BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

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Version 1.0

Study Co-Chairs

David Avigan, MD[1], Nina Shah, MD[2], David Chung, MD[3]

Protocol Team

Devine, Steven[4]
Fay, Joseph[5]
Geller, Nancy[6]
Holstein, Sarah[7]
Lazarus, Hillard[8]
Logan, Brent[9]
Mendizabal, Adam[10]
Nelson, Courtney[10]
Pasquini, Marcelo[9]
Poland, Nancy[11]
Rosenblatt, Jacalyn[1]
Rapoport, Aaron[12]
Soiffer, Robert[13]
Waller, Edmund[14]

Manufacturing Team:

Choi, Chris[7]
Copland, Ian[14]
Hei, Derek[15]
O'Donnell, Lynn[4]
Reese, Jane[8]
Somaiya, Poorvi[1]
Keever-Taylor, Carolyn[16]
Young, James[3]
Yvon, Eric[2]
Zurawski, Gerard[5]

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[1] Beth Israel Deaconess Medical Center
[2] University of Texas, MD Anderson Cancer Center
[3] Memorial Sloan-Kettering Cancer Center
[4] The Ohio State University
[5] Baylor Institute for Immunology Research, Baylor Research Institute
[6] National Heart, Lung, and Blood Institute
[7] Roswell Park Cancer Institute
[8] University Hospitals Case Medical Center, Case Western Reserve University
[9] Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin
[10] The EMMES Corporation
[11] National Marrow Donor Program
[12] University of Maryland
[13] Dana Farber Cancer Institute
[14] Emory University
[15] University of Wisconsin
[16] Medical College of Wisconsin

Approval Signature (Protocol Chair/Officer)

Approval Signature (Protocol Chair/Officer)

Core Study Participants:

Affiliate Study Participants:

PROTOCOL SYNOPSIS – BMT CTN 1401 PROTOCOL

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions

Co- Principal Investigators: David Avigan, MD, Nina Shah, MD, David Chung, MD

Study Design: The study is designed as a Phase II, multicenter trial of vaccination with DC/myeloma fusions with granulocyte macrophage colony-stimulating factor (GM-CSF) adjuvant plus lenalidomide maintenance therapy versus maintenance therapy alone or with GM-CSF following autologous transplant as part of upfront treatment of multiple myeloma (MM).

Primary Objective: The primary objective of this randomized trial is to compare the proportion of patients alive and in complete response (defined as CR or sCR) at one year post transplant between patients receiving DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to those receiving lenalidomide maintenance therapy with or without GM-CSF.

Clinical Secondary Objectives:

To compare DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to lenalidomide maintenance therapy with or without GM-CSF with respect to: myeloma response (sCR, CR, VGPR, PR, and SD), conversion of partial to complete response, disease progression, treatment-related mortality, progression-free survival, overall survival, toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, incidence of infections, and measures of minimal residual disease at one year post transplant (or approximately 10 months from randomization). Secondary exploratory analyses will also be conducted to compare in a pairwise fashion the vaccine arm, lenalidomide/GM-CSF arm, and lenalidomide alone arm, to describe the proportion of patients with collection of tumor cells who reach randomization, compliance with vaccine, and to describe the reproducibility of the vaccine manufacturing based on the release criteria.

Immunologic Objectives: The primary immunologic endpoint is to compare the effect of DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to lenalidomide maintenance therapy alone or with GM-CSF on treatment-induced expansion of myeloma-specific T cells, defined as a 2.4-fold increase from pre-therapy to peak

post-treatment levels.

Secondary immunologic endpoints will compare each of the treatment arms for: a) the percent of patients achieving at least a 10-fold expansion of myeloma-specific T cells; b) expansion of myeloma antigen-specific T cells by tetramer analysis; c) quantification of T cell subsets and PD-1 expressing lymphocytes; d) quantification of NK cells and identification of activation and inhibitory ligands; e) assessment of NK-mediated killing of myeloma targets; f) assessment of humoral response against whole myeloma cells and myeloma-associated antigens by SEREX and by characterizing myeloma-specific plasmablast responses.

Eligibility:

Patients must be considered transplant eligible by treating physician at the time of study. Patients will be enrolled prior to tumor cell collection for vaccine manufacturing. Eligible patients are 18-70 years of age with symptomatic multiple myeloma requiring treatment, without history of prior disease progression or prior HCT, Karnofsky performance score $\geq$70%, evidence of at least 20% plasma cells in a bone marrow differential within 60 days of enrollment, and have received $\leq$2 cycles of systemic anti-myeloma therapy. Patients with prior auto or allo transplant are not eligible. Patients with active autoimmune diseases will be excluded.

Treatment Plan:

After meeting the initial eligibility criteria, patients will undergo harvesting of myeloma cells for assessment of immune response and for vaccine generation. Patients will have 30 mL of marrow harvested and cryopreserved after undergoing immunophenotypic analysis. Patients will then complete initial systemic anti-myeloma therapy and autologous hematopoietic stem cell mobilization and collection according to institutional practices.

Approximately 2 months post-transplant, patients will undergo disease response assessment and will be randomized 2:1:1 to vaccine/GM-CSF plus lenalidomide maintenance, lenalidomide alone, or lenalidomide/GM-CSF. Patients randomized to the vaccine plus lenalidomide arm will undergo leukapheresis for dendritic cell generation for vaccine manufacturing. All patients will start lenalidomide maintenance Day 90-100 post transplant. Patients randomized to the vaccine arm will receive vaccine the first day of cycles 2, 3, and 4 of maintenance. Vaccine will be administered by subcutaneous injection with 100 ug GM-CSF given subcutaneously at the vaccine site on day of vaccination

and daily for a total of 4 days. Patients randomized to lenalidomide/GM-CSF will receive 100 ug GM-CSF given subcutaneously daily for a total of 4 days starting the first day of cycles 2, 3 and 4 of maintenance. Lenalidomide maintenance will continue for 2 years for patients who continue free of progression.

Vaccine Production and Characterization:

Vaccine Production will consist of the following steps:

1) Bone marrow aspiration of 30 mL, isolation of mononuclear cells by ficoll centrifugation, quantification of CD138+/CD38+ cells by immunocytochemistry, and cryopreservation.
2) Leukapheresis collection post transplant and after randomization.
3) Mononuclear cells isolated by ficoll density centrifugation. Adherent cells segregated following 1-2 hour culture and then cultured for 5-7 days with GM-CSF and IL-4. Cultures are re-fed with cytokines after 3 days. Maturation with TNFα for 48-72 hours. DCs are harvested and undergo characterization by immunocytochemistry for expression of DR, CD86, and CD83.
4) Tumor cells are thawed and re-characterized.
5) DC and tumor cells are pelleted and co-cultured in the presence of PEG at a ratio of 3:1.
6) Fusion cells are quantified by determining the percentage of dual expressing cells by immunocytochemistry.

Vaccine Release criteria:

1) Plasma cells comprise at least 20% of tumor cell harvest by staining
2) 50% of DC prep express CD86
3) Viability of DC prep > 70%
4) Fusion efficiency > 15%
5) Fusion viability > 50%
6) Sterility, mycoplasma, and endotoxin assays are negative

Accrual Objective: Target accrual is 132 patients randomized to vaccine/GM-CSF/ lenalidomide (n=66), lenalidomide alone (n=33), lenalidomide /GM-CSF (n=33), with an estimated total enrollment of 188, assuming about 30% of patients are unable to proceed with post-transplant immunotherapy.

Accrual Period: 36 months

Study Duration:	Patients will be followed for approximately 3 years after maintenance initiation

STUDY SCHEMA

Initial Inclusion Criteria

1. Transplant Eligible
2. Meet criteria for symptomatic multiple myeloma (Appendix A)
3. Age 18 – 70
4. Karnofsky Performance of ≥ 70%
5. 20% plasma cells in the bone marrow ≤ 60 days prior to enrollment[1]
6. Received ≤ 2 cycles of systemic anti-myeloma therapy
7. Creatinine clearance ≥ 40 mL/min (estimated or calculated)

[1] The required bone marrow evaluation will need to be repeated for patients who receive additional therapy between the initial bone marrow collection (pre-treatment) and study entry.

Initial Exclusion Criteria

1. Prior Autologous or Allogeneic HCT
2. Non secretory multiple myeloma (defined as normal serum and urine immunofixation and normal serum free light chain assay).
3. Patients with Plasma Cell Leukemia
4. Patient with High-Risk multiple myeloma
5. Patients with prior disease progression
6. Patients seropositive for the human immunodeficiency virus (HIV).
7. Patient receiving other investigational or anti-myeloma drugs within 14 days of enrollment.
8. Patients with active clinically significant autoimmune disease
9. Patients who have received mid-intensity melphalan (>50 mg IV) as part of prior therapy.
10. Additional exclusion criteria outlined in Chapter 2

Inclusion Criteria for Randomization

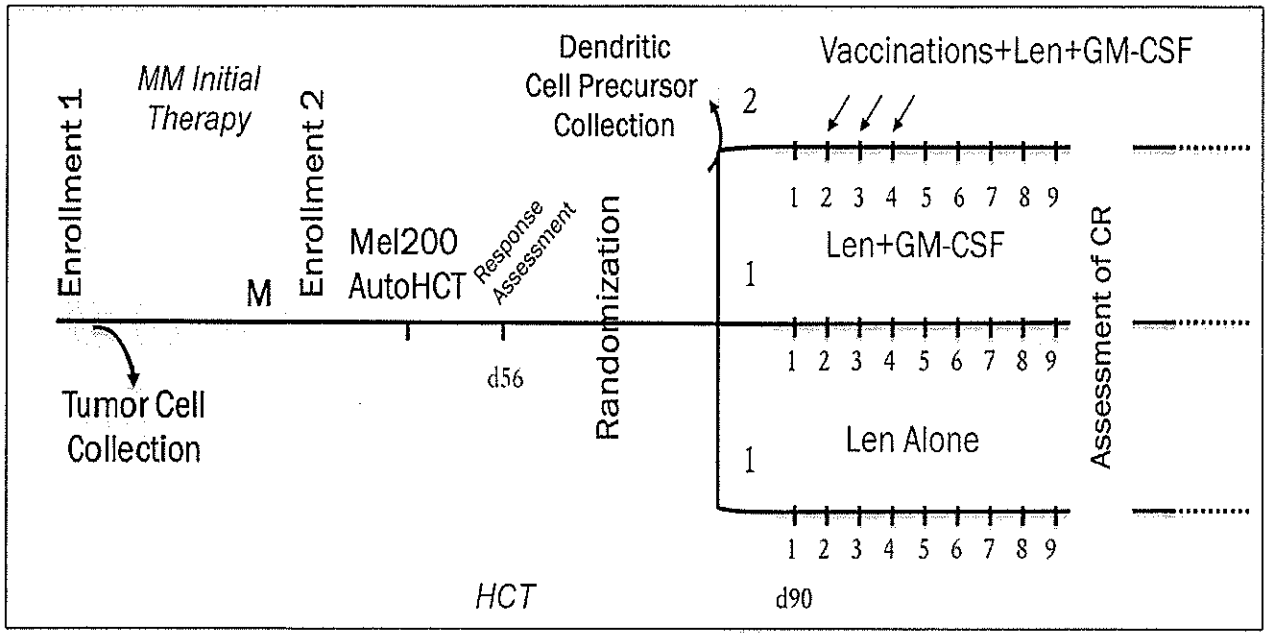
1. Patients received transplant ≤12 months from enrollment onto BMT CTN 1401
2. No disease progression since initiation of systemic anti-myeloma therapy
3. Received autologous transplant with melphalan 200mg/m^2 with a minimum cell dose of 2x10^6 CD34+ cells/kg
4. No evidence of uncontrolled infection requiring systemic therapy
5. Platelet count ≥75,000/mm^3 (without transfusion in previous 7 days).
6. Absolute neutrophil count (ANC) ≥ 1,500/mm^3 without filgrastim administration within 7 days, or pegfilgrastim within 14 days of measurement.
7. Bilirubin < 2x the upper limit of normal
8. ALT and AST < 2.5x the upper limit of normal
9. Creatinine clearance of ≥ 40 mL/min. Patients with creatinine clearance ≥30 but ≤ 40 will be considered with review/approval from the protocol chairs or officer if the cause of renal insufficiency is associated with multiple myeloma
10. Patients must be willing to receive DVT prophylaxis
11. Patient must be willing to follow birth control practices outlined in the protocol

Primary Clinical Endpoint: Complete response (CR or sCR) at one year between patients receiving DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to those receiving lenalidomide maintenance therapy with or without GM-CSF.

Primary Immunologic Endpoint:
Treatment-induced expansion of myeloma-specific T cells as defined by the 2.4-fold increase from pre-therapy to peak post-treatment levels comparing the vaccine arm with patients receiving lenalidomide maintenance therapy with and without GM-CSF.

Secondary Endpoints:
Clinical: Myeloma Response; Rate of conversion to CR; Disease Progression; Treatment-Related Mortality; Progression-Free Survival; Overall Survival; Toxicity and rates of infection; Minimal Residual Disease; CR and sCR rates will be compared between the vaccine arm and each of the no-vaccine arms; proportion of patients with tumor cell collection who reach randomization; compliance with vaccine; and reproducibility of the vaccine.
Immunologic:Secondary immunologic endpoint :a) the percent of patients achieving at least a 10 fold expansion of myeloma specific T-cells cells; b) expansion of myeloma antigen-specific T cells by tetramer analysis; c) quantification of T-cells subsets and PD-1 expressing lymphocytes; d) quantification of NK cells and identification of activation and inhibitory ligands; e) assessment of NK mediated killing of myeloma targets; f) assessment of humoral response against whole myeloma cells and myeloma associated antigens by SEREX and by characterizing myeloma-specific plasmablast responses.

OUTLINE OF TREATMENT PLAN



Note: Len = Maintenance lenalidomide

- Accrual targets 188 patients to be enrolled with a target of 132 patients to be randomized, assuming about 30% of patients are unable to proceed with post-transplant immunotherapy.
    - Arm A: Maintenance lenalidomide + vaccine + GM-CSF (n=66)
    - Arm B: Maintenance lenalidomode + GM-CSF (n=33)
    - Arm C: Maintenance lenalidomide alone (n=33)
- Patients will be stratified according to disease status at time of randomization between CR/ sCR and VGPR/PR/stable disease.

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CHAPTER 1

1. OVERVIEW

1.1.Background

Immune therapy has emerged as a leading area of cancer therapeutics due to its potential to recruit multiple effectors that broadly target malignant cells and overcome mechanisms of resistance. Multiple myeloma (MM) is characterized by the loss of critical mediators of immune surveillance, resulting in the suppression of antigen-presenting and effector cell function and the development of an immunologic milieu that fosters disease progression[1-6]. We have developed a tumor vaccine in which patient-derived myeloma cells are fused with autologous dendritic cells (DCs), such that a broad array of myeloma antigens are presented in the context of DC-mediated costimulation[7-10]. In diverse tumor models that include MM, vaccination of animals with DC/tumor fusions results in protection from an otherwise lethal challenge of malignant cells and, more significantly, eradication of disease in the setting of advanced metastatic involvement[11,12]. In a phase I study, 17 patients with advanced myeloma (median of 4 prior regimens) underwent vaccination with DC/MM fusions in conjunction with 4 days of GM-CSF administered at the vaccine site. As previously described, MM cells were isolated from bone marrow aspirates and fused with autologous DCs generated from adherent mononuclear cells cultured with GM-CSF, IL-4, and TNFα[13]. Vaccine production was successful in all patients and was well-tolerated without evidence of clinically significant autoimmunity. Vaccination resulted in a mean 10-fold expansion of CD4 and CD8 myeloma-specific T cells, as determined by the percentage of cells expressing IFNγ in response to ex vivo exposure to autologous tumor lysate. Similarly, vaccination resulted in the development of myeloma-specific antibody responses as documented by SERAX analysis[13].

