologous HCT might not be well tolerated in obese patients, retrospective analysis of 1087 patients undergoing transplants showed no increased risk for disease relapse or mortality in overweight and obese patients (personal communication, D Vogl et al). Additional retrospective analysis of patients undergoing hematopoietic cell transplant for lymphoma and acute myeloid leukemia showed no increased risk for transplant related mortality or disease relapse in overweight and obese patients. Most analysis that associate obesity with outcome are retrospective and utilize body surface area as a surrogate of obesity. The BMT CTN 0702 trial allows a prospective approach for examining the role of obesity in MM outcomes. Additionally, incorporating anthropomorphic measurements to BMI may better define obesity for the analyses. Waist and hip circumference ratios have been associated with increased mortality among older patients without malignancy.

This ancillary study has the objective to correlate the anthropomorphic measures such as body mass index (BMI) and waist to hip ratio, with post transplant outcomes among patients enrolled in the BMT CTN 0702.

Variables
Variables for the ancillary study will be the same as the ones collected in parent trial. Additional variables to be analyzed in this ancillary study include:

- Body mass index
- Waist and hip circumference
- Waist to hip ratio
- Melphalan dose
- CD34+ dose

Outcomes and Preliminary Analytical Plan
The following endpoints will be analyzed for this ancillary study.

- Progression-free survival
- Overall survival
- Rates of VGPR or better response

- Rates of ≥grade 3 toxicities and infectious complication
- Incidence of transplant-related mortality
- Incidence of myeloma progression

Additional outcomes not analyzed in the parent trial:

1. Neutrophil after a single autologous HCT: defined as absolute neutrophil count >500/μ" for three consecutive days. Death prior to neutrophil recovery will be considered a competing risk for this outcome.
2. Platelet engraftment after a single autologous HCT: defined as achievement of a continued platelet count than 20,000/μL without transfusion support. Death prior to platelet recovery will be considered as a competing risk for this outcome.

Hematologic recovery analysis will incorporate graft cell dose and the weight status prior to transplant.

Time points for Anthropomorphic Measurements
Patients will be measured at three time points during the first year of the BMT CTN 0702 trial: baseline, prior to maintenance and at one year after randomization to BMT CTN 0702. Patients who discontinue protocol-specified therapy for any reason, will not be required to have subsequent anthropomorphic measurements taken.

Anthropomorphic Measurement
Assessment of anthropomorphic measurements will be standardized by the following:

1. Measurements will be taken by medical personnel in accordance with the techniques described below in the "Assessment of Anthropomorphic Measures."
2. It is preferred that each institution designate two personnel who assess anthropomorphic measurements.
3. Measurements should be taken in accordance with guidelines below.

Height – measured without shoes, recorded in centimeters (cm) and meters (m)

Weight – measured without shoes and in light clothing, recorded in kilograms (kg)

Body Mass Index[1]
Height and weight should be measured without shoes and in light clothing or hospital gown by medical personnel.

Self-reported height is acceptable only if the patient is unable to stand.

Body mass index (BMI) = weight (kg) / height $(m)^2$

Waist and Hip Measurements
Waist and hip measurements should be taken in underwear or with light clothing or hospital gown by medical personnel, and should be recorded in centimeters.

Measure waist at the point mid-way between the lower ribs and the iliac crest, with patient standing and exhaling gently.

Measure hips at the widest hip circumference with patient standing – see illustration below.

APPENDIX N

PRIMeR ANCILLARY STUDY

APPENDIX N

Prognostic Immunophenotyping in Myeloma Response
Prognostic Immunophenotyping in Myeloma Response (PRIMeR)

Principal Investigators
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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
RHL107213A

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[5] Memorial Sloan-Kettering Cancer Center
[6] The EMMES Corporation
[7] National Marrow Donor Program
[8] Ohio State University
[9] Vanderbilt University
[10] Hackensack University Medical Center

PROTOCOL SYNOPSIS – PRIMeR Ancillary Study Protocol

Prognostic Immunophenotyping in Myeloma Response

Co-Principal Investigators: Marcelo C. Pasquini, MD, MS and Theresa Hahn, PhD

Study Description: This is a laboratory ancillary study to the BMT CTN 0702 (STaMINA) parent clinical trial. Comprehensive immunophenotyping (IP) using a 7-color flow cytometry technique will be performed in bone marrow aspirate samples at three time points during the first year of the STaMINA trial. Two bone marrow evaluations are already scheduled to be collected as part of the STaMINA trial. One additional bone marrow aspirate will be required for the PRIMeR study, which will be collected prior to initiation of maintenance therapy in patients enrolled in the ancillary study.

Primary Objective: The primary objective is to assess the rate of minimal residual disease (MRD) using IP and compare the differences in rates of MRD across treatment arms of the STaMINA trial. Determine whether the rate of undetectable MRD at 1 year after first autologous hematopoietic cell transplantation (autoHCT) differs by treatment arm.

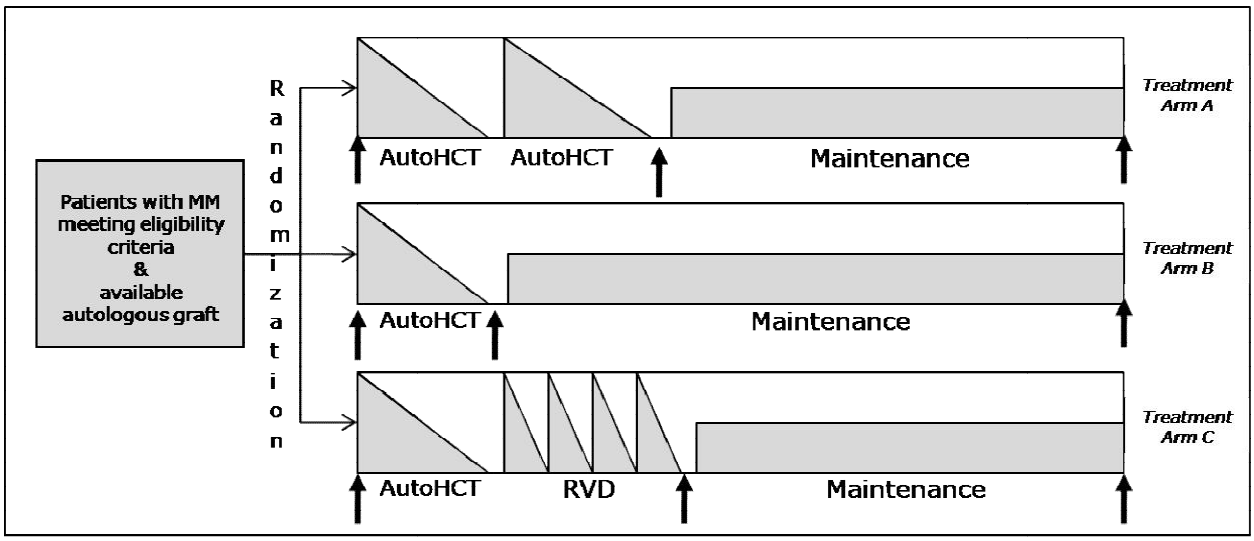
Secondary Objectives: Estimate the probability of converting from detectable to undetectable MRD prior to maintenance, and at 1 year after first autoHCT in each treatment arm of the parent trial. Determine the association between a comprehensive IP and standard clinical and laboratory myeloma response, measure concordance between a basic 4-color IP panel and a comprehensive 7-color IP panel for detection of MRD, assess the impact of MRD status on progression-free and overall survival.

Eligibility Criteria: All STaMINA trial participants who are enrolled are eligible for the PRIMeR ancillary study.

Accrual Objective: 472 patients.

Accrual Period: The estimated accrual period is 2.5 years.

Outline of PRIMeR Ancillary Study



The arrows demonstrate the time points for collection of bone marrow aspirates for immunophenotyping. Bone marrow collection prior to and one year post-randomization to BMT CTN 0702 are already collected as part of the parent trial. Patients enrolled in the PRIMeR study will undergo an additional bone marrow aspiration prior to initiation of maintenance therapy.

1. BACKGROUND AND RATIONALE

1.1 Background

MM is an incurable plasma cell malignancy with approximately 20,580 newly diagnosed cases and 10,580 deaths in 2009 in the U.S.(1) Median age at diagnosis is >70 years; men and African-Americans are disproportionally affected.(2) Standard treatment has included autoHCT for more than a decade,(3) after it was demonstrated to prolong survival compared to conventional chemotherapy.(4) MM is the most common indication for autoHCT in North America and Europe.(5, 6) The advent of novel agents (thalidomide, lenalidomide, and bortezomib) has improved disease responses and long-term survival outcomes.(7) AutoHCT continues to be an important part of MM therapy and its combination with novel agents may maximize disease response.(3) Three different approaches that combine autoHCT with novel agents for treatment of MM are under investigation in a multi-center randomized trial sponsored by the BMT CTN supported by NCI and NHLBI.

The BMT CTN 0702 or Stem cell Transplant for multiple Myeloma Incorporating Novel Agents (STaMINA) Clinical Trial, evaluates 3 different post-autoHCT interventions: A) a second autoHCT followed by lenalidomide maintenance, B) maintenance lenalidomide only, C) 4 cycles of chemotherapy including lenalidomide (Revlimid®), bortezomib (Velcade®), and dexamethasone (RVD) followed by lenalidomide maintenance (Figure 1). All patients receive maintenance therapy with lenalidomide for three years. The primary objective of the STaMINA

trial is the comparison of 3-year PFS between treatment arms. This trial will enroll 750 patients from about 50 transplant centers in the U.S. Accrual initiated in June of 2010.

1.2 Traditional Disease Staging and Response to Therapy for MM

MM is characterized by malignant plasma cells which proliferate abnormally, most commonly in the bone marrow and produce monoclonal immunoglobulin heavy chains (IgG, IgA, IgM, IgD, IgE) and/ or light chains (kappa, lambda). MM is a heterogeneous disease with variability in the subtype of monoclonal protein involved (heavy and light chain, light chain only or non-secretory), disease manifestations at diagnosis, and the rate of disease progression. MM can range from indolent disease not requiring therapy to rapidly progressive disease with organ failure and significant morbidity.(8) Symptomatic MM is an indication for therapy and includes the presence of anemia, hypercalcemia, any degree of renal insufficiency or lytic bone lesions.(9) Monoclonal proteins are important for the diagnosis and evaluation of disease response in secretory MM. Monoclonal proteins in the urine and serum can be identified by immunofixation electrophoresis (IFE) and quantified by protein electrophoresis (UPEP or SPEP). Changes in monoclonal protein concentrations are used to determine response to therapy or disease progression (Table 1.2). Other assessments include evaluation of plasma cell concentration in the bone marrow and whether there are evidence of new lytic bone lesions or plasmacytomas. The level of response is associated with longer time to disease progression,(10) making disease assessment an important measurement of treatment success. CR prior to the use of novel agents were uncommon and responses were divided into several disease states, including stable, minimal, partial, very good partial and complete responses. Improvements in therapy and methodologies to detect monoclonal proteins allowed better stratification of good responses. Patients fulfilling the definition of CR with normal UPEP/SPEP and bone marrow $\leq$ 5% plasma cells may still have disease detected by IFE, which is defined as a near CR (nCR).(10, 11) Similarly, utilization of sensitive serum free light chain (sFLC) assays may detect remaining imbalances of kappa and lambda concentrations suggestive of persistent disease in patients who were otherwise deemed to be in CR.(12)

TABLE 1.2 - LEVEL OF RESPONSE

Response	IFE	SPEP/UPEP	K/L free light chain ratio	BM Plasma cells
Stringent CR (sCR) *	Neg	Neg	**Normal**	**<5%**
Complete Response (CR)	Neg	Neg	**Abnormal**	**<5%**
Near CR (nCR) (10, 11)	**Pos**	Neg	Any	**<5%**
Very Good PR (VGPR)	**Pos**	$\geq$90% reduction (serum) & <100 mg/24 hours (urine)	Any	Any
Partial Response (PR)	**Pos**	$\geq$50% reduction (serum) & <200 mg/24 hours (urine)	Any	Any

Table 1.2: Level of response according to the International Myeloma Working Group (IMWG) criteria. (16) nCR is not part of the IMWG criteria, but frequently used in clinical trials to further characterize the spectrum of good responses. * sCR also requires no clonal cells in the bone marrow detectable by immunohistochemistry or immunofluorescence using flow cytometry.