1.1.1. Vaccination with DC/Myeloma fusion cells following autologous transplant

Vaccination with DC/Myeloma fusion cells following autologous transplant is associated with potent immune response and conversion from PR to CR in a subset of patients[14]. We completed a clinical trial in which MM patients were vaccinated with DC/MM fusion cells in conjunction with autologous transplantation (ASCT). In the first cohort of the study, twenty-four patients received serial vaccinations following post-transplant hematopoietic recovery. A second cohort of 12 patients received a pre-transplant vaccine followed by post-transplant vaccinations. Vaccine preparation was successful in all patients. Mean yield of the DC and MM cells was 1.74 x 10^8 and 6.5 x 10^7 cells, respectively. Mean fusion efficiency, as determined by the percentage of cells that co-expressed unique DC (CD80, CD86, and/or CD83) and MM (CD38 and/or CD138) antigens, was 38%. The mean dose administered was 3.6 x 10^6 fusion cells. Mean viability of the DC, myeloma, and fusion preparations was 87%, 87%, 79%, respectively. The DC/MM fusion preparations exhibited potent antigen presenting capacity, as evidenced by their stimulation of allogeneic T cell proliferation, with a mean stimulation index of 36.6, similar to that observed with the DC preparation prior to fusion (mean stimulation index of 52.3). In contrast, the unfused myeloma cells demonstrated minimal capacity for T cell stimulation (mean stimulation index of 13.7). All vaccine-associated toxicities were of grade I-II intensity. The most common toxicity was erythema and induration at the vaccine injection site associated with T cell infiltration on biopsy. The other common side effects were transient pruritus, rash, fatigue, fever, and myalgias. One patient had a transiently elevated ANA level without clinical evidence of autoimmunity. One patient developed transient grade 2 leukopenia, but no evidence of graft

compromise was observed following vaccination. Consistent with prior reports, the post-transplant period was associated with the relative suppression of general measures of cellular immunity as manifested by decreased T cell proliferative responses to mitogen or recall antigens. In contrast, the period of post-transplant lymphopoietic reconstitution was associated with the expansion of myeloma-specific T cells that was further boosted following vaccination, as determined by percentage of CD4+ and CD8+ T cells expressing IFNγ in response to ex vivo exposure to autologous tumor lysate. In the first cohort that received only post-transplant vaccination, the mean log10 fold increase in myeloma-specific CD4+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 3.55 (95% CI 0.81;15.49) and 10.72 (95% CI 3.89;29.51), respectively. Similarly, the mean log10 fold increase in myeloma specific CD8+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 6.76 (95% CI 3.02;15.49) and 11.48 (95% CI 4.17;32.36), respectively. A smaller subset of patients underwent a single pre-transplant vaccination followed by post-transplant boosting. Of note, no difference in peak levels of CD4+ or CD8+ circulating myeloma-specific T cells was observed between the cohort receiving a pre-transplant vaccine and that undergoing post-transplant vaccination alone (p=0.185 and p=0.689, respectively). For the entire study population, the mean log10 fold increase in myeloma-specific CD4+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 3.55 (95% CI 1.58;8.13) and 9.55 (95% CI 5.37;16.98), respectively. The mean log10 fold increase in myeloma-specific CD8+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 4.37 (95% CI 2.40;7.76) and 8.32 (95% CI 4.68;15.14), respectively. Notably, vaccination was associated with the expansion of T cells targeting the myeloma-specific antigen, MUC1, as determined by tetramer analysis. In a cohort of patients who were HLA-A2, the median percentage of MUC1-specific T cells was 0.12 pre-transplant and increased to 1.84 at 3 months after completion of vaccination ($p<0.05$), representing a median fold increase of 17.5. The expansion of T cells targeting MUC1 in response to vaccination is of particular interest, as we have identified a population of CD34+/MUC1+ cells in the bone marrow of patients with myeloma that demonstrate myeloma-initiating capacity.

Seventy-eight percent of patients achieved a CR or VGPR (47% CR/nCR; 31% VGPR). Thirty-one percent achieved a CR/nCR in the early post-transplant period, whereas an additional 17% (6 patients: 4 from VGPR, 2 from PR) achieved CR/nCR as best response only after day 100 post-transplant and after undergoing vaccination. The presence of late responses several months after ASCT is consistent with an impact of vaccine therapy on post-transplant residual disease.

1.1.2. Post-transplant lenalidomide maintenance

Post-transplant lenalidomide maintenance prolongs disease-free and overall survival[15]. This is thought to be potentially due to its immunomodulatory characteristics. In pre-clinical studies, we demonstrated that lenalidomide potently enhances immune response to vaccination[16]. T cells were stimulated in vitro with DC/MM fusions in the absence or presence of lenalidomide. After 5–7 days of stimulation by the vaccine, the percentage of CD8+ T cells expressing IFNγ increased significantly in the presence of lenalidomide (from 6.37 to 9.9 %; n = 7, p = 0.03). A concomitant statistically significant decrease in the proportion of regulatory T cells was also observed (4.4 % in the lenalidomide group as opposed to 9.6 % in the control group; n = 3, p = 0.02). As determined by a flourochrome assay measuring granzyme B release in target cells, CTL-mediated lysis of autologous MM tumor targets was increased by 50% when T cells were

stimulated by DC/MM fusions in the presence of lenalidomide, as compared to those cultured with fusions alone (mean 29.2% vs. 19.7%; n=3, p=0.004).

1.2.Study Specific Information

Based on these encouraging data, the DC/MM fusion vaccine was chosen to be the first cellular immunotherapy to be evaluated in a multicenter cooperative group study involving several nationally prominent cancer centers (BMT CTN protocol 1401). We will conduct a multicenter phase II randomized study comparing post-transplant vaccination with DC/MM fusions/GM-CSF and lenalidomide maintenance to lenalidomide maintenance with and without GM-CSF, with vaccine manufacturing performed locally at each participating center. The primary objective is to assess the impact of post-transplant immunotherapy on the percentage of patients in CR at 1 year between the vaccine arm and both no-vaccine arms combined. Secondary endpoints include determining the effect of therapy on progression-free survival, myeloma response, minimal residual disease, toxicities, transplant-related mortality, and overall survival. Additionally, this study includes several immunologic endpoints to understand the effect of the vaccine on the anti-myeloma immunity, the immune effects of lenalidomide, and general immune reconstitution after transplant. The primary immunologic endpoint is to compare the expansion of myeloma-specific T cells across all three arms.

1.3.Rationale for Study

MM is associated with immune suppression, including defects in antigen presentation and effector cell function that are thought to play a role in disease progression. Although the outcomes for myeloma patients have improved greatly over the past decade, the majority of patients relapse even after autologous stem cell transplant and post-transplant maintenance therapy with lenalidomide. Early phase clinical data demonstrate that post-transplant vaccination with a DC-MM fusion product with GM-CSF adjuvant increases the number of MM-specific T cells. Furthermore, it appears that lenalidomide can specifically augment vaccine-stimulated induction of MM-specific T cells. We are therefore interested in combining standard immunomodulatory therapy (lenalidomide) with a potential immune stimulant (DC-MM vaccination) to increase post-transplant clinical response. Finally, pre-clinical data has suggested that immunomodulatory agents augment NK cell activity[17] and that NK cells interact with and can be activated by DCs[18]. Thus we are interested in further defining the NK immmunophenotype in the setting of post-transplant maintenance lenalidomide and the changes to this phenotype in the setting of DC-MM fusion vaccination. We postulate that post-transplant lenalidomide maintenance will augment post-transplant anti-myeloma immunity, thus providing an ideal platform for DC/MM fusion vaccination. Additionally, to understand the effect of vaccine versus the adjuvant in the post-transplant setting, we split the non-vaccine arms into lenalidomide alone and lenalidomide plus GM-CSF, with GM-CSF administered in the exact same schedule and dosing as in the vaccine arm. Although there is no evidence that GM-CSF has an anti-myeloma effect, this additional control arm is important to understand whether any effect of the vaccine is due to its adjuvant and whether GM-CSF influences any of the immunologic outcomes. We further hypothesize that vaccination in this setting will effectively target post-transplant residual disease, increase the percentage of patients achieving CR, and create durable responses.

The results of this trial will provide information on whether this patient-specific vaccine administered after transplant is promising for further comparison with current standard of care treatment. Furthermore, this trial will address several important aspects of anti-myeloma

immunity, including how lenalidomide maintenance influences post-transplant recovery and myeloma control. Lastly, isolating the effect of the GM-CSF adjuvant will address whether any effect observed is related solely to the vaccine.

CHAPTER 2

2. STUDY DESIGN

2.1.Study Overview

The study is a three-arm, phase II randomized, open-labeled clinical trial to evaluate vaccination with DC/myeloma fusions/GM-CSF plus lenalidomide maintenance therapy compared to lenalidomide maintenance therapy with or without GM-CSF following autologous transplant as part of upfront treatment for patients diagnosed with multiple myeloma. Patients meeting initial eligibility will be enrolled, and tumor cells will be harvested. Patients will proceed or continue with systemic anti-myeloma therapy and stem cell mobilization according to institutional practices. Patients with available cryopreserved tumor cells who are eligible to proceed to transplantation will be randomized in the study around day 56 post-transplant.

Approximately 2 months post transplant, patients will undergo their first disease response assessment and will be randomized 2:1:1 to the vaccine/GM-CSF plus lenalidomide arm, lenalidomide/GM-CSF arm, or lenalidomide alone arm. Patients assigned to vaccine plus lenalidomide maintenance will subsequently undergo leukapheresis for collection of dendritic cell precursors and vaccine production (DC/myeloma vaccine). For all patients, lenalidomide maintenance will start at Day 90-100 post-transplant and continue for two years or until disease progression, whichever comes first. Vaccines will be administered on the first day of cycles 2, 3, and 4 of lenalidomide maintenance, followed by four daily doses of GM-CSF for patients randomized to the vaccine arm. Patients randomized to lenalidomide/GM-CSF will receive GM-CSF in the same schedule and dose as patients in the vaccine arm. Primary end point assessment will occur at 1 year post-transplant.

2.2.Hypotheses and Specific Objectives

2.2.1. Hypothesis

Vaccination with DC/myeloma fusions plus lenalidomide maintenance therapy will result in improved responses in patients with multiple myeloma after autologous HCT.

2.2.2. Study Objectives

Compare the proportion of patients alive and in complete response (CR or sCR) at one year post-transplant, corresponding to approximately 10 months after randomization between patients receiving DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to those receiving lenalidomide maintenance therapy with or without GM-CSF.

2.2.3. Clinical Secondary Objectives

Compare myeloma response, rate of conversion to CR, myeloma progression, treatment-related mortality, progression-free survival, overall survival, incidence of grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, incidence of infections, measures of minimal residual disease, between the vaccine and the combined no-vaccine treatment arms. A secondary pairwise analysis of the proportion of patients alive and in CR at one year post-transplant will also be conducted between the vaccine arm, lenalidomide/GM-CSF arm, and the lenalidomide alone arm. Additionally the study will describe the proportion of

patients with collection of tumor cells who reach randomization, compliance with vaccine, and the reproducibility of the vaccine manufacturing based on the release criteria.

2.2.4. Immunologic Secondary Objectives
Primary immunologic endpoints:

- Compare the expansion of treatment-induced myeloma-specific T cells, defined as a 2.4-fold increase from pre-therapy to peak post-treatment levels between the vaccine arm and each of the no-vaccine arms separately.

Secondary immunologic endpoints:

- Determine the percentage of patients achieving at least a 10-fold expansion of myeloma-specific T cells in each treatment arm.
- Quantify myeloma antigen-specific T cells by tetramer analysis.
- Quantify T cell subsets and PD-1 expressing lymphocytes.
- Quantify NK cells and identify activation and inhibitory ligands.
- Assess NK cell-mediated killing of myeloma targets.
- Assess humoral response against whole myeloma cells and myeloma-associated antigens by SEREX and by characterizing myeloma-specific plasmablast responses.

2.3.Patient Eligibility
Patients must meet specified eligibility criteria outlined in section 2.3.1 and 2.3.2 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 Inclusion Criteria

1. Patients must be considered transplant eligible by the treating physician at time of study entry.

2. Patients must meet the criteria for symptomatic multiple myeloma (Appendix A) prior to initiating systemic anti-myeloma treatment.

3. Age $\geq$18 years and $\leq$ 70 years at the time of enrollment

4. Karnofsky Performance status of $\geq$ 70%

5. Patients must have $\geq$ 20% plasma cells in the bone marrow aspirate differential $\leq$60 days prior to enrollment. The required bone marrow evaluation will need to be repeated for patients who received more than 1 cycle of anti-myeloma therapy (cortiscosteroid with or without other anti-myeloma agents)

6. Patients must have received $\leq$ 2 cycles of systemic anti-myeloma therapy.

7. Renal: Creatinine clearance of $\geq$ 40 mL/min, estimated or calculated.

2.3.2. Initial Exclusion Criteria

1. Patients with a prior autologous or allogeneic HCT
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 and the absence of involved serum free light chain >100 mg/L]. Patients with light chain MM detected in the serum by free light chain assay are eligible.
3. Patients with Plasma Cell Leukemia
4. Patients with High-Risk Multiple Myeloma. High-risk is defined by the presence of any one of the following: deletion of chromosome 13 by conventional cytogenetics, hypodiploidy, abnormality in chromosome 1(1q amplification or 1p deletion), t(4;14), t(14;16), t(14;20) or deletion of 17p by fluorescence in situ hybridization (FISH) or conventional karyotyping; high-risk criteria based on commercially available gene expression profiling (GEP) detected at any time prior to enrollment;
5. Patients with disease progression prior to enrollment (see Section 3.1.2 for disease progression definition).
6. Patients seropositive for the human immunodeficiency virus (HIV).
7. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix H), 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 will be documented by the investigator as not medically relevant.
8. Patients with active clinically significant autoimmune disease, defined as a history of requiring systemic immunosuppressive therapy and at ongoing risk for potential disease exacerbation. Patients with a history of autoimmune thyroid disease, asthma, or limited skin manifestations are potentially eligible.
9. Patients receiving other investigational immunotherapy or anti-myeloma drugs within 14 days before enrollment.
10. Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent $\leq$ 5 years prior to enrollment will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs. Cancer treated with curative intent > 5 years prior to enrollment is allowed.
11. Female patients who are pregnant (positive β-HCG) or breastfeeding.