The International Myeloma Working Group definition incorporated this new disease response as stringent CR.(13) The rationale for adding the sFLC ratio to the MM response criteria was to provide a more sensitive and precise indication of CR for use in comparative clinical trials by enabling the detection of small quantities of abnormal proteins in patients with little or no detectable monoclonal protein on SPEP and IFE.(14) However, the utilization of sFLC ratios to evaluate disease response has provoked some controversy. De Larrea, et al., reported that an abnormal sFLC ratio is frequently (73% of CR patients) due to presence of oligoclonal bands as part of normal immune reconstitution after autoHCT and is actually associated with a good prognosis.(15) Singhal et al. demonstrated a high degree of discordance between the serum IFE and the sFLC ratio: 79% of patients with a positive serum IFE had a normal sFLC ratio, whereas only 6% of those with negative serum IFE had an abnormal sFLC ratio, resulting in a sensitivity and specificity for the sFLC ratio compared to the serum IFE of 66% and 69%, respectively.(16) Similarly, Giarin et al., showed discordance between sFLC ratios and IFE in patients who received transplantation, although when using a method that assesses total serum light chain concentration (free and bound), the concordance with IFE was better.(17) Preliminary results by Kumar et al., demonstrated that in patients with a negative IFE after MM therapy, normalization of the sFLC ratio is associated with improved OS.(18) The major value of sFLC assessment is in patients with light chain MM due to lack of sensitivity of electrophoretic methods to detect serum light chains. (19) Conversely, secretory MM with fully assembled immunoglobulins may have normal sFLC ratios in 5% of cases.(20) The IMWG recently updated their guidelines for monitoring sFLC ratios in MM.(21) In summary, as methods to detect circulating protein become more sensitive and treatments more effective, detection of small amounts of protein are a challenge to interpret due to difficulties in discerning imbalances that indicate residual disease versus normal immune reconstitution. This supports the case for MRD methods that focus on detecting the actual malignant clone and not its product (monoclonal proteins).

1.2.1. The Role of Complete Response in MM

Achievement of CR is associated with significantly longer OS and PFS than nCR or PR regardless of the therapy utilized.(4, 22-25) In addition, patients who improve their response after autoHCT enjoy a longer OS and PFS. Hoering, et al., analyzed 231 Total Therapy 1 (TT1), 668 TT2, and 303 TT3 patients for the timing and onset of sCR using the IMWG criteria.(26) Patients who achieved and sustained sCR for 3 years had significantly longer OS than those who did not achieve sCR and those who achieved sCR but relapsed within 3 years.

1.2.2. Detection of MRD in MM Patients

With increased rates of CR with modern MM therapy, there is increasing need for more sensitive evaluations of disease responsiveness and disease burden over time.(27) There are 2 methods for detecting MRD that focus on the malignant MM clone: allele-specific oligonucleotide real time quantitative polymerase chain reaction (ASO-RT-qPCR) and immunophenotyping by flow cytometry (IP). Both methods have similar sensitivity(28) and demonstrated prognostic importance.(29-31) ASO-RT-qPCR can be expensive, time-consuming and is applicable to only about 2/3 – 3/4 of patients due to inability to detect amplifiable malignant clones in all patients.(32) IP can detect 1 myeloma plasma cell in 10,000 normal plasma cells for a sensitivity

of 0.01%, can be used in all MM patients at a fraction of the cost of ASO-RT-qPCR and is much more sensitive than IFE, SPEP and UPEP for detecting residual disease.(32)

1.3. Prognostic Immunophenotyping in MM

While IP is standard practice in leukemia and lymphoma, it is still considered investigational in MM.(32) Two studies have reported the association of IP with PFS and overall survival (OS) in large numbers of uniformly treated patients. Mateo, et al., prospectively analyzed the ability of 7 immunophenotypic markers tested at MM diagnosis to predict PFS and OS in 685 MM patients treated on the GEM2000 protocol (6 alternating cycles of VBCMP and VBAD followed by autoHCT).(33) Pre-autoHCT, response rates to induction therapy were 12% CR, 12% nCR, 70% PR and 6% progressive disease. The day +100 post-autoHCT response rates were 36% CR, 17% nCR, 43% PR and 3% progressive disease. At a median follow-up of 48 months, IP analysis of diagnostic bone marrow samples demonstrated a significantly shorter PFS and OS in patients who were CD19+ or CD28+, but longer OS for CD117+ and no association with other markers. This was the first study to demonstrate that IP in MM is prognostic for survival.

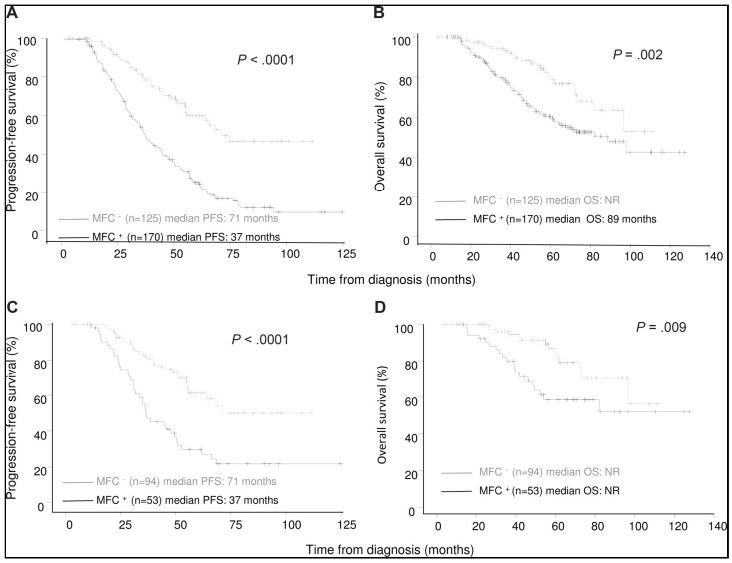


Figure 1.3: MRD positivity is associated with significantly shorter progression-free (panel A) and overall (panel B) survival in all patients and in the subset who achieved a CR to autoHCT (panels C, D). (5)

Paiva, et al., prospectively analyzed the association of PFS and OS with MRD measured using a 4-color IP panel (CD38/CD56/CD19/ CD45) tested at diagnosis and day+100 post-autoHCT in 295 MM patients treated on the GEM2000 protocol.(29) Day +100 post-autoHCT response rates were 50% CR, 14% nCR and 36% PR. At a median follow-up of 57 months, IP analysis demonstrated a significantly shorter PFS and OS in patients who had detectable MRD at day +100 post-autoHCT (Figure 1.3, median PFS 37 vs. 71 months, $p<0.001$; median OS 89 months vs. not yet reached, $p=0.002$). Multivariate analysis demonstrated that detectable MRD and high risk cytogenetics were independently associated with shorter PFS, and detectable MRD and age with shorter OS (Table 1.3). Two studies in fewer (<100) patients confirmed the prognostic value of MM IP for MRD detection after autoHCT and survival outcomes.(30, 31)

There is only one small study comparing MRD detection using IP by treatment. San Miguel, et al., prospectively analyzed 87 MM patients treated with either autoHCT (n=47) or 8 additional cycles of chemotherapy (n=40) after 4 cycles of induction.(31) At day+100 post-HCT, 36% of autoHCT recipients were negative for MRD compared to only 15% of patients 1 month after

completion of 12 cycles of chemotherapy (p=0.04). In patients who achieved a nCR, 51% had MRD detectable by flow cytometry compared to 14% of CR patients who were MRD positive by IP.

TABLE 1.3: RELATIVE RISKS (RR) FOR TREATMENT FAILURE AND OVERALL MORTALITY AT DAY 100 POST TRANSPLANT (5)

Prognostic Factors	**RR**	**p-value**
Treatment Failure		
MRD positive	3.64	<0.01
High risk cytogenetics	1.79	<0.01
Overall Mortality		
MRD positive	2.02	0.02
Age >60 years at diagnosis	1.63	0.04

1.4. Rationale for Study

To date, no studies have evaluated MRD detected by IP in a large MM clinical trial comparing different treatment strategies, and no MRD studies using IP are reported in patients treated with novel agents or HCT. As sCR, CR and nCR rates increase with the use of these novel agents, more sensitive methods for detecting MRD are needed to compare the effectiveness of clearing disease using different treatment strategies. Electrophoretic or sFLC ratio techniques used to detect plasma cell products are valuable to detect disease when there are clear differences between monoclonal and polyclonal immunoglobulins. After treatments which affect all immunoglobulin production, such as autoHCT, detection of residual disease by IFE, SPEP, UPEP and sFLC becomes less precise. IP can complement standard disease assessment tests by detection of the malignant clone and not its product (immunoglobulins). The STaMINA clinical trial offers a unique opportunity to test the utility of MRD assessment by multiparameter flow cytometry in a multi-center, randomized, phase III trial of 3 autoHCT strategies including novel agents. The PRIMeR study will correlate MRD with survival once the STaMINA clinical trial data have matured and the primary analysis of the parent trial is completed. The PRIMeR study has the potential to change clinical practice by providing evidence of the ability of IP to predict long-term survival and guide treatment decisions. In addition, it may show the utility of MRD as a surrogate endpoint for clinical trials, thereby speeding the development of future therapies.

2. STUDY DESIGN

2.1. Study Overview

The study is a laboratory ancillary study that will assess for the presence of minimal residual myeloma through comprehensive IP in bone marrow aspirates of patients enrolled in the STaMINA trial. These assessments will occur three times during the first year of the trial, at

study entry, prior to initiation of maintenance and at one year post-randomization to the STaMINA trial.

2.2 Hypothesis and Specific Objectives

2.2.1. Hypothesis

The proportion of patients with MRD after one year of treatment under the STaMINA trial will be different depending on the treatment arm. Patients enrolled in the arms with second transplant or consolidation will have a higher rate of undetectable MRD than patients on maintenance only.

Secondary hypothesis is that patients who achieve a disease response without detectable MRD, experience a prolonged progression-free and overall survival compared to patients with detectable MRD.

2.2.2 Study Objectives

The primary objective of this ancillary study is to assess the differences in detectable MRD among patients enrolled in the STaMINA trial. Differences in detectable MRD will be compared across treatment arms at the one year time point.

Secondary objectives include:

- Assess the probability of converting from MRD positive to negative in two periods, from study entry to immediately prior to maintenance and from prior to maintenance to one year post-randomization to the STaMINA trial. The assessment in the first period reflects the probability of converting to undetectable MRD after 1) a single autoHCT, 2) tandem autoHCT, and, 3) single autoHCT followed by RVD consolidation. The assessment in the second period reflects the probability of converting to undetectable MRD during maintenance after post-transplant strategy listed in the first period.
- Determine the association between a comprehensive IP panel and standard clinical and laboratory evaluations for assessment of myeloma disease response.
- Measure the concordance between a basic 4-color IP panel versus a comprehensive 7-color IP panel for detection of MRD in myeloma.
- Assess the impact of achieving a CR without detectable MRD on progression-free and overall survival.

2.3. Patient Eligibility

Patients must be enrolled in the STaMINA trial in order to be enrolled in this study.

2.3.1. Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Patients meeting eligibility criteria and enrolled in the STaMINA trial.
2. Signed informed consent form for participation in the ancillary study.

2.3.2. Patient Exclusion Criteria

1. Patients unable to undergo bone marrow aspiration.

2.4. Participant Risks

Recipients of autologous transplantation incur risks from pre-transplant conditioning and post-transplant therapy, as described in the parent clinical trial protocol. This ancillary study adds one bone marrow aspirate to what is performed in the parent trial. Major risks following a bone marrow aspiration include: pain, hematoma or hemorrhage.