12. Females of childbearing potential (FCBP)[1] or men who have sexual contact with FCBP unwilling to use contraceptive techniques (Appendix D) during the length of lenalidomide maintenance therapy.
13. Patients who have received mid-intensity melphalan (>50 mg IV) as part of prior therapy.
14. Prior organ transplant requiring immunosuppressive therapy.
15. Patients who previously received lenalidomide and have experienced toxicities resulting in treatment discontinuation.
16. Patients who experienced thromboembolic events while on full anticoagulation during prior therapy with lenalidomide or thalidomide.
17. Patients unwilling to take DVT prophylaxis.
18. Patients unable or unwilling to provide informed consent.
19. Patients unable or unwilling to return to the transplant center for their assigned treatments.

2.3.3. Patient Eligibility Criteria for Randomization

1. Patient received transplant $\leq$ 12 months of enrollment onto BMT CTN 1401.
2. No disease progression since initiation of systemic anti-myeloma therapy as determined within seven days of randomization/enrollment.
3. Received an autologous cell transplant with melphalan 200mg/m^2 with a minimum cell dose of 2x10^6 CD34+ cells/kg (actual body weight).
4. Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
5. No evidence of uncontrolled infection requiring systemic therapy. Patients who completed treatment for an infection but are continuing antibiotics, anti-viral, or anti-fungal therapy for prophylaxis are eligible to continue on protocol.
6. Platelet count $\geq$75,000/mm^3 (without transfusion in previous 7 days).
7. Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3 without filgrastim administration within 7 days, or pegfilgrastim within 14 days of measurement.
8. Hepatic: bilirubin < 2x 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 2x the upper limit of normal.)
9. Renal: Creatinine clearance of $\geq$ 40 mL/min, estimated or calculated. Patients with creatinine clearance $\geq$30 but <40 will be considered with review/approval from the

1 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).

protocol chairs or officer if the cause of renal insufficiency is associated with multiple myeloma.

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

11. Females of childbearing potential (FCBP) as defined in section 2.7.1.1 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 prescribing lenalidomide (prescriptions must be filled within 7 days)

12. FCBP must either commit to abstain continuously from sexual intercourse or use 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, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of lenalidomide.

13. FCBP must agree to ongoing pregnancy testing as required by the RevlimidREMs program.

14. 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 while taking lenalidomide, during dose interruptions and for 28 days after discontinuing lenalidomide.

15. Patients must be willing to receive DVT prophylaxis.

2.4.Treatment Plan

2.4.1. Tumor Cell Collection

An initial eligibility assessment will be performed at time of study entry prior to tumor collection for immune monitoring and subsequent vaccine production. Eligible patients will undergo aspiration of 30 mL of bone marrow from which myeloma cell preparations will be generated (Appendix C). Bone marrow will be aspirated into sterile heparinized syringes with approximately 5-8 mL aspirated per syringe to avoid significant hemodilution of bone marrow mononuclear cells. Bone marrow aspirate samples will be transferred in sterile syringes to the cell manipulation facility, and mononuclear cells will be isolated by ficoll density gradient centrifugation. Autologous plasma will be obtained by harvesting supernatant following centrifugation of 50 mL of peripheral blood. Bone marrow mononuclear cells will be cultured in media with 10% autologous plasma. An aliquot of the tumor cells will be sent to BIDMC for centralized immunohistochemical staining as detailed in Appendix C. Tumor lysate will be prepared by freeze/thawing or sonication of an aliquot of tumor cells for immunological analysis. The remaining myeloma cells will be frozen in 10% DMSO/90% autologous plasma stored in liquid nitrogen for potential subsequent vaccine generation.

2.4.2. Systemic Anti-myeloma Therapy

Pre-transplant systemic anti-myeloma therapy will be administered per investigator discretion.

2.4.3. Stem Cell Mobilization
Stem cell mobilization and collection should be done according to institutional guidelines.

2.4.4. Autologous Stem Cell Transplantation
Autologous hematopoietic cell transplant will be done with high-dose melphalan (200mg/m^2) at the schedule and timing according to institutional practices.

2.4.4.1.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. Cryopreservation and thawing of product will comply with FACT standards and local institutional practice.

2.4.5. Maintenance Therapy
All patients who meet the eligibility criteria to proceed to maintenance and who have completed the post-transplant disease response assessment will be randomized at day 60 $\pm$ 7 days post-transplant and within 10 days of a disease response assessment.

Patients will begin maintenance therapy with lenalidomide between 90 and 100 days after stem cell infusion. Lenalidomide will be administered initially at a dose of 10 mg per day continuously. Cycle duration during maintenance therapy is 28 days. Patients will continue lenalidomide for two years from initiation of therapy or until one of the criteria in section 2.8 applies. Patients who stop maintenance therapy for any reason prior to two years from initiation of maintenance will continue to be followed per protocol for 3 years post maintenance initiation. Upon completion of protocol specified maintenance therapy, patients will be treated at the investigator's discretion. However, it is recommended that patients continue receiving lenalidomide as per standard of care.

2.4.5.1.Lenalidomide maintenance dose modifications
Lenalidomide dose will be adjusted for toxicity. Table 2.4.5b describes the dose reduction steps to be utilized during maintenance therapy. In the presence of lenalidomide-related toxicities (Table 2.4.5a), the study drug will be held until the toxicity resolves then restarted at a reduced dose as described in Table 2.4.5b. If lenalidomide is held for >8 weeks for any reason, study chair approval must be obtained prior to re-starting lenalidomide. Patients will be given DVT prophylaxis. DVT prophylaxis for patients will be given per institutional guidelines. See section 2.5.2 for suggested dose and more information.

Table 2.4.5a – Required Treatment Modification Guidelines for Lenalidomide Maintenance Therapy for Non-Hematologic Toxicities

Grade by NCI CTCAE#[1]	Action
Grade 3 neutropenia associated with fever (temperature $\geq$ 38. 5° C) or Grade 4 neutropenia	Hold lenalidomide. Follow CBC weekly. If the toxicity resolves to $\leq$grade 2 restart lenalidomide at next lower dose level. If neutropenia is the only toxicity for which a dose reduction is required, granulocyte growth factors could be considered at the discretion of the treating physician and the lenalidomide dose maintained. .

Table 2.4.5a – Required Treatment Modification Guidelines for Lenalidomide Maintenance Therapy for Non-Hematologic Toxicities

Grade by NCI CTCAE#[1]	Action
Thrombocytopenia (platelet count < 30,000/mm³)	Hold lenalidomide. Follow CBC weekly. If the toxicity resolves to ≤grade 2 restart lenalidomide at next lower dose level.
Non-blistering rash Grade 3 (Generalized rash ≥ 25% BSA)	Hold lenalidomide: Follow weekly. Treatment with antihistamine may be initiated at the discretion of the investigator. If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level.
Non-blistering rash Grade 4	Discontinue lenalidomide permanently. Continue to follow the patient per-protocol
Desquamating (blistering) rash any Grade	Discontinue lenalidomide permanently. Continue to follow the patient per-protocol
Venous thrombosis/embolism ≥ Grade 3 (DVT or cardiac thrombosis; intervention indicated)	Hold lenalidomide and start anticoagulation per institutional guidelines. Restart therapy and maintain dose level.
Other non-hematologic toxicity assessed as Lenalidomide-related ≥ Grade 3	Hold lenalidomide. If the toxicity resolves to ≤ grade 2 restart lenalidomide at next lower dose level.
Hyperthyroidism or Hypothyroidism	Hold lenalidomide. Evaluate etiology, and initiate appropriate therapy. Restart lenalidomide at next lower dose level .
Pregnancy[3]	Discontinue lenalidomide study drug.

[1]Please consult NCI CTCAE version 4 http://ctep.cancer.gov/reporting/ for complete Grade descriptions. The "≥ Grade 3" descriptions listed above are minimums

[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 2.4.5b – Lenalidomide Dose Reduction Steps During Lenalidomide Maintenance Therapy

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

2.4.5.2.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 2.4.5c, one step per cycle to a maximum of 10 mg daily.

Table 2.4.5c – Lenalidomide Dose Re-Escalation Steps During Lenalidomide Maintenance Therapy

Current Patient Dose	Dose Re-Escalation
2.5 mg daily for 21 days every 28 days	5 mg daily for 21 days every 28 days
5 mg daily for 21 days every 28 days	5 mg daily
5 mg daily	10 mg daily
10 mg daily	No more dose escalations permitted

2.4.6. Vaccine Manufacturing and Administration

Vaccine preparation is outlined in detail in the BMT CTN 1401 SOPs and will be performed locally at each participating institution. Patients randomized to receive the DC/MM fusion vaccine will undergo leukapharesis for DC and vaccine generation. The leukapheresis product will be transferred in a sterile container to the cell manipulation facility, and PBMC will be isolated from the leukapheresis product and cultured in the presence of autologous plasma for 1-2 hours and then cultured for 5-7 days with GM-CSF and IL-4. Cultures are re-fed with cytokines after 3 days. Twenty five ng/mL of TNFα will be then be added for 48-72 hours to induce DC maturation. An aliquot of the DC preparation will be sent to BIDMC for immunocytochemical staining for immunophenotypic analysis. Tumor cells and DC preparations will be co-cultured at ratio of 1:3 and washed in serum-free medium. After low-speed centrifugation, the cell pellet will be re-suspended in 50% solution of polyethylene glycol (PEG) and will be progressively diluted by the slow addition of serum-free medium. An aliquot of the DC, tumor, and fusion cell preparations will be sent to BIDMC for immunocytochemical analysis for vaccine characterization. Three doses of 3 x 10^6 fusion cells will be prepared. The fusion cells will then be separated into appropriate aliquots of fusion cells, radiated at 30 Gy, and frozen in 10% DMSO/90% autologous plasma in liquid nitrogen. A minimum of 2 doses will be required to proceed with treatment. An aliquot of the vaccine product will be sent for microbiological assessment consisting of endotoxin, mycoplasma and sterility testing as detailed in the CMC section. Release criteria for vaccine administration are:

1) > 50% of DC prep express CD86
2) Viability of DC prep > 70%
3) Fusion efficiency > 15%
4) Fusion viability > 50%
5) Sterility, mycoplasma, and endotoxin assays are negative

At time of administration, fusion cells will be thawed. Patients randomized to the vaccine arm will receive the DC/myeloma fusion vaccine/GM-CSF (vaccine) on day 1 of cycles 2, 3, and 4 of lenalidomide maintenance. Vaccine will be administered by subcutaneous injection with 100 ug GM-CSF given subcutaneously at the vaccine site on day of vaccination and daily for a total of 4 days of each cycle.

2.4.6.1.Failure to Meet Release Criteria
Sites experiencing difficulties with production as evidenced by failure to meet release criteria for 3 products will have vaccine production temporarily halted while undergoing onsite review of procedures by a member from the protocol team and central site. Additional training or guidance will be provided if needed.

Table 2.4.6a –Vaccine Administration Guidelines for Vaccine, GM-CSF and/or Lenalidomide Toxicities

Toxicity	Action
Hold/delay in lenalidomide therapy	Hold/delay vaccine. When lenalidomide is restarted, adjust date of vaccine administration to coincide with Day 1 of cycles 2, 3 and 4 of lenalidomide maintenance .
Discontinuation in lenalidomide therapy	Administer vaccine at monthly intervals for a total of 3 doses
Grade 4 toxicity judged to be related to vaccine alone	No additional vaccines.
Grade 3 toxicity judged to be related to vaccine alone	Hold Vaccine Dose. If the toxicity resolves to ≤ grade 2 by time of subsequent vaccine administration, vaccine may continue.
Grade 3-4 toxicity judged to be related to GM-CSF alone	Omit GM-CSF administration for subsequent vaccine injections or subsequent scheduled admnistrations in the non-vaccine arm. Re-challenging GM-CSF administrated when toxicity resolves to ≤ grade 2 can be considered at the discretion of the treating investigator.
Grade 3-4 toxicity possibly related to combination of lenalidomide and vaccine	Follow lenalidomide dose adjustments.

2.4.7. GM-CSF Administration
For patients randomized to the vaccine and GM-CSF plus lenalidomide maintenance and lenalidomide maintenance plus GM-CSF arms, GM-CSF will be administered at cycles 2, 3, and 4 of maintenance therapy. 100 ug GM-CSF will be given subcutaneously (at the vaccine site for patients receiving vaccine) on days 1-4 of cycles 2, 3, and 4.

On the first day of GM-CSF administration, 100 ug of GM-CSF subcutaneously will be administered subcutaneously. The patient will be trained to inject the remaining three GM-CSF injections (100ug dose once a day at the vaccination site) for self-administration subcutaneously at home. Alternatively, if patients are unwilling or unable to self-administer the GM-CSF, they can return to the transplant center for subsequent injections. For patients receiving vaccine, tumor vaccine will be administered before the GM-CSF injection. If a patient experiences a grade 2 or higher (graded according to CTCAE v4.0) injection site reaction during the days when GM-SCF is administered, subsequent doses of GM-CSF may be held until the injection site reaction improves to grade 1 or less at the discretion of the treating investigator. For subsequent administrations, patients will receive pre-medication with diphenhydramine (Benadryl) 25-50 mg and/or acetaminophen (Tylenol) 650-1000 mg to minimize potential allergic-related symptoms.

2.5.Supportive Care

2.5.1. Post Autologous Transplantation(s)
All supportive care will be given at the investigator's discretion.

2.5.2. Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Prophylaxis
Prophylaxis for DVT/PE will be done according to institutional guidelines. Upon initiation of lenalidomide maintenance it is recommended that patients without a history of thromboembolic events should be on aspirin daily (81mg, 165mg or 350 mg); low molecular weight heparin or warfarin is usually administered in patients with a history of thromboembolic events or those that cannot tolerate aspirin.

2.6.Risks and Toxicities

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 4.0 with BMT CTN 1401 specific definitions when appropriate.

2.6.2. 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.
- Second Primary Malignancies

Pregnancy reporting:
See Section 4.4.4, Adverse Event Reporting.

Other instructions related to lenalidomide:
During maintenance, only one cycle (maximum 28-day supply) of therapy may be dispensed to the patient each month. 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 2.7.1.1, Chapter 4, Appendices D (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and E (Revlimid REMS program).

2.6.3. DC/Fusion Vaccine - Manufacturing and Administration

2.6.3.1. Tumor Collection
All eligible patients will undergo a bone marrow biopsy and collection of 30 mL of bone marrow aspirate. The risks of this procedure are not different than bone marrow aspirates performed for diagnosis or disease status assessments. The risks include: bleeding, pain in the site of marrow collection, claudication and bruising.

2.6.3.2.Dendritic Cell Precursor Collection
Collection of dendritic cell precursors will occur in patients randomized to receive vaccine post transplant. Collection will be done through leukapheresis in a single session. Risks of this collection are related to placement of an intravenous leukapheresis catheter that can be associated with bleeding and pain. The leukapheresis procedure has a risk of hypocalcemia, thrombocytopenia, anemia, leukopenia and bleeding diathesis.