2.5. Participation in the Ancillary Study

Patients who agree to participate in the ancillary study will provide three bone marrow aspirates during the course of the first year of the parent clinical trial. Patients who fulfill criteria of disease progression in the parent clinical trial (disease progression or start off-protocol anti-myeloma therapy) in the first year are excluded from ancillary study bone marrow evaluation(s).

3. Immunophenotyping and STUDY ENDPOINTS

3.1. Myeloma Immunophenotyping

3.1.1. Immunophenotyping Panels for Detection of Minimal Residual Disease

All samples will include an auto-fluorescent control to define background. These myeloma panels (Table 3.1.1a) are designed to test several gating strategies to define which combination of markers has the greatest sensitivity at detecting MRD based on the essential and recommended antigens to test for MM MRD from a consensus conference (Table 3.1.1b). CD38, in combination with CD138 and/or CD45 will be tested as well as CD138 and CD45. Each panel also includes a viability reagent (Invitrogen's fixable live dead yellow) to exclude dead cells which can non-specifically bind mAbs and reduce sensitivity at detecting MRD.

TABLE 3.1.1a – SUMMARY OF 7-COLOR IP PANELS FOR MRD

Panel #	PB	LD	FITC	PE	PcP	Pc7	APC
1	CD38	+	CD45	CD56	CD138	CD19	CD20
2	CD38	+	CD45	cLambda	CD138	CD19	cKappa
3	CD38	+	CD45	CD117	CD138	CD27	CD28

Table 3.1.1a: Summary of the three 7-color IP panels for MRD. LD: fixable live dead viability stain for exclusion of dead cells

TABLE 3.1.1b – ANTIGENS FOR DETECTION OF ABERRANT PLASMA CELLS IN MM

Antigen	Normal Expression profile (% in normal PC)	Abnormal Expression Profile	Cases with abnormal expression (%)	Requirement
CD19	Positive (>70)	Negative	95	Essential
CD56	Negative (<15)	Strongly Positive	75	Essential
CD117	Negative (0)	Positive	30	Recommended
CD20	Negative (0)	Positive	30	Recommended
CD28	Negative/weak (<15)	Strongly Positive	15-45	Recommended
CD27	Strongly Positive (100)	Negative/weak	40-50	Recommended
CD81	Positive (100)	Negative/weak	NA	Suggested
CD200	Weakly Positive	Strongly Positive	NA	Suggested

Table 3.1.1b: List of the most useful antigens for the detection of aberrant plasma cells in MM from Rawstron et al (34).

3.1.2. Malignant Plasma Cells

Panel #1: CD38/CD45/CD56/CD138/CD19/CD20
Rationale: This combination is used to detect plasma cells and to delineate normal from malignant plasma cells. Normal plasma cells are positive for CD38, CD138, CD19 and CD45 and negative for CD20, whereas aberrant plasma cells will be positive for CD38, CD138 and CD20 and negative to very dim for CD19 and CD45. Abnormal populations are easily resolved as CD38 bright, CD45 negative and/or CD138 positive since no other cells fall into this region, and therefore are excellent for the detection of MRD. Dim to negative expression of CD19 and/or positive expression of CD56 and/or CD20 confirms their identity as aberrant versus normal plasma cells. In a study evaluating prognostic factors for MM patients after autoHCT, the combination of CD38/CD45/CD56/CD19 resolved malignant from normal plasma cells in > 90% of nearly 300 cases studied.(29)

Panel #2: CD38/CD45/cLambda/CD138/CD19/cKappa
Rationale: This combination demonstrates the light chain restriction of the aberrant plasma cells which is the hallmark of malignancy. It is used to confirm the identity of abnormal or suspicious cells detected in Panel #1, or occasionally to detect a population missed by the first panel. By manually using different gating strategies, suspicious populations can be isolated and their light chain restriction checked. Myeloma cells express CD38 at high levels and in about 80% of myeloma cases, CD138 is also expressed at high levels. In the remaining 20% of cases it is heterogeneously expressed which may represent B cells in early transition to myeloma. CD19 is included in this panel as a potential gating strategy to exclude normal CD19 positive plasma cells and further isolate the light chain restricted myeloma cells.

Panel #3: CD38/CD45/CD117/CD138/CD27/CD28
Rationale: This combination is used to assess the expression of CD28 and CD117 on aberrant plasma cells. Published reports show that expression of both CD19 and CD28, as well as the absence of CD117, are associated with a significantly shorter PFS and OS.(33) CD28 expression correlates with t(14;16) and del(17p) while CD117-negative patients is associated with t(4;14) and del(13q).(5) Simultaneous assessment of CD28 and CD117 antigens allows for stratification of MM patients into three risk categories: poor (CD28+/CD117-), intermediate (CD28+/CD117+ or CD28-/CD117-) and good risk (CD28-/CD117+). CD27 is included to increase our sensitivity at detecting MRD as it is virtually always brightly positive on plasma cells and negative to dim in approximately 50% of MM. By combining the data of aberrantly expressed antigens from each of the 3 panels using identical gating strategies, we will be able to define which combination of markers yield the greatest sensitivity using the minimum number of reagents.

Figure 3.1.3. shows the three gating strategies to define myeloma cells using CD38, CD138 and CD45 (top histograms). The abnormal cells are green in each. The bottom three histograms show the abnormal expression of CD56 which is associated with a more favorable prognostic outcome because it is also CD117+/CD28+. Light chain expression (shown in lower, far right in a histogram gated on CD38 and CD138) is restricted for cytoplasmic kappa light chain.

3.1.3. Immunophenotyping Data Analysis

The most subjective part and biggest area of variation in flow cytometry is data analysis. Regions are defined around populations of cells visually and these gates are applied to the analysis of populations of interest. The procedure is typically done manually and it is not humanly possible for two people to select identical regions. Nevertheless, methods can be practiced to minimize this variation. At RPCI, each mAb cocktail is assayed using a series of individualized, automated macros in conjunction with WinList (Verify Software House) analysis program. These macros ensure that the same templates, compensation settings, gating logic and initial regions are used by all technologists thus ensuring that the logic used for the first patient entered into the PRIMeR study is the same as the last.

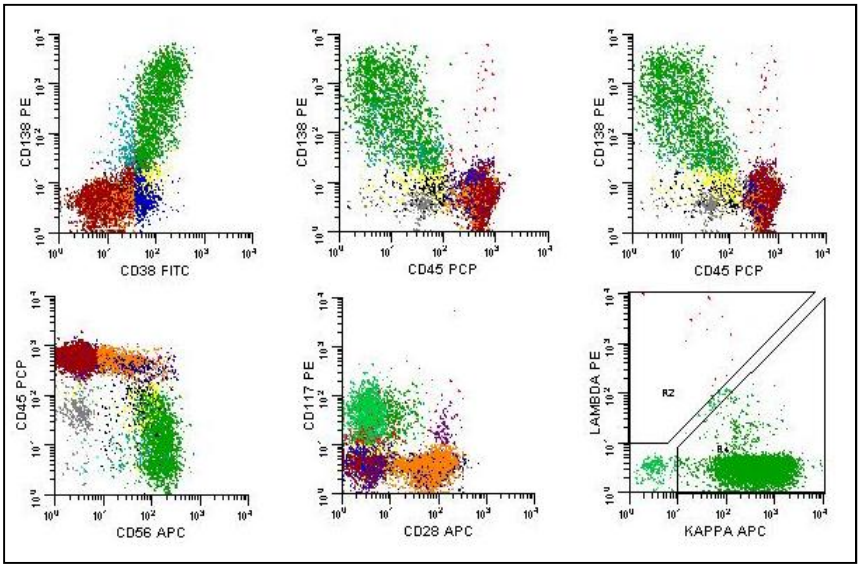


Figure 3.1.3. – Gating Strategies Using CD38, CD138 and CD45

Two additional approaches are used to standardize how and where regions are set by different individuals. First, to ensure consistency, one person will review and sign-off on all patient and clinical protocol reports. Dr. Wallace will be blinded to treatment arm assignment and sample time point. The actual process includes a review of the analyzed data including histograms and calculated values. Analyses requiring revision are returned to the technologist who analyzed the report and then the report is reviewed by the Director again. This process is repeated until all necessary corrections have been made before official sign off and release of the data. Second, to standardize analyses, 1-2 datasets are reviewed on a monthly basis. Each month raw data files are placed on the server for every technologist who routinely analyzes clinical reports to review and analyze as they normally would a single patient sample during the month. The individual's analyses anonymously placed on the server are reviewed at weekly meetings. The goal is to have the numerical values among all of the reports be as close as possible. Discrepancies are reviewed and the reasons explored using raw data files. The process is educational and generates discussion to help identify areas of confusion.

3.1.4. Development of 4-Color Bsic IP Panel

IP data to determine MRD will be re-analyzed using the subset of mAbs in panel #1 (CD38/CD45/CD56/CD19), which has been demonstrated to have prognostic value.(29) Subsequently, additional value of using the each mAbs from panel #1, cytoplasmic light chains (panel #2) and plasma cell and B-cell markers (panel #3) to detect MRD will be assessed. Together panels 1, 2 and 3 have 3 gating mAbs (CD38, CD138, CD45) plus a viability dye to define plasma cells and 8 unique mAbs to ascertain abnormal antigen expression. We will determine (i) which gating strategy most reliably detects MRD (CD38 vs CD45, CD38 vs CD138, CD138 vs CD45 or the combination of all three); (ii) the impact of excluding dead cells with the live dead reagent and (iii) the frequency in which CD19, CD20, CD27, CD28, CD117 and cytoplasmic light chains are abnormally expressed. Data will be analyzed once using a common series of macros and templates and scored on a sample-by-sample basis for each of

these parameters. The additional mAbs have the potential to be more sensitive and specific for detection of MRD. However this adds complexity to the analysis and may impact wide-spread reproducibility in some centers with limited IP capabilities. This aim will analyze the data with one 4-color and three 7-color panels to assess whether the ability to detect MRD is the same.

3.1.5. Immunophenotyping Reports

The PRIMeR study database will be linked with the STaMINA trial database. Results from the IP will be merged with STaMINA trial database for the analysis.

3.2. Definition of Disease Status

Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria. Until disease progression, all disease classifications are relative to the patient's disease status prior to the first autologous transplantation (i.e., study entry).

This ancillary study will utilized the same definition of disease status and response as described in Chapter 3 of the parent trial protocol.

3.2.1. Assessment of Disease Status

The STaMINA trial collects sFLC ratio, SPEP, UPEP and IFE in the urine and serum to perform standard MM response assessment and staging prior to each intervention and every 3 months after initiation of maintenance. The STaMINA trial requires bone marrow biopsies only at baseline and to confirm CR thereafter. Response data will not be available to the PRIMeR study team in real time, thus all patients who provide informed consent for the ancillary study will have IP assessment regardless of their traditional disease response as assessed by conventional methods. IP assessment will be done without knowledge of MM response by conventional methods. This allows for comparison of these two approaches.

One important issue in assessing response after intensive therapy is to discern between early disease progression, CR and oligoclonal reconstitution. Consequently, the evaluation of MRD immediately prior to maintenance (shortly after completion of intensive therapy) will be of particular interest, especially if it differs from the baseline and 1-year evaluations.

3.2.2. Definition of MRD

MRD will be defined as the positive detection of abnormal/malignant plasma cells, cytoplasmic light chains and/or immature B-cells by any one or more of the 3 IP panels listed in Table 3.1.1a. Undetectable MRD will be defined as no detection of abnormal cells or light chains on all 3 IP panels.

3.3. Primary Endpoint

3.3.1. Proportion of Patients with undetectable MRD

The primary endpoint will compare the proportion of patients who are alive, progression-free, and with undetectable MRD at one year post- post-randomization to the STaMINA trial.

3.4. Secondary Endpoints

3.4.1. Conversion to Undetectable MRD

This endpoint will assess the proportion of patients with detectable MRD at study entry who convert to undetectable MRD prior to maintenance and the proportion of patients with detectable MRD prior to maintenance who convert to undetectable MRD at one year post-randomization to the STaMINA trial. The probability of conversion to undetectable MRD will be assessed separately by treatment arms.