2.6.3.3.Vaccine Administration
Vaccines will be administered at three time points approximately one month a part. GM-CSF will also be administered at the site of vaccine for 4 consecutive days. Toxicities related to the vaccine are:

- Hematologic: Leucopenia
- Neurologic: Headache
- Gastrointestinal: Diarrhea, decrease appetite.
- Constitutional: Weakness, chills and fever.
- Musculoskeletal: arthralgia and myalgia.
- Dermatologic: rash, itching, periorbital edema and local reaction in the site of infusion (swelling, pain, erythema and pruritus).
- Endocrine: elevated TSH.
- Other: ANA positivity

2.6.4. GM-CSF
Potential side effects of GM-CSF treatment include fever, chills, nausea, vomiting, diarrhea, fatigue, weakness, headache, decreased appetite, facial flushing, bone and muscle pain, local reaction at the site of injections, rashes, low blood pressure, shortness of breath and low blood counts. Rarely patients may develop blood clots, rapid or irregular heartbeats, feeling of faintness, kidney and liver problems, allergic reactions or fluid retention, including potential fluid retention in lungs or around the heart, and keratitis (inflammation of the cornea).

2.7.Study Drug Supply

2.7.1. Lenalidomide
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).

2.7.1.1.Lenalidomide (NSC 703813)

NOTE:
Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) study patients must be be counseled through the Revlimid REMS program. A maximum 28-day supply may be dispensed to a patient at one time. For more information please refer to www.revlimidrems.com. Only use the study specific drug request form per patient for ordering through Biologics.

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) and 2.5 mg 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™. Prescriptions must be filled within 7 days for FCBP and 14 days for all other risk categories.

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 to the clinical site and destroyed per institutional guidelines.

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 REMs program.

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 prescribing study drug. The first pregnancy test must be performed within 10-14 days prior to prescribing study drug and the second pregnancy test must be performed within 24 hours prior to prescribing 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.
- FCBP must commit either to abstain continuously from heterosexual intercourse or to use TWO methods of reliable birth control AT THE SAME TIME—one highly effective form of contraceptions and one additional effective contraceptive method as defined below. Contraception must begin 4weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of lenalidomide.
    - HIGHLY EFFECTIVE:
        - Tubal Litigations
        - IUD
        - Hormonal contraceptives (birth control pills, injections, hormonal patches, vaginal rings or implants)
        - Partners Vasectomy
    - EFFECTIVE:
        - Male latex or synthetic condom
        - Diaphragm
        - Cervical cap

Male Subjects:

- Must agree to use a latex or synthetic condom during sexual contact with females of childbearing potential while participating in the study, during dose interruptions 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.

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 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 (Lenalidomide 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 REMs program. Physician registration allows access to the REMs software to enroll patients in the REMs program. The prescriber should submit the Registration Form via fax number 919-256-0794 or REMsOnline ***(RAO)***for Revlimid) to Celgene Customer Care. Please reference Appendix E (REMsprogram) 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 REMs study specific electronic prescription form referenced in Appendix E (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 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 (REMsprogram).

2.8.Patient Withdrawal from Study and Off Study Criteria

Patients on the BMT CTN 1401 study have voluntarily agreed to the study and may withdraw at anytime. Additionally, the treating physician may discontinue therapy with reasonable justification. The following criteria would result in discontinuation of study therapy:

- Disease progression
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

After randomization, patients who stop therapy for any reason prior to two years from initiation will continue to be followed per protocol for 3 years post maintenance initiation unless the

patient withdraws consent for study follow up. In the event of patient withdrawal, written documentation of the withdrawal must be provided to the BMT CTN.

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITIONS

3.1.Definition of Disease Status

Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria[19]. Until disease progression, all disease classifications are relative to the patient's disease status prior to autologous transplant (i.e. study entry). At time of disease progression, disease classifications are relative to the patient's best response since time of study entry.

3.1.1. Response Categories

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):
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)*.
- 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.

Very Good Partial Remission (VGPR)
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.
- For free light chain only disease, VGPR requires a 90% reduction of involved light chain

Partial Response (PR)
PR requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and 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 if present at baseline (by radiography or clinical examination).

Stable Disease (SD)

- Patients who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease (section 3.1.1.2) are considered to have stable disease (SD).

3.1.2. Progressive Disease (PD)

Disease Progression (PD)
Progression 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 measured from the time of randomization:

- >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.

3.2.Primary Endpoint

The primary objective of this randomized trial is to compare the proportion of patients alive and in complete response (CR or sCR) at one year post transplant between patients receiving DC/myeloma vaccine/GM-CSF with lenalidomide maintenance therapy to those receiving lenalidomide maintenance therapy with or without GM-CSF.

3.3.Clinical Secondary Endpoints

3.3.1. Response to treatment

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 both arms from the time of randomization. Assessment of disease response will be done immediately prior to randomization and prior to initiation of maintenance then monthly for 6 months then every 3 months until approximately 22 months from randomization or evidence of disease progression. Rates of VGPR or better responses will be compared between the two arms. For patients not in CR at randomization, the rate of CR conversion (CR and sCR) will be compared between the vaccine and no-vaccine arms combined.. A secondary pairwise analysis will compare the CR rates at 1 year between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.2. Myeloma Progression

Myeloma progression defined according to Section 3.2 or initiation of off protocol anti-myeloma therapy is the event for this endpoint. Death without documentation of disease progression is the competing event. Patients alive without disease progression at last contact are considered censored for this event. The cumulative incidence of myeloma progression will be compared between vaccine and no-vaccine arms combined. A secondary pairwise analysis will compare the cumulative incidence of myeloma progression between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.3. Minimal Residual Disease Assessment

Minimal residual disease (MRD) is defined as the presence of malignant plasma cells detected by multicolor flow cytometry among patients who are in complete remission. Multichannel flow cytometry will be used to establish MRD based on the presence of malignant plasma cells that are CD45 (-/dim), CD38+,CD138+,CD19-, CD56+ kappa or lambda restricted. The result will determine whether that patients has MRD (MRD +) or not (MRD -). The proportion of patients who are MRD negative at one year will be compared between vaccine and no-vaccine arms combined. A secondary pairwise analysis will be conducted comparing the proportion of patients who are MRD negative at one year between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.4. Treatment-related Mortality

TRM is defined as death occurring in a patient from causes other than disease relapse or progression. Disease progression is the competing event for TRM. Patients alive without disease progression at last contact are considered censored for this event. TRM from time of randomization will be compared between vaccine and no-vaccine arms combined starting at time of randomization. A secondary pairwise analysis will compare TRM between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.5. Incidence of Toxicities Grade ≥3 per CTCAE version 4.0

All Grade ≥ 3 toxicities will be tabulated for treatment arms. The proportion of patients developing Grade ≥ 3 toxicity will be compared between the vaccine and no-vaccine arms combined until disease progression or end of follow up. A secondary pairwise analysis will compare the incidence of toxicities between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.6. Incidence of Infections per BMT CTN Technical MOP

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient. The proportion of patients in each treatment arm with these infections will be compared from randomization until disease progression or end of follow up.

3.3.7. Progression-free survival

Patients are considered a failure of this 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 study whichever comes first and it will be compared between the vaccine and no-vaccine arms combinedfrom time of

randomization. A secondary pairwise analysis will compare progression-free survival between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.3.8. 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 the study, whichever comes first. Patients alive at the time of last observation are considered censored. Overall survival will be compared between the vaccine and no-vaccine arms combined from time of randomization. A secondary pairwise analysis will compare overall survival between the vaccine arm, lenalidomide/GM-CSF arm and lenalidomide alone arm.

3.4.Primary Immunologic Endpoints

3.4.1. Myeloma-Reactive T-cells
The effect of DC/Myeloma Fusion Vaccine/GM-CSF with lenalidomide maintenance; lenalidomide maintenance; and lenalidomide maintenance with GM-CSF on levels of circulating myeloma reactive T cells will be quantified. Myeloma-reactive T cells, as defined by the percentage of circulating CD4+ and CD8+ T cells that express IFNγ following ex vivo exposure to autologous tumor lysate will be assess in both treatment arms. The percent of patients achieving at least a 2.4-fold increase in tumor reactive T cells will be compared between the vaccine and each of the no-vaccine arms separately.

3.5.Secondary Immunologic Endpoints:

3.5.1. Myeloma-Reactive T-cells
The percent of patients achieving at least a 10-fold increase in tumor-reactive T cells will be compared between the vaccine and no-vaccine arms separately as described above.

3.5.2. Assessment of antigen specific reactivity:
The effect of DC/Myeloma Fusion Vaccine/GM-CSF + lenalidomide maintenance; lenalidomide maintenance; and lenalidomide maintenance + GM-CSF on immunologic responses directed against previously identified myeloma antigens will be assessed. In HLA-A2.1 patients, circulating CD8+ T cells binding tetramer constructed from MUC1, SOX2, NY-ESO, and XBP-1 will be quantified. At serial time points PBMC and BMMC will undergo dual staining for CD8 and the appropriate tetramer, and analyzed by multichannel flow cytometry. When cell yields allow, functional characteristics of the tetramer positive population will be determined by measuring IFNγ, granzyme B, IL-4, and IL-10 expression in the tetramer positive cells by intracellular staining.

3.5.3. Quantification of T-cell subsets:
Quantification of regulatory T cells and activated memory effector cells will be performed at the serial time points(Appendix C). T cell subsets will be quantified with respect to the relative proportion of CD4 and CD8+ T cells and the presence of naïve, effector memory, and central memory cells will be determined by staining for CD45RA, and CD45RO, CD27, and CD62L by multichannel flow cytometry. Regulatory T cells will be quantified as CD4/CD25/FOXP3 cells. T cells expressing PD-1 will be quantified at the time points indicated above. Quantification of

granulocytic and monocytic myeloid derived suppressor cells will be performed from peripheral blood and bone marrow samples undergoing multichannel flow cytometry for CD11b, HLA-DR, CD14, CD15 and CD33.

3.5.4. Assessment of effect on NK cell populations:
The effect of lenalidomide alone and in combination with DC/MM vaccination on the phenotype and function of circulating NK cell populations will be assessed as detailed in Appendix C. The expression of a panel of NK receptors including activating receptors (NKp30, NKp44, NKp46, NKG2D, NKG2C, DNAM1), inhibitory receptors (NKG2A and KIRs) and markers of NK function (CD16, CD25, CD132) will be assessed. The effector function of NK cells against MHC class I-deficient leukemia targets and primary MM cells (where available) from the recipient will be assessed by intracellular cytokine assay for interferon-gamma (IFN-γ) production, and cytotoxicity, including CD107a degranulation and 51chromium release assay. The expression of receptors important in the regulation of human NK cell trafficking and homing in vivo, including CD62L, CXCR4, CXCR3, CCR6 and CCR7 will be measured. The effect of treatment on NK function will be assessed by examining expression of the canonical transcription factors eomesodermin (Eomes) and T-bet prior to and serially following initiation of therapy. Surface expression of CD57 and KLRG1, both markers of mature NK cells, will be evaluated.

3.5.5. Assessment of humoral immune response:
Serological Analysis of Recombinant cDNA Expression Library (SEREX) will be performed on serum samples to assess humoral response targeting myeloma antigens in patients treated with lenalidomide maintenance alone or in conjunction with DC/MM fusion vaccination as detailed in Appendix C. Peripheral blood will be transported for a cell based assay to assess the kinetics, magnitude and specificity of vaccine-induced myeloma specific plasmablast responses, as detailed in appendix C.

CHAPTER 4

4. PATIENT REGISTRATION, ENROLLMENT, AND EVALUATION

4.1.Enrollment Procedures

Patients are enrolled in to the Segment A prior to initial systemic therapy (≤2 cycles) and first autologous transplant. At the time of enrollment, an authorized user at the clinical center completes the demographics and primary eligibility form which includes questions confirming that the patient signed the consent and meets the eligibility criteria for study entry. This will occur prior the collection of tumor cells.

Once the patient is enrolled in the study (Eligibility Form, Segment A competed):

1. A visit schedule based on enrollment date will be available for printing
2. Following enrollment and tumor cell collection the patient should proceed with initial systemic therapy and first autologous transplant. Patients should be transplanted within one year of enrollment into Segment A.
3. Patient will be seen 60 days (± 7 days) after the autologous HCT for disease response and eligibility assessments prior to randomization/enrollment in Segment B. An authorized user at the clinical center completes a checklist confirming that the patient is eligible to proceed to the next stage of treatment on the study.
4. If the patient is eligible, they will be enrolled in Segment B and randomized to their treatment assignment and the treatment plan is continued.
5. A visit schedule based on the date of randomization will be available for printing.

4.2.Study Monitoring

4.2.1. Follow- Up Schedule

The follow up schedule for study visits after Segment A enrollment and subsequently after randomization are outlined below in tables 4.2.1A and 4.2.1B, respectively. The follow up schedule is the intended schedule; however, the date of the follow up evaluations may vary due to delays in treatment or treatment interruption related to Adverse Events and toxicities. The visit window for the scheduled evaluations is included in each table. Patients will be followed for three years post maintenance initiation.

4.2.1A: FOLLOW UP SCHEDULE AFTER ENROLLMENT (SEGMENT A)

Study Visit	Target Day
Pre- Enrollment Screening	≤ 8 weeks prior to enrollment
Tumor cell collection	7 days post enrollment±7[1]
Pre- Randomization Screening	≤ 14 days prior to randomization
Randomization	60 ± 7 days post transplant[2]
Pre- Maintenance Screening	≤ 14 days prior to maintenance initiation
Maintenance Start	90-100 days post- transplant[3]

[1] Tumor cell collection by bone marrow aspirate can occur the same day of enrollment and up to 14 days after enrollment
[2] Randomization must also occur within 10 days of a disease response assessment
[3] Start of maintenance should fall 30 to 43 days after randomization.

4.2.1B: FOLLOW UP SCHEDULE POST RANDOMIZATION TO MAINTENANCE

Study Visit	Target Day Post Maintenance (± 7 days)[1]
Baseline	≤ 14 days prior to randomization
Prior to initiation of maintenance	≤ 14 days prior to maintenance
Start of Maintenance[2]	Day 1
1 month	28 days
2 month	56 days
3 month	84 days
4 month	112 days
6 month	180 days
9 month	270 days
12 month	365 days
15 month	455 days
18 month	545 days
21 month	635 days

[1]After 9 months of maintenance therapy, patients can be seen ± 14 days from the target date.
[2]Maintenance will begin between 90 and 100 days post transplant or 30 to 43 days after randomization.

4.2.1C: FOLLOW UP SCHEDULE ENDPOINT ASSESSMENTS[1]

Endpoints	Days From Randomization
12 months post transplant (12T)[2]	Day 270 ± 14 days
24 months post transplant (24T)[3]	Day 635 ± 14 days

[1]Endpoint assessments will occur yearly post transplant for 2 years or until disease progression. These assessments may be conducted at the required visits outlined in table 4.2.1b if they fall within 14 days of the target date for the post randomization visit.
[2]The 12 month post transplant visit should correspond to the 10th cycle of maintenance unless the patient has been delayed for any reason.
[3]The 25 month post transplant visit should correspond to the 22st cycle of maintenance unless the patient has been delayed for any reason.

4.3.Patient Evaluations

4.3.1. Pre- Enrollment Segment A Evaluations and Requirements

The following evaluations must be determined $\leq$ 8 weeks prior enrollment on BMT CTN 1401. See table 4.31A.