3.4.2. Disease Assessment Comparison

The parent trial will assess the rates of VGPR or better (VGPR, nCR, CR and sCR) responses according to the International Uniform Response Criteria (STaMINA protocol Section 3.2) at specific time points in all arms. The ancillary study will assess patients according to the presence of MRD at baseline, prior to maintenance therapy and at one year post-randomization to the STaMINA trial. This endpoint will compare detection of MRD using IP with best response (VGPR or better) using standard disease assessment techniques. These comparisons will occur at all three time points when MRD is being assessed.

3.4.3. Concordance between 4-Color and 7-Color IP

Assessment of MRD will utilize 3 comprehensive 7-color panels. Monoclonal antibodies (mAbs) used in all three panels will be tested to identify a subset of four mAbs that are most sensitive and specific to detect MRD. Detection of MRD will be analyzed with a 4-color IP panel and compared with results using a 7-color IP panel.

3.4.4. Progression-Free and Overall Survival and MRD

The event for PFS and OS are defined in the parent clinical, and the same definition is used for the ancillary study. These endpoint in the ancillary study will incorporate the MRD status on the analysis of PFS and OS.

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

The BMT CTN 0702 protocol includes an option for patients to provide bone marrow aspirate samples for future research.

Patients can consent for an additional aliquot of the bone marrow aspirate sample to be collected for future research (see Appendix C of the STaMINA protocol). BMT CTN Core and Affiliate centers that choose to collect the research bone marrow aspirate sample at the same time as the routine bone marrow aspirate and biopsy for disease assessment will use the Screening Consent Form (Appendix B of the STaMINA protocol). BMT CTN Core and Affiliate centers will enter the date the patient signed the consent form in AdvantageEDC Segment 0 (Screening Segment) to obtain a patient study number. Entering a patient in Segment 0 does not guarantee that the patient will be enrolled in BMT CTN 0702; if the patient is determined to be not eligible for BMT CTN 0702, the bone marrow aspirate collected for future research will be discarded.

For the PRIMeR study, the first bone marrow collection will be the same as the parent trial in order to minimize the number of bone marrow procedures performed in the trial. Centers that utilize the screening consent, will also be required to consent for the PRIMeR study in order for an aliquot of bone marrow aspirate to be used for immunophenotyping. Similarly for the bone marrow sample for future research, if patients are enrolled in the PRIMeR study at the screening phase and subsequently deemed ineligible, their bone marrow sample will be discarded and the data from the immunophenotyping will not be used for the study.

4.1.1.1. Enrollment

BMT CTN Core and Affiliate Centers will register patients using the Advantage Electronic Data Capture (AdvantageEDC^{SM}) system and cooperative group centers register through the Clinical Trials Support Unit (CTSU) for the parent trial. Once patients are registered either to segment 0 or segment A they are eligible for the ancillary study. Patients can be consented for the ancillary study at the same time as the parent trial. The parent trial baseline form includes a question regarding participation in the PRIMeR study. Once patients are registered to the ancillary study a schedule of bone marrow assessment according to the arm the patient was randomized will be generated.

4.2. Ancillary Study Bone Marrow Aspirate Schedule

Three bone marrow assessments are scheduled for all patients enrolled in the PRIMeR study. The first is at study entry and the third is at one year post-randomization to the STaMINA trial. Both of these assessments are scheduled independent of treatment assignment and should coincide with the time of bone marrow assessments that are done as part of the scheduled evaluations in the parent trial. The second bone marrow assessment will occur at the time immediately prior to initiation of maintenance, which varies depending of the treatment arm.

The timing of the second bone marrow assessment should be anytime within 21 days before initiation of maintenance lenalidomide.

Table 4.2 – Bone Marrow Assessment Schedule – By Treatment Arm
Assessments based on date of first transplant

Bone marrow aspirates*	Arm A	Arm B	Arm C
#1	0	0	0
#2	150 ± 30d	90 ± 30d	150 ± 30d
#3	365 ± 30d	365 ± 30d	365 ± 30d

*Bone marrow assessments #1 and #3 should coincide with bone marrow biopsy/aspirate performed as part of the scheduled evaluations in the parent trial. Assessment #2 needs to be within 21 days prior to initiation of maintenance.

4.2.1. Data Reporting

Data required for the PRIMeR study is collected in the parent trial. No additional data reporting specific for the PRIMeR study will be required.

4.2.2. Adverse Event Reporting

Any adverse events that may occur as a result of a bone marrow aspiration performed for the PRIMeR study will be captured through the mechanism specified in the parent trial.

4.2.3. Schedule of Assessments in the Parent Trial and Ancillary Study

The PRIMeR study MRD assessment will require an aliquot of approximately 1 mL from a bone marrow aspirate at each of the time points.

Tables 4.2.3a-d in the parent trial protocol include the addition of specific bone marrow assessment time points for the PRIMeR study.

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The primary objective of this ancillary study is to assess the status of MRD through IP and to compare the proportion of patients with undetectable MRD at one-year post first autoHCT across treatment arms. The main outcome is the MRD status as defined in Section 3.2.1. Other objectives include estimating the probability of converting from detectable MRD to undetectable MRD in two different time periods (from prior to first autoHCT to immediately prior to

maintenance and from prior to maintenance to 1 year post first autoHCT); estimating the correlation between MRD assessment using IP and best disease response using standard clinical laboratory methods used in the parent trial; and assessing the concordance of MRD status between a basic 4-color IP panel and a comprehensive 7-color panel. Once long-term outcome data from the parent trial become available, we will assess the impact of MRD status on PFS and OS.

5.2. Sample Size and Power Calculations

Accrual to this study is limited to patients participating in the STaMINA trial. The target accrual for this study is 472 patients. Assuming 10% of patients will not have a 1 year post-autoHCT sample available due to patient refusal, loss of follow-up or patient receiving off-protocol anti-myeloma therapy, resulting in approximately 425 patients evaluable at one year. This sample size was utilized to calculate the power to detect the difference in proportion of patients with undetectable MRD at one year post-randomization to the STaMINA trial across three treatment arms. To account for death or progression during the first year, undetectable MRD is defined as being alive, progression-free and having MRD negative status at one year. Using a two-sided Type I error of 0.017 to account for three pair-wise comparisons among treatment groups, a sample size of 142 patients per arm provides over 80% power to detect a 19% change in the proportion of patients with undetectable MRD at one year between any two arms, assuming a baseline undetectable MRD proportion around 50%.