1. History, physical examination, height and weight
2. Karnofsky Performance Score
3. CBC with differential, platelet count
4. Liver Functions and blood chemistries: Serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT
5. Evaluation of creatinine clearance
6. Laboratory Disease Evaluation:
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC)
7. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required to assess plasma cell involvement in the marrow as per eligibility criteria outlined in section 2.3.1
8. Skeletal bone survey to include cranium, axial skeleton and proximal long bones

4.3.2. Tumor Cell Collection Evaluations and Requirements at Enrollment

1. Tumor Cell Collection
    a. Bone marrow aspiration (30mL) is required for vaccine production and eligibility validation.
    b. Peripheral Blood (50mL) collection
2. Protocol-required Samples for Correlative Studies (Table 4.3B)
    a. Bone marrow aspirate (4mL) for immunologic endpoints (see appendix C for details)
    b. Peripheral Blood (40mL) collection for immunologic endpoints (see appendix C for details)
3. Optional Samples for Future Research
    a. Bone marrow aspirate (3mL) (see appendix C for details)
    b. Peripheral Blood (6mL) collection (see appendix C for details)

4.3.3. Pre- Randomization Evaluations and Requirements

The following evaluations to determine eligibility for randomization must be performed ≤ 14 days prior to randomization unless otherwise noted below.

1. History and physical examination
2. Assessment for toxicities
3. Laboratory Disease Evaluation(≤10 days from randomization):
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC)
4. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients unless required for BMT CTN 1401 correlative studies .
5. Protocol-required Samples for Correlative Studies (Table 4.3B)
    a. Bone marrow aspirate (6mL)(for immunologic endpoints (see Appendix C for details)
    b. Peripheral Blood collection (30mL) for immunologic endpoints (see Appendix C for details)
6. Optional Samples for Future Research
    a. Bone marrow aspirate (3mL) (see Appendix C for details)
    b. Peripheral Blood (6mL) collection (see Appendix C for details)
7. Skeletal bone survey to include cranium, axial skeleton and proximal long bones
8. CBC with differential, platelet count
9. Liver Functions and blood chemistries: Serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT
10. Evaluation of creatinine clearance
11. Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL) for FCBP.

4.3.4. Pre- Maintenance Evaluations and Requirements

The following evaluations to determine eligibility for maintenance initiation must be performed ≤ 14 days prior to the initiation of lenalidomide maintenance therapy unless otherwise noted below.

1. History and Physical Exam
2. Assessment for toxicities
3. CBC with differential, platelet count
4. Liver Functions and blood chemistries: Serum creatinine, total bilirubin, alkaline phosphatase, AST, 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 prescribing lenalidomide,
   b. The second is required within 24 hours of prescribing lenalidomide.

4.3.5. Evaluations during Maintenance

1. The following evaluations will be done monthly for the first 4 months and then every 3 months thereafter:
   a. History and physical exam
   b. CBC with differential, platelet count
   c. Liver Functions and blood chemistries: Serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT

2. Assessment for Toxicities monthly for the first 4 months and then at cycles 6, 9, 15, 21, and 24[1].

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.

[1] Patients experiencing adverse events outside of the toxicity assessment timelines are still required to adhere to the adverse event reporting requirements in section 4.4.4 and Appendix J.

4. Laboratory Disease Evaluation at prior to cycles 3, and 6, and every 3 months thereafter. Disease evaluations will also be collected yearly post transplant:
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC)

5. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients

6. Skeletal bone survey to include cranium, axial skeleton and proximal long bones at cycles 9 and 21.

7. Samples for Correlative Studies (Table 4.3B)
    a. Bone marrow aspirate (6mL) just prior to the start of cycle 9 of maintenance for immunologic endpoints (see Appendix C for details).
    b. Bone marrow aspirate (6mL) following cycle 9 of maintenance (~1 year post transplant) for immunologic endpoints (see Appendix C for details).
    c. Peripheral Blood collection prior to cycles 1, 2, 3, 4, and 9 and at day 7 of cycles 2 and 4 for immunologic endpoints (see Appendix C for details).

8. Optional Samples for Future Research
    a. Bone marrow aspirate (3mL) collection at cycle 9 of maintenance (see Appendix C for details)
    b. Peripheral Blood (6mL) collection at cycle 9 of maintenance (see Appendix C for details)

TABLE 4.3A: PATIENT CLINICAL ASSESSMENTS

Study Assessments	Pre-Enrollment	Pre-Randomization	Pre maintenance	Cycles of maintenance										
			1	2	3	4	6	9	12	15	18	21	24
History, physical exam, weight and height[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance score	X												
CBC, differential, platelet count, and blood chemistries[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of Creatinine Clearance	X	X											
Pregnancy test[3]		X	X	X	X	X	X	X	X	X	X	X	X
Quantitative serum immunoglobulins	X	X			X		X	X	X	X	X	X	X
SPEP and immunofixation	X	X			X		X	X	X	X	X	X	X
24 Hour Urine for UPEP, protein excretion and immunofixation	X	X			X		X	X	X	X	X	X	X
Serum free light chain ratio	X	X			X		X	X	X	X	X	X	X
Skeletal Survey	X	X						X				X	
Bone marrow aspirate and biopsy	X[4]	X[5]			X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Toxicity assessment[6]		X	X	X	X	X	X	X		X		X	

[1]Height and Weight are only required at pre-enrollment and pre-randomization visits.
[2]Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST and ALT as required per protocol.
[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]Bone Marrow aspirate and biopsy required within 60 days of enrollment; must be repeated if patient receives additional therapy between initial pre-treatment BM and enrollment
[5]Bone Marrow aspirate and biopsy required only to confirm CR in patients
[6]The toxicity assessment will include a review of **all** toxicities and appropriate lab evaluations experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC using CTCAE version 4.

TABLE 4.3B: Sample Collection time points

Sample Collection	Tumor Cell Collection (At Enrollment)[4]	Pre-Randomization	Cycles of maintenance							
			1	2	2 +7d	3	4	4 + 7d	6	9
Bone Marrow Aspirate										
Bone marrow aspirate for tumor collection (30mL)	X[1]									
MRD Assessment (6 mL)[2]		X								X[6]
Myeloma Reactive T Cells (4 mL)	X[1]									X
Optional Repository Sample for Future Research (3mL)	X[1]	X								X
Total Maximum Marrow Volume (mL)[5]	**37**	**9**								**13**
Peripheral Blood										
Plasma for Vaccine Production (50mL)	X[5]									
Plasmablast Responses (30mL)		X		X[3]	X[3]		X[3]	X		
Myeloma Reactive T Cells (40mL)	X[5]		X	X		X	X			X
NK cell reconstitution (30mL)			X		X	X		X		X
Optional Repository Sample for Future Research (6mL)	X[5]	X								X
Total Maximum Blood Volume (mL)	**96[5]**	**36**	**70**	**70[3]**	**60[3]**	**70**	**70[3]**	**60**		**76**

[1] Bone marrow aspirate for collection of tumor cells should be done with 1-2 pull(s) per site until the total volume is achieved. The first 30mL will be dedicated for vaccine production, which will be cryopreserved at the transplant center. The remainder volume (10mL) will be aliquot in three samples, which will be shipped to the BMT CTN repository and to BIDMC.

[2] Minimal residual disease (MRD) assessment will be done at the center and centrally at RPCI, the MRD sample will be aliquot in two 3 mL samples, one will be sent to RPCI and the other for analysis at the transplant center. Patients with overt evidence of disease progression are not required to submit sample for MRD assessment.

[3] Assessment for plasmablast only applies to patients who were randomized to the vaccine arm.

[4] The Tumor Cell Collection Visit should occur $\leq$ 7 days post enrollment

[5] Blood collection at study entry can be collected over a 10 day period to avoid collection of excessive volumes in a single day.

[6] MRD assessment should be collected following cycle 9 of maintenance or at ~ 1 year post transplant

4.4.Data Reporting

4.4.1. Criteria for Forms Submission

Forms that are not entered into AdvantageEDC^{SM} within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC^{SM} and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File.

4.4.2. Reporting Patient Deaths

Recipient death information must be entered into AdvantageEDC^{SM} 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 AdvantageEDC^{SM}.

4.4.3. 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 in BMT CTN 1401 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post- transplant Comprehensive 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.

4.4.4. Adverse Event Reporting

Reporting of adverse events on the BMT CTN 1401 protocol has unique requirements due to the addition of lenalidomide as part of the protocol. Adverse event reporting requirements are summarized below and further described in Appendix J.

4.4.4.1.Definitions

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

Expectedness: An adverse event can be Expected or Unexpected

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

- **Unexpected adverse events** are those that vary in nature, intensity or frequency from information in the current adverse event list, the Investigator's Brochure, the package insert, or when it is not included in the informed consent document as a potential risk.

4.4.4.2. BMT CTN Adverse Event Reporting Guidelines

It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment. Reporting of AEs for BMT CTN 1401 will be consistent with the BMT CTN Administrative Manual of Procedures. Additional requirements specific to this protocol are outlined below and in Appendix J.

In BMT CTN studies, expected adverse events are reported via the web-based electronic data capture system, AdvantageEDC. Events are captured on calendar-driven case report forms (e.g., Toxicity) or event-driven case report forms (e.g., Progression, and Death).

From the time of enrollment until randomization, only deaths, secondary primary malignancies and progressions are required to be reported. From time of randomization until 3 years post maintenance initiation, unexpected, grades 3-5 AEs, irrespective of the attribution of the event to the study drug /procedure/treatment, will be reported through the expedited AE reporting system via AdvantageEDC, and will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The BMT CTN 1401 protocol has two distinct interventions: transplant and maintenance therapy. Determination of expectedness for events occurring post-transplant and/or post-maintenance therapy will be at the discretion of the investigator as described in Appendix J. **Unexpected, grades 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.** The NHLBI Data and Safety Monitoring Board will receive summary reports of all adverse experiences at least twice yearly.

Since this study is under an FDA Investigational New Drug, all suspected and unexpected fatal or life-threatening adverse events are reported to the FDA within seven calendar days after receipt of the information, following FDA guidelines. All suspected and unexpected Grade 3 serious adverse events are reported to the FDA via a written report within fifteen days of receipt of the information (21 CFR 312.32). If the Medical Monitor assesses the event to be unrelated to the study, then the event will not require expedited reporting but will be included in a summary report issued annually. All expected adverse events (i.e., those listed in the informed consent, product inserts, or study materials) not covered under the above requirements need not be reported via the AE Form. They will be captured on other CRFs. Although death and graft failures are not considered unexpected post-transplant events, they are reported to the FDA via annual reports. Safety reporting to the FDA will be done by the BMT CTN based upon date of initial entry on the Adverse Event Forms and requires no additional action from the participating site.

All second primary malignancies (SPM), excluding non-melanoma skin cancers, experienced by patients enrolled on the study will be reported using the expedited AE reporting system in AdvantageEDC and must be reported within three business days of knowledge of the event. The Event Description entered in AdvantageEDC should include histologic type.

4.4.4.3. Additional Adverse Event Reporting

Celgene Corporation (Celgene) is supplying lenalidomide for this study and a description of additional reporting requirement for this study is detailed in **Appendix J**. The additional adverse event reporting period for lenalidomide begins with the first dose and continues until 28 days after permanent discontinuation of lenalidomide.

4.4.4.4.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 J 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 3 years post-maintenance initiation.

4.4.4.5.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 J 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 J 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.

4.4.5. Pregnancy Reporting

Pregnancies, suspected exposure of a pregnant woman (including female partner of a male patient and exposure to lenalidomide while dispensing) and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported through the expedited AE reporting system in AdvantageEDC. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the expedited AE reporting system in AdvantageEDC. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality through the expedited AE reporting system in AdvantageEDC. In addition, any infant death after 28 days that the Investigator suspects is related to the inutero exposure to lenalidomide should also be reported through the expedited AE reporting system within 24 hours of the Investigator's knowledge of the event

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.

4.4.6. Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

4.4.7. Reporting of other Special Events of Interest
There are other special events of interest to Celgene that require reporting through the AE expedited reporting system in AdvantageEDC. If any of the following events occur, they are required to be reported within 3 business days of the site's knowledge of the event:

- overdose, abuse and misuse that meets one of the criteria of a serious adverse event
- medication errors that meets one of the criteria of a serious adverse event
- occupational exposure of any kind
- public health emergency
- Celgene product technical complaint that leads to an adverse event

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1.Study Design

The study is designed as a Phase II randomized, open label, multicenter trial to evaluate the use of vaccination with DC/myeloma fusions/GM-CSF plus lenalidomide maintenance therapy compared to lenalidomide maintenance therapy with and without GM-CSF following autologous transplant as part of upfront treatment for patients diagnosed with multiple myeloma. Patients meeting initial eligibility will be enrolled for the purpose of harvesting tumor cells. Randomization will then occur approximately 2 months after autologous transplant and within 7 days of disease assessment. The target enrollment is 132 patients randomized; assuming that 30% will drop out between tumor collection and randomization, the study will target 188 patients for initial enrollment. As the impact of GM-CSF without vaccine on clinical outcomes is expected to be minimal, analysis of clinical outcomes will focus on comparing the vaccine arm vs. the combined no-vaccine arms. This will help maintain power for these primary analyses. Further randomization of the no-vaccine arms into maintenance vs. maintenance +GM-CSF is done to isolate the effect of the GM-CSF adjuvant on immunological outcomes and address whether any observed effect of vaccine is truly related to the vaccine.

5.1.1. Accrual

It is estimated that 36 months of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age.

5.1.2. Randomization

Randomization will occur approximately 2 months after autologous transplant and within 7 days of disease assessment. Randomization will be performed in a 2:1:1 ratio using random block sizes for the vaccine/GM-CSF (n=66), lenalidomide/GM-CSF (n=33) and lenalidomide alone (n=33) treatment arms, respectively. Randomization will be stratified according to disease response at time of randomization between sCR/CR and VGPR/PR/Stable disease.

5.1.3. Primary Endpoint

The primary endpoint is the proportion of patients alive and in CR or sCR at one year post transplant, corresponding to approximately 10 months post randomization. The primary analysis will be performed using the intent-to-treat principle so that all randomized patients will be included in the analysis.

5.1.4. Primary Hypothesis

The primary objective of the study is to determine whether vaccination with DC/myeloma fusions/GM-CSF in combination with lenalidomide maintenance therapy increases the proportion of patients alive and in CR or sCR at one year compared to the combined maintenance groups without vaccine. Letting P denote the proportion of patients alive and in CR and sCR at one year, the hypotheses of interest are:

$H0: P_{VACCINE/GMCSF+MAINT} = P_{MAINT\pm GMCSF}$ vs. $Ha: P_{VACCINE/GMCSF+MAINT} > P_{MAINT\pm GMCSF}$.

5.1.5. Duration of follow-up
All patients will be followed for approximately 3 years post-maintenance initiation for primary and secondary endpoints.

5.2.Sample Size and Power Considerations

5.2.1. Primary Endpoint (Clinical)
Based on the prior cooperative group studies, we anticipate approximately 40% of patients will achieve CR and sCR at 1 year. In the prior phase II study of patients undergoing post-transplant vaccination in the absence of lenalidomide maintenance, CR was achieved in 29% and 54% of patients at 100 days and 1 year post-transplant respectively. Given that we anticipate that lenalidomide maintenance will enhance vaccine efficacy, we will consider the experimental arm of vaccine/GM-CSF + maintenance promising if the CR rate at 1 year is improved from 40% to 60%. A sample size of 66 patients (132 total) randomized to the vaccine arm and the combined no-vaccine arms will have 85% power to detect this improvement in the CR rate at 1 year from 40% to 60%, using a two-sample comparison of proportions with a one-sided type I error of 10%. Because randomization occurs post collection of tumor sample and post transplant, we anticipate needing to enroll 188 at the time of initial tumor collection pre-transplant assuming that 30% will drop out between tumor collection and randomization.

Secondary comparisons of CR rate at 1 year post HCT between the vaccine/GM-CSF arm vs. either lenalidomide/GM-CSF or lenalidomide alone separately will have 80% power to detect a 23% increase in the CR rate, using the same one-sided alpha level of 10%. Comparison between the two no-vaccine arms will have 80% power to detect a 26% improvement in the CR rate.

5.2.2. Power Considerations for Primary Immunologic Endpoint
The primary immunologic endpoint will be to quantify the expansion of myeloma reactive T cells as determined by the pretreatment and peak post-treatment levels. The anticipated standard deviation of the log 10 peak change in tumor reactive T cells from baseline is 0.61, based on prior studies. Assuming 15% of patients will not be evaluable for immune reconstitution studies, the expected evaluable sample sizes will be 56 for the vaccine group and 28 for each of the no-vaccine groups. Comparisons between the vaccine group and either of the no-vaccine groups will have 80% power to detect a log 10 fold change of 0.4, corresponding to a 2.5 fold expansion of myeloma specific T cells, using a two-sample t-test with a 5% two-sided significance level. Comparisons between the two no-vaccine groups will have 80% power to detect a log 10 fold change of 0.46, corresponding to a 2.9 fold expansion of myeloma specific T cells. Note that a stricter alpha level is used for immunologic endpoints to reduce the risk of type I errors while still being adequately powered to detect larger quantitative differences likely to translate into clinical improvements.

5.3.Interim Analysis and Stopping Guidelines

5.3.1. Interim Analysis for Efficacy
There will be no interim analyses for efficacy.

5.3.2. Interim Analysis for Futility
There will be no interim analyses for futility.

5.3.3. Guidelines for Safety Monitoring
Monitoring of a key safety endpoint will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guideline serves as trigger for consultation with the DSMB for additional review.

The key safety endpoint for this study is treatment limiting toxicity (TLT) within the first month of combined therapy, defined as any grade V event regardless of attribution to combined therapy, grade IV hematologic (lasting greater than 7 days) and grade III-IV non-hematologic toxicity judged to be related to combined therapy. At least three events must be observed in order to trigger review. The rate of TLT within the first month is expected to be no higher than 25%. Each month, the null hypothesis that the 1 month TLT rate is 25% will be tested. This outcome will be monitored using a truncated Sequential Probability Ratio Test (SPRT) for binary data as described below. The SPRT conserves type I error at 5% across all of the monthly examinations.

The SPRT can be represented graphically. At each interim analysis, the total number of patients enrolled is plotted against the total number of patients who have experienced transplant-related mortality. The continuation region of the SPRT is defined by two decision boundaries. Only the upper boundary will be used for monitoring the study to protect against high incidences of TLT. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that the TLT incidence is higher than predicted by the observed number of patients enrolled on study. Otherwise, the SPRT continues until enrollment reaches the target goal. The SPRT for TLT was developed from the following SPRT:

A SPRT contrasting 25% versus 40% 1 month incidence, with nominal type I and II errors of 12% and 15%, respectively, which results in decision boundaries with a common slope of 0.322 and an upper intercept of 2.824.

The actual operating characteristics of this truncated test, shown in Table 5.3.2, were determined in a simulation study that assumed uniform accrual of 66 individuals over a three-year time period.

TABLE 5.3.2: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR 1 MONTH TLT FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

True 1 month Incidence	25%	35%	40%	45%
Probability Reject Null	0.100	0.595	0.836	0.957
Mean Month Stopped	34.8	25.0	18.3	13.5
Mean # Endpoints in 1 month	15.5	15.4	13.1	10.6
Mean # Patients Enrolled	62.1	43.8	32.7	23.7

For example, the testing procedure rejects the null hypothesis in favor of the alternative 10% of the time when the true 1 month TLT rate is 25%, and 84% of the time when the rate is 40%. This corresponds to a type I error rate of $\alpha = 0.1$ and a type II error rate of $\beta = 0.16$. When the true 1 month TLT rate is 40%, on average, the DSMB will be consulted 18 months after opening, when 13 events have been observed in 33 patients.

5.4.Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, pre-randomization disease response. Between group comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test.

5.5.Analysis of Primary Clinical Endpoint

The intent-to-treat principle will be followed, so that all patients who are randomized will be included in the analysis. The proportion of patients alive and in CR/sCR at 1 year post transplant will be described in the vaccine and no vaccine groups with 80% confidence intervals and compared between groups using a two-sample Z test comparing binomial proportions. A one-sided significance level of 0.1will be used for this comparison to indicate whether the vaccine plus maintenance treatment is promising compared to the combined no-vaccine groupsin this phase II trial. An 80% two-sided confidence interval (consistent with one-sided significance level of 0.1) will be constructed for the difference in proportions. A secondary analysis stratified on disease response prior to randomization will be conducted using a Cochran-Mantel-Haenszel test, and a stratified odds ratio along with 80% confidence intervals will be estimated. A secondary pairwise analysis of CR rates comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.Analysis of Secondary Clinical Endpoints

5.6.1. Response to treatment

The distribution of disease response will be tabulated at each time point. The proportion of patients alive and with a response of VGPR or better will be compared between the vaccine arm with the no-vaccine arms combined at 6 months, 1 year, and 2 years post-transplant using a chi-square test. A secondary pairwise analysis of response to treatment comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted. Rates of conversion to CR will also be compared using a chi-square test among the subset of patients who are not in CR at the time of randomization.

5.6.2. Myeloma Progression
Incidence of myeloma progression will be estimated using cumulative incidence function, treating death as a competing risk. Incidence of myeloma progression will be compared between the vaccine arm with the no-vaccine arms combined using Gray's test. A secondary pairwise analysis of myeloma progression comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.3. Treatment-related Mortality
Incidence of TRM will be estimated using the cumulative incidence function, treating myeloma progression as a competing risk. Incidence of TRM will be compared between the vaccine arm with the no-vaccine arms combined using Gray's test. A secondary pairwise analysis of TRM comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.4. Progression-free survival
Progression-free survival curves will be estimated using the Kaplan-Meier estimator, and compared between the vaccine arm with the no-vaccine arms combined using the log-rank test. Hazard ratios, along with confidence intervals, will be estimated from a Cox model with treatment group as a covariate. A secondary pairwise analysis of PFS comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.5. Overall survival
Overall survival curves will be estimated using the Kaplan-Meier estimator, and compared between the vaccine arm with the no-vaccine arms combined using the log-rank test. Hazard ratios, along with confidence intervals, will be estimated from a Cox model with treatment group as a covariate. A secondary pairwise analysis of overall survival comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.6. Incidence of toxicities grade ≥ 3 per CTCAE version 4.0
All Grade ≥ 3 toxicities will be tabulated by grade for each treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as well as cumulative over time.

5.6.7. Incidence of infections
The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after transplant. The cumulative incidence of infections, treating death as a competing event, will be compared between the vaccine arm with the no-vaccine arms combined using Gray's test. A secondary pairwise analysis of the incidence of infections comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.6.8. Minimal Residual Disease assessment
The proportions of patients with MRD present (MRD+) will be described using frequencies at each timepoint and compared between the vaccine arm with the no-vaccine arms combined using the chi-square test. A secondary pairwise analysis of MRD comparing the vaccine arm, lenalidomide/GM-CSF arm and the lenalidomide alone arm will also be conducted.

5.7.Analysis of Immunological Endpoints

5.7.1. Primary immunologic endpoint: Myeloma reactive T-cells
Log transformations will be used to induce normality in quantitative measurements, and if still non-normal, then nonparametric tests will be used. The primary endpoint of log 10 peak change in tumor reactive T cells from baseline will be compared across the 3 groups using analysis of variance, and if significant then two-sample t-tests will be conducted for each pairwise comparison to determine which groups are different from one another. A secondary analysis of peak change in tumor reactive T cells will be done by comparing the proportions of patients who experience >10-fold increase in IFNγ expression, using a chi-squared test. Myeloma reactive T-cell response profiles over time will be compared between the treatment groups using linear mixed models for repeated measures data. Peak immune response as well as most recent immune response will be compared between those in CR and those not in CR at each assessment, using a two-sample t-test, to assess the relationship between immune response and clinical response. Peak and most recent immune response will also be considered as time-dependent covariates in a Cox proportional hazards model to assess their impact on progression-free survival.

5.7.2. Secondary immunologic endpoints:
Additional exploratory analyses will be conducted in a similar fashion to examine a number of secondary immunologic endpoints, including: 1) antigen specific reactivity by tetramer analysis, 2) quantification of T-cell subsets and PD-1 expressing lymphocytes by flow cytometry 3) quantification of NK cell populations with inhibitor and activating markers, 4) NK-cell cytotoxic function as measured by IFNγ and CD107a degranulation in response to ex vivo exposure to autologous MM cells, and 5) humoral response against autologous MM cells and myeloma associated antigens such as MUC1, and vaccine-induced myeloma-specific plasmablast responses. In each case, log transformations will be considered to induce normality, and if still non-normal then nonparametric tests will be used. Profiles of these secondary immunologic endpoints will be described at each time point for each group using summary statistics and compared between the groups using mixed models for repeated measures data. The correlation between the immune environment measures and the myeloma specific T-cell response will be assessed and reported using Spearman rank correlation at each time point.

5.8.Endpoint Review Committee
An Endpoint Review Committee of appointed physicians will convene to adjudicate the primary endpoint of complete response as defined by a protocol endpoint review charter. The charter outlines the primary and secondary endpoints to be evaluated and details the endpoints to be adjudicated, process for adjudication, procedures for discrepancy resolution, and recording of results. This review will be done in a blinded manner.

APPENDIX A

CRITERIA FOR SYMPTOMATIC MULTIPLE MYELOMA

APPENDIX A

CRITERIA FOR SYMPTOMATIC MULTIPLE MYELOMA

All three required:

- Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma
- Monoclonal protein present in the serum and/or urine[a]
- Myeloma defining events (1 or more)
    a. Myeloma- related organ dysfunction[b]:
        i. Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal)
        ii. Renal insufficiency (serum creatinine > 2mg/dl)
        iii. Anemia (hemoglobin <10 g/dL)
        iv. Lytic bone lesions or osteoporosis[c]
    b. Any one or more of the following biomarkers of malignancy:
        i. Clonal bone marrow plasma cell percentage ≥ 60%
        ii. Involved:uninvolved serum free light chain ratio ≥100
        iii. >1 focal lesion of MRI

*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

INFORMED CONSENT FORM

Informed Consent to Participate in Research

BMT CTN 1401 v1.0

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

Your Name: _____

Study Title: Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

Protocol: BMT CTN 1401 v1.0

Principal Investigator: *Insert local PI information*

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

• Introduction

We invite you to join this clinical trial, also known as a research study. You are being asked to join because:

- You're between the ages of 18 and 70
- You have multiple myeloma (MM)
- Your doctor thinks an **autologous transplant** is a possible treatment option for you.

The standard of care for patients with MM is an autologous transplant and **maintenance treatment**. Maintenance treatment is chemotherapy after transplant. There's no cure for MM, so patients get maintenance treatment to slow the return of MM after a transplant.

We're doing this study to learn if maintenance treatment works better alone or with a vaccine made from your own blood cells.

This study will take at least 3 years and will include 188 participants. **Your participation will last for a maximum of 4 years from when you are enrolled.**

This consent form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [*insert name of facility or institution*].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.

- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

• Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

For this study, you will receive an **autologous transplant** (transplant). An autologous transplant uses blood-forming cells that are collected from your blood stream. After they are collected and frozen, you will get a high dose of chemotherapy. Chemotherapy before a transplant is called the "conditioning regimen".

The goal of chemotherapy is to kill as many cancer cells in your body as possible. It also destroys most of the normal cells in your bone marrow. To restore your marrow, your frozen blood-forming cells are thawed and transplanted back into your blood stream. The cells find their way into the bone marrow where they start making healthy blood-forming cells.

The standard of care for patients with MM is an autologous transplant and **maintenance treatment**. Maintenance treatment is chemotherapy after transplant. There's no cure for MM, so patients get maintenance treatment to slow the return of MM after a transplant.

Some patients may receive a **vaccine, and/or GM-CSF (also known as Leukine)** with their maintenance therapy. GM-CSF helps your body make new white blood cells after transplant.

The vaccine is made from dendritic cells and MM tumor cells in a laboratory. We will collect a sample of your cells through your central line (or catheter). This process is called leukapheresis. If the vaccine is made successfully, it will be frozen and stored to give to you later.

We're doing this study to learn if maintenance treatment works better alone, or with a vaccine made from your own blood cells.

• Study Purpose

We are inviting you to take part in this study because you have multiple myeloma (MM) and an autologous transplant is a treatment option for you. We are doing this study to learn more about ways to prevent or slow the return of MM after transplant.

We will use 3 treatments to see which one works best to prevent or slow the return of MM. See **Table 1** for information on each treatment group.

Table 1. Study Treatment Groups

Treatment Group A (maintenance treatment with GM-CSF and vaccines)	**Treatment Group B** (only maintenance treatment)	**Treatment Group C** (maintenance treatment with GM-CSF)
• Melphalan (chemotherapy drug) • Autologous transplant • Lenalidomide (maintenance treatment) • GM-CSF • Vaccine	• Melphalan (chemotherapy drug) • Autologous transplant • Lenalidomide (maintenance treatment)	• Melphalan (chemotherapy drug) • Autologous transplant • Lenalidomide (maintenance treatment) • GM-CSF

This study will help doctors make the best choice about treatment after transplant for patients with MM. See section **5: Study Tests and Treatments** for information on how your treatment group will be determined and for information about the drugs listed in **Table 1**.

• Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, during your treatment, and for 3 years after you begin your maintenance treatment.

Before You Start Your Treatment

You will need to have several check-ups and tests to see if you can be in the study. These check-ups and tests are part of your regular cancer care and would be done even if you were not part of this study. These tests include:

- Medical history and physical exam
- Blood tests for cell counts
- Liver and kidney function tests
- Tests to measure your disease
- Bone marrow tests
- Skeletal survey
- A pregnancy test (if you are a woman able to have children)

During Your Treatment

Tumor Cell Collection

After you join the study, we will collect about 30mL (approximately 2 tablespoons) of bone marrow and 50mL (approximately 3 tablespoons) of blood. The bone marrow and blood samples will be frozen until it is determined if you will receive the vaccine as part of your treatment. This tumor cell collection is not part of your standard of care treatment

If you are assigned to Treatment Group A after your transplant, your bone marrow will be thawed and used to make your vaccine. If you are assigned to Treatment Group B or C, your

bone marrow sample will not be used in this study. Your doctor may talk to you about other uses for your stored bone marrow samples not related to this study.