5.3. Analysis of the Primary Endpoint

Descriptive statistics include proportion of patient who died, progressed, are alive without progression, are missing a bone marrow sample, have detectable MRD or not will be summarized at each assessment time point for each treatment group.

Logistic regression models will be used to compare the proportions of undetectable MRD across the treatment arms. Additional covariates at study entry will be tested in the model and will include: age, gender, race, MM risk stratification, disease status at study entry, and MRD status at study entry. Stepwise selection procedures will be used for model building. All covariates significant at level 0.05 will be included in the final model. Two-way interactions between treatment and other significant covariates will be checked especially between treatment and MRD status at study entry, to test whether baseline MRD status differentially affects whether a person has undetectable MRD at 1 year by treatment arm. The study is not powered to detect an interaction between treatment arm assignment and MRD status due to limitations in the sample size available for the ancillary study. However, this interaction will be explored by testing for an interaction between baseline MRD status and treatment in the logistic regression model. Additional exploratory subgroup analysis comparing the proportion of patients without MRD at 1 year after first autoHCT between treatment arms separately according to MRD status at baseline. If there are indications of differential treatment effect due to MRD status at baseline, the interaction term will be included in the final model. Appropriateness of the final model will be checked as described in Agresti.(42) If there are indications of nonlinearity in the predictors, transformations will be evaluated.

In this study, it is expected that <10% of patients will have incomplete data at 1 year and the plan is to analyze only cases with complete data, i.e. all three evaluations. The logistic model for the primary endpoint as described above includes baseline characteristics, disease status and MRD status at entry as covariates which likely accounts for data missing at random. If the proportion of missing data is higher than expected, additional factors which might affect the likelihood of bone marrow samples being missing will be considered along with alternative imputation schemes and/or sensitivity analyses to account for data missing not at random, as described in Fairclough and Daniels and Hogan (34, 35). Pattern of missing data will be investigated by graphical presentations and logistic regression. Logistic regression models will be used to identify factors associated with missing data. Sensitivity analysis will be performed using various imputation techniques such as imputing data using the last observation carried forward approach, pattern mixture models, and multiple imputations where the missing values are imputed according to a logistic regression prediction model.

5.4. Analysis of the Secondary Endpoints

5.4.1. Conversion to Undetectable MRD

Conversion from detectable to undetectable MRD will be assessed in two different periods. The first period will begin at study entry and end immediately prior to maintenance; the second will begin immediately prior to maintenance and end at 1 year post first autoHCT. The analysis for each period will include only patients who are alive with detectable MRD at the initial assessment for that period. The probability of converting to undetectable MRD in each period will be assessed separately by treatment arm, because the time of the second assessment (immediately prior to maintenance) varies by treatment arm, making conversion probability comparison across treatment arms inappropriate. However, estimates within each treatment arm will provide clinically meaningful information regarding conversion to undetectable MRD at each treatment strategy (arm) as well as conversion rates while on maintenance. The probability of converting from detectable to undetectable MRD within each period and for each treatment arm will be estimated using simple proportions if the timing of assessments across patients within each group are sufficiently close together (± 1 month). If assessment time ranges are wider, differential timing of evaluations will be accounted for using the current status estimator for competing risks proposed by Jewell et al. (36) and Groeneboom et al. (37). Death and progression prior to the assessment time will be treated as competing risks, since they prevent evaluation of MRD status. The current status estimator is needed since the time to conversion is not directly observed as only MRD status at the time of evaluation will be known.

5.4.2. Disease Assessment Comparison

MRD assessment by IP will be compared to standard MM assessment. The proportion of undetectable MRD among patients in VGPR or better disease status (VGPR, near CR and CR) according to standard response criteria will be described at baseline and each assessment time point (Table 5.4.2).

The proportions of undetectable MRD in each of the 4 response categories in Table 5.4.2 will be compared using a chi-square test separately at each time point.

Table 5.4.2: Proportion of patients with undetectable MRD at each time point of the PRIMeR study.

	Standard Response Criteria			
Time points	sCR	CR	nCR	VGPR
Baseline	A	B	C	D
Pre-Maintenance Therapy	E	F	G	H
One year	I	J	K	L

A through L are the proportion of patients without MRD who are a very good partial response (VGPR) or better. The degree of discordance will be compared across disease status evaluated by standard criteria (A-D, E-H, I-L), and across different time points (A/E/I, B/F/J, C/G/K, D/H/L).

5.4.3. Comparison of 4-Color and 7-Color IP

The proportion of MRD positivity will be described for each panel and a Kappa statistic will be used to measure the agreement between the 4-color and 7-color panels. IP data will be compiled only from the baseline disease assessment for this endpoint.

5.4.4. Overall and Progression-Free Survival

After the PFS and OS data is analyzed in the parent trial, they will be available for analysis in this ancillary study. Both univariate and multivariate analyses to assess the effect of IP results on PFS and OS will be performed. In the univariate analysis, PFS and OS curves will be compared between detectable and undetectable MRD groups. In the multivariate analysis, Cox proportional hazards models will be built for each outcome with MRD status as a time-varying covariate, to investigate the direct association between MRD status and PFS or OS. We will also compare treatment effects from a model with both treatment and MRD status with that from a model with treatment alone, in order to investigate the potential utility of MRD as a surrogate marker. (38) Other baseline characteristics such as age, gender, race, MM risk stratification will be considered as covariates in the model. We will also evaluate the added ability of detectable MRD by IP at study entry to predict PFS and OS at 3 years after the first autoHCT by estimating the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) described by Pencina et al. (39). We will compute the NRI and the IDI between models which include all significant baseline characteristics including disease status assessed according to standard response criteria with and without MRD by IP at study entry. We will also calculate the NRI and IDI measures for models with a 7-color vs. a 4-color IP panel to determine which has better predictive accuracy.

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APPENDIX O

REFERENCES

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