We will also talk with you about giving extra blood and marrow samples for future research (see section **17: Blood and Marrow Samples for Future Research**). The extra blood and marrow samples are also completely optional.

Initial Treatment for Multiple Myeloma (MM)

The first step (initial) is standard chemotherapy treatment (chemo). Chemo lowers the number of MM cells in your body. Different chemotherapy drugs can be used to treat MM. Your doctor will decide which drug or combination of drugs is best for you.

You will be asked to sign a separate consent form that will explain the side effects of whichever drug your doctor chooses. This step may last several months.

Blood-Forming Cell Collection

Next, we'll collect blood-forming cells from your blood stream. This is known as apheresis. These cells will be frozen and stored until your transplant day.

Conditioning Regimen Before Transplant

The third step is the conditioning regimen, or the chemo and radiation, you will get before your transplant. The conditioning regimen helps the blood-forming cells start to grow and make new cells in your bone marrow (engraft). The regimen includes a chemo drug called **melphalan**, given by intravenous infusion (IV) in your arm.

Your doctor will decide when you are ready to get melphalan. You will start this treatment step no more than 12 months after you start on this study. Melphalan works better for some patients than it does for others. If the drug does not work well for you, you may not be able to have a transplant. Your doctor will talk to you about other treatment options.

Infusion of Blood Forming Cells (Transplant)

On your transplant day (Day 0), your cells will be given to you through your catheter. The cells will travel to your bone marrow where they will start to make healthy, new blood cells (engraft).

Your Treatment Group

Approximately 2 months after transplant, we will check to see if you're healthy enough to start maintenance treatment. If you are found healthy enough, we will randomize you to 1 of the 3 treatment groups. **"Randomize"** means that you will be put in one or another group by chance, just like flipping a coin. We will use a computer program to assign you by chance to Treatment

Group A, B, or C. You won't be able to choose your group. Once you are assigned to a group, you can't change to another group. The study doctor can't change your group either.

Half of the patients on this study (about 66), will be assigned to Treatment Group A. One-fourth of the patients (about 33) will be assigned to Treatment Group B; and one-fourth of patients (about 33) will be assigned to Treatment Group C. See the section below, **Your Maintenance Treatment After Transplant**, for a description of the treatments.

Once all these tests are done, you will be randomized to Treatment Group A, B or C. See **Table 2** for a schedule of these tests.

If you're not healthy enough after transplant, you won't be randomized. If this happens, your Follow up on this study is complete

Your Maintenance Treatment After Transplant

You will start maintenance treatment about 3 months after your transplant.

- **Treatment Group A: Lenalidomide, Vaccine, and GM-CSF injections**

If you are assigned to Treatment Group A, you will get: lenalidomide, vaccines, and GM-CSF injections.

We will collect extra blood samples to make the vaccine. We will insert a catheter into a large vein in your neck or chest. The catheter will collect some blood cells and the rest are returned to your body. This process is called leukapheresis. We will use the blood cells and the marrow that was collected and frozen to create your vaccine. The vaccine will be made in a laboratory and frozen until you're ready for maintenance treatment.

You will take lenalidomide as a pill every day for 2 years or until your disease returns. You will receive enough pills for 1 cycle (28 days in each cycle) at a time. It's important to take the pill at the same time every day. Be sure to talk with your doctor to figure out a good time to take the pill every day.

You will also receive 3 doses of the vaccine. This will be given to you on the first day of your 2^{nd}, 3^{rd}, and 4^{th} cycle of lenalidomide. The vaccine is the part of the treatment we are testing in this study. This is also called the research treatment.

With each vaccine, you will also get an injection of GM-CSF in your arm or stomach. GM-CSF helps to boost the effect of the vaccine. You will receive the GM-CSF injection on the day you get the vaccine and every day for 3 days after the vaccine. This will either be given to you in the clinic or you will be taught to give the injections to yourself at home.

See **Table 2** for a timeline of the drugs for Treatment Group A.

Table 2: Treatment Group A

Treatment Group A drugs:	**Amount:**	**Timeline for Maintenance Treatment Drugs**										
	Cycle: (28 days in each cycle)	1	2	3	4	6	9	12	15	18	21	24
Lenalidomide	1 dose every day for 2 years	X	X	X	X	X	X	X	X	X	X	X
Vaccine	3 doses total		X	X	X							
GM-CSF	12 doses total		X (+3 days)	X (+3 days)	X (+3 days)							

- **Treatment Group B: Lenalidomide**

If you are assigned to Treatment Group B, you will take lenalidomide every day for 2 years or until your disease returns. You will receive enough pills for 1 cycle (28 days in each cycle) at a time. It's important to take the pill at the same time every day. Be sure to talk with your doctor to figure out a good time to take the pill every day.

- **Treatment Group C: Lenalidomide and GM-CSF**

If you are assigned to Treatment Group C, you will get: lenalidomide and GM-CSF injections.

You will take lenalidomide every day for 2 years or until your disease returns. You will receive the enough pills for 1 cycle (28 days in each cycle) at a time. It's important to take the pill at the same time every day. Be sure to talk with your doctor to figure out a good time to take the pill every day.

You will also get an injection of GM-CSF in your arm or stomach. You will get the GM-CSF injection every day for 4 days starting the first day of cycles 2, 3 and 4. This will either be given to you in the clinic or you will be taught to give the injections to yourself at home.

See **Table 3** for a timeline of the drugs for Treatment Group C.

Table 3: Treatment Group C

Treatment Group C drugs:	**Amount:**	**Timeline for Maintenance Treatment Drugs**										
		Cycle: (28 days in each cycle)	1	2	3	4	6	9	12	15	18	21	24
Lenalidomide	1 dose every day for 2 years		X	X	X	X	X	X	X	X	X	X	X
GM-CSF	12 doses total			X (+ 3 days)	X (+ 3 days)	X (+ 3 days)							

Maintenance treatment dose (All treatment groups)

How We Will Give You Lenalidomide

Lenalidomide is available only from a certified pharmacy through the Revlimid REMS® program. During maintenance therapy, only a 28-day supply (1 cycle) will be given to you at a time.

If this is the first time you've taken lenalidomide, you'll have to sign-up, or register, for the program. This will include a separate consent process, which calls out the reproductive risks of taking this medicine. You'll have to give your name, address, phone number, birth date, and social security number to sign-up for the program. This information will be provided to Celgene Corporation and Biologics Incorporated to show you're taking part in this study.

After you're registered, you'll be counseled at the site or through the program:

- When you're first given the drug
- At least every 28 days while you're taking it, and
- When you stop taking it

You will be counseled about:

- Side effects
- Not sharing lenalidomide (or other study drugs)
- Risks of exposing a fetus (unborn baby)

- Donating blood
- How to take the pills

We'll give you the, "*Lenalidomide Information Sheet for Patients Enrolled in Clinical Research Studies*" with each new supply of lenalidomide to remind you of these safety issues.

How to Take the Lenalidomide Pills

- Swallow the whole lenalidomide pill with water at the same time each day. Do not break, chew or open the capsules.
- If you miss a dose, 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 a double dose to make up for the missed dose).
- If you take more than the prescribed dose you should seek emergency medical care if needed and contact study staff right away.
- Women who can become pregnant that care for you should wear gloves whenever they need to touch the lenalidomide pills or bottles.

Checking Your Health

We will watch your health closely during your maintenance treatment, including how well your organs work. We will lower your dose if your organs don't handle the treatment well.

We won't start a new cycle until your organs work well again. If we lower your dose and then your organs start working normally, we may raise your dose again.

We will stop the maintenance treatment if you:

- Have a serious side effect
- Have low blood cell counts
- Are a woman and become pregnant, or there is a chance that you are pregnant
- Go more than 56 days before starting a new maintenance treatment cycle
- Don't follow the study directions, or
- Choose to leave the study.

You will need to visit your clinic for several check-ups and tests during your maintenance treatment. These tests are shown in **Table 4. These assessments are standard of care for patients receiving lenalidomide maintenance therapy.**

Table 4. Timeline of Tests Before and During Your Maintenance Treatment

Tests	Before you're Randomized	Timeline for Maintenance Treatment Tests (CYCLES)										
		1	2	3	4	6	9	12	15	18	21	24
Physical exam, height, and weight	X		X	X	X	X	X	X	X	X	X	X
Tests for toxicities, and infections	X	X	X	X	X	X	X		X		X	X
Blood tests for cell counts, liver and kidney function	X	X	X	X	X	X	X	X	X	X	X	X
Tests to see how much cancer you still have	X			X		X	X	X	X	X	X	X
Pregnancy test (women able to have children)	X	X	X	X	X	X	X	X	X	X	X	X

Blood and Bone Marrow Samples

Throughout the study, we will collect blood and marrow samples to check if the treatments are working. These samples are being done as a part of the standard of care disease assessment. In addition, blood and marrow samples are also collected as part of this research study to check your immune response to the vaccine and are not part of your standard of care. The maximum amount of blood we will collect for this study in one day is 70mL (approximately 4.5 tablespoons). If more blood is required at a particular time, we will collect blood on 2 or more days spread out over 1-2 weeks.

The maximum amount of bone marrow sample we will collect is 37mL (approximately 2.5 tablespoons). **Table 5** shows the timeline and amount of samples we may collect from you during the study.

Table 5: Timeline and Sample Amount Collected during Study (in approximate tablespoons (Tbsp) or teaspoons (tsp))

Sample	When you join the study	Before you're randomized	Maintenance Cycles						
			1	2	2 (day 7)	3	4	4 (day 7)	9
Bone marrow	2.5 Tbsp	1 tsp							2 tsp
Optional bone marrow samples for future research	<1 tsp	<1 tsp							<1 tsp
Blood-forming cells	6.5 Tbsp *over 10 days	2 Tbsp	4.5 Tbsp	4.5 Tbsp	4 Tbsp	4.5 Tbsp	4.5 Tbsp	4 Tbsp	4.5 Tbsp
Optional blood samples for future research	1.5 tsp	1.5 tsp							1.5 tsp

6. Risks and Discomforts

You may have side effects while on the study. Side effects can range from mild to serious. The risks and discomforts of autologous transplant are the same if you join this study, or if you don't join this study.

You might do better or worse than you would with a standard transplant. Your healthcare team may give you medicines to help with side effects like nausea (feeling sick to your stomach). In some cases, side effects can last a long time or may never go away.

Risks of Making the Vaccine

We will collect bone marrow samples on all patients.

We will take the bone marrow samples from your hip bone with a large needle. This is called a bone marrow aspirate. After, you may feel pain and bleed at the site where the needle went in your hip. A small number of patients will have pain that runs down their legs, pain that lasts more than a few days, and/or get an infection.

If you are assigned to Treatment Group A, we will collect blood and bone marrow samples to make the vaccine (see **Table 5. Timeline and Sample Amount Collected during Study**).

We will also collect extra samples of blood through a catheter in your neck or chest (leukaphereis). The risks of leukapheresis include:

- Bleeding
- Punctured lung (hole in lung)
- Infection
- Low blood cell counts.

Risks of Medications

The risks of the chemotherapy and maintenance drugs you will get as part of the treatment are listed below.

Melphalan - Conditioning Regimen Drug (Before Transplant)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
• Loss of appetite • Constipation • Diarrhea • Nausea (feeling sick to your stomach) • Vomiting (throwing up) • Temporary hair loss • Sensitive skin	• Changes in heart beat • Dizzy • Feeling faint • Shortness of breath • Hepatitis (swelling of the liver) • Kidney failure • Weight loss • Feeling weak	• Allergic reaction • Lung infection • Scarring of lung tissue • Seizure • Vasculitis (inflammation of blood vessels) • Low blood pressure • Sweating too much • Sterility (unable to have

• Infection • Low number of white blood cells ▪ Low number of platelets in the blood with increased risk of bleeding • Anemia (low number of red blood cells) • Mouth sores • Sore throat (red with swelling) • Skin breakdown (if drug leaks from vein)		children) • Liver damage • Heart stops beating • New cancer of bone marrow cells

Vaccine

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
• Twitching • Itching • Discomfort • Swelling • Bruising at the injection site	None	• Fluid retention (too much water in your body) • Fatigue • Muscle aches • Itching • Fever • Abnormal Antinuclear Antibody

		(ANA) blood test • Allergic reaction leading to rashes, joint pain, kidney, heart or lung damage, drop in blood counts • Tumor growth or the spread of your cancer • Infection at the vaccine site • Change in thyroid function (fatigue, weight gain, sensitivity to cold and lack of interest or emotion)

GM-CSF (Leukine)

Likely (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
• Fever • Chills • Nausea • Vomiting • Diarrhea • Fatigue • Feeling weak • Headache • Loss of appetite • Flushed face (red or pink cheeks) • Bone and muscle pain in arms, legs and feet • Red skin, swelling, or itching at needle injection site • Low blood pressure • Shortness of Breath	• Rapid, irregular heartbeats • Feeling lightheaded or dizzy • Allergic reaction • Fluid in lungs or around your heart • Changes in vision • Low blood cell counts • Infection at needle injection site	• Blood clots

Lenalidomide- Maintenance Treatment Drug

Likely (May happen in more than 10% of patients)	**Less Likely** (May happen in less than 10% of patients)	**Rare, but Serious** (May happen in less than 2% of patients)
• Low number of white blood cells (with or without fever) • Anemia; Decrease in cells that help your blood clot • Vision Blurred • Diarrhea • Pain, Constipation • Indigestion • Nausea • Vomiting • Feeling weak and unwell • Tired • Swelling • Fever • Chills • Pneumonia or other infections • Sore throat • Stuffy nose • Weight loss • Decreased appetite • High blood sugar	• Abnormally low number of blood cells • Destruction of red blood cells • Heart attack • Abnormal heart beats • Heart stops working • Low oxygen to heart tissue • Dry mouth • Decreased action of intestine • Bile flow from liver slowed or blocked • Gout • Fall • Bruise • Lowered level of consciousness with drowsiness, listlessness, and apathy • Abnormal liver lab tests • Increase in liver protein that indicates inflammation in body • Loss of fluid • Diabetes • High uric acid in blood • Iron build up in body	• Swelling of lungs • Over and underactive thyroid • Severe allergic conditions including:Swelling under skin; Severe skin reactions involving lining of the nose, mouth, stomach and intestines or rash leading to the separation of the top layer of skin • TLS

• Chemical imbalance in blood • Pain including muscles, joints, and non-cardiac chest pain • Dizziness • Altered sense of taste • Headache • Eye lens cloudy • Abnormal sense of touch • Pain and decreased sensation in nerves • Shaking • Cough • Shortness of breath • Nosebleed • Blood clot in lower extremities, lungs, heart, brain, and other organs • Dry skin • Itching • Allergic reaction • Feeling sad • Not sleeping well	• Muscle weakness • Cancer • Stroke • Tingling of skin • Fainting • Moody • Kidney failure • Breathing disorder • Excessive sweating • Night sweats • Skin redness • Swelling of skin filled with blood • Swelling of blood vessels • High or low blood pressure • Blood not getting to extremities • Clot in vein • Sudden increase in tumor size • Rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage • Blood cancer that causes decreased number of red blood cells, white blood cells, and platelets because they do not develop normally. •	

You shouldn't donate blood while you're in the study and for 28 days after you stop taking lenalidomide.

Risk to the Unborn

Lenalidomide can cause severe birth defects or death of a baby if the mother or the father is taking this medicine at the time of conception or during pregnancy. **Because of this, it is extremely important that you don't get pregnant while you're taking lenalidomide.**

If you're pregnant or nursing, you're not eligible to take part in this study. Women who can become pregnant must use **at least 2 forms of effective birth control** while in the study or abstain from all reproductive sexual intercourse. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (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
5. Placement of an IUD (intrauterine device)
6. Use of a cervical cap or a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Females taking lenalidomide have blood clots more often. Because of this, you should talk to your doctor about birth control pills and hormone replacement therapy, and the risks and benefits.

You do not need to use effective birth control only if you are a woman and cannot have children because you:

- Had a hysterectomy (your ovaries and uterus were removed), OR
- Had a bilateral oophorectomy (your ovaries were removed), OR
- Went through menopause (post-menopausal).

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children, or cause birth defects if you take them while you are pregnant or nursing.

Both women who can become pregnant and their male partners should use birth control while on this study and for 28 days after maintenance treatment is stopped. **If you or your partner becomes pregnant during this study, you must tell the study doctor immediately.**

Your doctor will discuss the risks to your unborn child and options with you.

It is important that females who aren't pregnant or nursing don't become pregnant while part of the study. If you are a woman and become pregnant while on this study, we will stop the maintenance treatment drug right away.

Your study doctor will watch your health closely while you are pregnant and for 30 days after the pregnancy ends.

- **Females who join the study**

If you are female and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you're in the study. Women who have gone through puberty might experience irregular menstrual cycles or their cycle might stop forever. This doesn't mean that you can't become pregnant. You must still use 2 effective forms of birth control during the study and continue with it for 28 days after you finish maintenance treatment.

Be sure to talk with your doctor about options for fertility planning, like storing your eggs, before starting chemotherapy treatment.

- **Males who join the study**

If you are male, your body may not be able to produce sperm (become sterile). Be sure to talk with your doctor about options for fertility planning, like banking your sperm, before starting chemotherapy treatment.

Damage to the vital organs in your body

Your vital organs include your heart, lungs, liver, intestines, kidneys, bladder and brain. The chemotherapy and GVHD drugs may hurt these organs. You may develop lung problems from chemotherapy or an infection.

Some patients can have veno-occlusive disease (VOD) of the liver. Patients with VOD become jaundiced (yellow skin), have problems with their liver, retain too much water (feel swollen and uncomfortable), and have stomach swelling and pain.

If there is serious damage to your vital organs, you may have to stay in the hospital longer or return to the hospital after your transplant. Many patients get better, but these complications can

cause permanent damage to your organs or death.

Serious infections

It may take many months for your immune system to recover from the chemotherapy, GVHD and maintenance therapy drugs. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infection, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Relapse (return) of disease or a new blood cancer

Your disease may come back even if the transplant was successful at first.

We don't know if new blood cancers are caused by lenalidomide or other drugs. Other research looked at the number of patients who got new blood cancers after taking lenalidomide for:

- Diseases other than multiple myeloma, AND
- Relapsed multiple myeloma.

In these studies, no difference was shown in the number of patients who got new blood cancers.

Researchers for other studies of lenalidomide are still watching patients to see if they get new blood cancers. We will give you any new information that we learn about new blood cancers.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study.

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study.

For more information about risks and side effects, ask your study doctor.

All Patients Taking Lenalidomide

In order to participate in this study you must register into and follow the requirements of the REVLIMID REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You 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 for you and take telephone surveys regarding your compliance with the program.

You have been informed of the risk of birth defects. If you are female, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to patients under a special distribution program called REVLIMID REMS ™.

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.

Other Risks

Serious infections

It may take many months for your immune system to recover from the chemotherapy and maintenance therapy drugs. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infection, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Unforeseen Risks

Chemo drugs can damage your blood cells, which may cause a new blood cancer to grow. We know from other MM research studies, that more patients had a second cancer after chemo and/or autologous transplant with maintenance lenalidomide than those who didn't get lenalidomide. We don't know if taking lenalidomide for a long time raises the risk of having a second cancer.

Other new risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. 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.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study.

For more information about risks and side effects, ask your study doctor.

7. Other Treatments

Participation in this study is optional. If you choose not to take part, you may still receive non-transplant treatments or an autologous or an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other options may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant.
- An allogeneic (donor) blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about drugs used to treat MM.

This information could help people with multiple myeloma who may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy.

All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

The individuals below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. By agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

9. /Institution/
10. The Center for International Blood and Marrow Transplant Research (CIBMTR)
11. The National Marrow Donor Program (NMDP)
12. The Food and Drug Administration (FDA)
13. The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
14. Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
15. Data and Safety Monitoring Board (DSMB), not part of /Institution/
16. Study investigators.
17. Celgene, the manufacturer of lenalidomide

Information that does not include personally identifiable information about this study has been or will be submitted to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain studies to be submitted to the data bank.

For questions about access to your medical records, please contact /name/ at /number.

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

12. You do not meet the study requirements.

13. You need a medical treatment not allowed in this study.

14. The study doctor decides that it would be harmful to you to stay in the study.

15. You are having serious side effects.

16. You become pregnant.

17. You cannot keep appointments or take study drugs as directed.

18. The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs (see **Section 6: Risks and Discomforts**) too soon after transplant, your body could reject the stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

If you decide to leave this study after getting the study treatment, or are asked to leave by your doctor for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. There is no provision for free medical care or monetary compensation from the study sponsor, The National Institutes of Health or the study contributor, Celgene Corporation.
In case you are injured in this study, you do not lose any of your legal rights to ask for or receive payment by signing this form.

13. Compensation or Payment

You will not be paid for your participation in this research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

Taking part in this study might help researchers make products to sell. Celgene or others may profit from these products. You will not have any rights to the patents or discoveries that could happen from this research, and you will not receive any payments from it.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care for your autologous transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for blood and marrow samples for research on this study. You will not pay for any extra tests that are being done for the study. Lenalidomide will be provided to you for free for two years. After that your doctor will discuss what treatment is best for you.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff.

They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

The ethical aspects of this study have been reviewed and approved by *[name of IRB]*.

17. Blood and Bone Marrow Samples for Future Research (Optional)

This section of the informed consent form is about future research studies that will use blood and bone marrow samples from people who are taking part in the main study. You may choose to give samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give samples for future research studies.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

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

- We will collect 3 extra blood samples at the same time you have routine blood tests done (Table 3):
    - Around the time of your enrollment
    - About 2 months after your transplant
    - Before the start of your 9th cycle of maintenance therapy

- The amount of blood collected from you is about 1 teaspoon (6 ml) each time.
- We will collect 3 bone marrow samples at the same time you have routine bone biopsies done. The amount of tissue collected from you is about a half of a teaspoon (3 mL) each time. We will collect samples at 3 different dates in the study (see **Table 3**):
    - Around the time of your enrollment
    - About 2 months after your transplant
    - Before the start of your 9th cycle of maintenance therapy.
- The blood and bone marrow samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples.
- Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.
- Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.
- DNA from your stored blood 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). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

  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.

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

1. We will only store samples from people who give us permission.

2. Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.

3. A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.

4. Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

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. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _*[contact information]*.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Research Samples

The purpose of storing blood and tissue samples, 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 tissue for 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 voluntarily agree that my blood, tissue, and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories 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.

Blood

☐ I agree to allow my blood samples to be stored for research.

☐ I do not agree to allow my blood samples to be stored for research.

Bone marrow

☐ I agree to allow my bone marrow samples to be stored for research.

☐ I do not agree to allow my bone marrow samples to be stored for research.

_____ _____

Signature Date

Health Insurance Portability and Accountability Act 1 (HIPAA3) Authorization to use and disclose individual health information for research purpose

- **Purpose:**

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

- **Individual Health Information to be Used or Disclosed:**

My individual health information that may be used or disclosed to do this research includes:

1. Demographic information (for example, date of birth, sex, weight)
2. Medical history (for example, diagnosis, complications with prior treatment)
3. Findings from physical exams
4. Laboratory test results obtained at the time of work up and after transplant (for example, blood tests, biopsy results)

- **Parties Who May Disclose My Individual Health Information:**

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

- **Parties Who May Receive or Use My Individual Health Information:**

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

1. Dr. David Avigan, Co-Principal Investigator
2. Dr. Nina Shah, Co-Principal Investigator
3. Dr. David Chung, Co-Principal Investigator
4. Celgene, its collaborators or designees

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

5. National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
6. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center
7. 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)
8. 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.

- **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 treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

- **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.

- **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.

- **Genetic Information Nondiscrimination Act (GINA)**

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 may not request your genetic information that we get from this research. This means that they must 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.

- **This authorization does not have an expiration date.**

Consent to Take Lenalidomide

Lenalidomide is related to thalidomide. **Thalidomide is known to cause serious, life-threatening human birth defects.** 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.

A. For Females Who **Are Able** To Become Pregnant

Sexually mature female who hasn't had a hysterectomy (surgical removal of the uterus); or bilateral oophorectomy (surgical removal of both ovaries); or hasn't been naturally postmenopausal for at least 24 months straight).

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've been warned by my doctor that my unborn baby may have birth defects and can even die, if I'm pregnant or become pregnant while 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 have vaginal sex with a man; my uterus and/or both ovaries haven't been removed; I've 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 1 highly effective method of birth control plus 1 other effective method of birth control at the SAME TIME.

Highly Effective Methods	Other 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: 1) for at least 28 days before starting lenalidomide therapy; 2) while taking part in the study even while treatment is stopped; and, 3) for at least 28 days after I stop taking lenalidomide. I must use these methods unless I completely abstain from vaginal sex. If a 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 other effective 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'm not pregnant now, and I won't try to get pregnant for at least 28 days after I have completely stopped 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 to return any unused drug supply to the Revlimid REMS® Program.

_____ I know that I can't 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).

<u>For All Males</u>

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've 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.

_____ My doctor told me that I must NEVER have unprotected sexual contact with a woman who can become pregnant. It's not known whether lenalidomide is present in semen. My doctor explained that I must completely abstain from vaginal sex with women 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 birth control. 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 to return any unused drug supply to the Revlimid REMS® Program.

_____ I know that I can't 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'm not pregnant now, nor am I able to have children because I've been in 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 to return any unused drug supply through the Revlimid REMS® Program.

_____ I know that I can't donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

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.

TITLE: Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell /Myeloma Fusions

PROTOCOL NUMBER: BMT CTN #1401

PRINCIPAL INVESTIGATOR:

Name:

Address:

Email:

Phone:

Fax:

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

_____ _____

Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____ _____

Name of Counseling Physician

Date

Signature of Counseling Physician

Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

Collection of MANDATORY Samples for TC-DC/Myeloma Fusion Vaccine Production and Immunologic Endpoints

Bone marrow aspirate and peripheral blood will be collected for patients who consent to the BMT CTN 1401 study. Sample collection will be performed periodically throughout the study and will provide clinical samples required for: (1) DC/Myeloma fusion cell vaccine production and (2) correlative laboratory testing associated with critical immunologic study endpoints.

- **TC-DC/Myeloma Fusion Vaccine Production:** Upon enrollment on the BMT CTN 1401 study, all patients will have both peripheral blood and marrow aspirate samples collected, and delivered to the clinical center's cell processing facility for the isolation and storage of myeloma tumor cells as summarized in the table below. A sample of the processed myeloma tumor cells will be shipped to the BIDMC Central Laboratory for phenotypic characterization.

  For patients randomized to the cellular vaccine arm of the study, a therapeutic apheresis product will be collected and delivered to the clinical center's cell processing facility for the isolation of therapeutic cell dendritic cells (TC-DC) and the manufacturing of the TC-DC/Myeloma fusion cell vaccine as summarized in the table below. A sample of the processed TC-DC cells and manufactured TC-DC/Myeloma fusion cell vaccine will be shipped to the BIDMC Central Laboratory for phenotypic characterization. And finally, additional samples of the manufactured TC-DC/Myeloma fusion cell vaccine will be shipped to Labs, Inc. Reference Laboratory for final product release sterility testing, endotoxin testing and mycoplasma screening.

- **Research Samples for Laboratory Correlatives Associated with Immunologic Endpoints:** Required research samples for study-specific immunologic correlatives include the collection of blood and marrow aspirate samples as summarized in the table below (and in table 4.3B). The correlative studies include MRD Assessment, measurement of Plasmablast Response, NK Cell Reconstitution and the evaluation of Myeloma Reactive T-Cells. Once the samples are collected at specified time points they will be shipped on the day of collection directly to specified ancillary study laboratory for processing and testing. These samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures and shipping instructions will be found in the BMT CTN 1401 Research Sample Information Guide.

Collection of OPTIONAL Samples for Future Research

Bone marrow aspirate and peripheral blood will be collected from patients who signed consent to provide additional 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 on the day of collection to the BMT CTN Central Processing Laboratory for final processing and storage at the BMT CTN Research Repository. The collection, processing and shipping of these biospecimens are summarized in the table below (and in table 4.3B). These samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures and shipping instructions will be found in the BMT CTN 1401 Research Sample Information Guide.

- **Bone Marrow Aspirate Samples**
  Patients who consented for marrow sample collection for future research studies will have 3 mL of bone marrow aspirate collected at three time points (1) time of enrollment, (2) time of randomization, and (3) just prior to the initiation of cycle 9 of maintenance (~1 year post transplant)
- **Peripheral Blood Samples**
  Patients who consented for peripheral blood sample collection for future research studies will have 6 mL blood samples collected at three time points (1) time of enrollment, (2) following randomization onto the study, and (3) just prior to the initiation of cycle 9 of maintenance (~1 year post transplant)

Mandatory Research Samples & Testing Associated with TC-DC/Myeloma Fusion Vaccine Production					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Cell Processing Laboratory**	**Shipping Location**
Myeloma Tumor Cell Collection	30 mL Bone Marrow Aspirate	Bone marrow aspirates will be collected using sodium-heparin anticoagulant, following standard institutional procedures and promptly delivered to the center's cell processing facility for the isolation and storage of myeloma tumor cells.	At time of enrollment for all study patients	Bone marrow aspirate sample will be processed and myeloma tumor cells stored for possible future use for DC/Myeloma cell fusion vaccine production. Processing will be performed according to protocol-specific standardized procedures used by all BMT CTN 1401 center cell processing laboratories.	Transplant Center
Autologous Plasma for Vaccine Production	50 mL Peripheral Blood	Collect blood sample in five 10 mL fill green top plastic BD Vacutainer® tubes, containing Sodium-Heparin anticoagulant, and promptly deliver to the center's cell processing facility.	At time of enrollment for all study patients	Peripheral blood samples will be processed and plasma recovered for use in tumor cell processing/storage as well as subsequent DC/Myeloma fusion cell vaccine manufacturing steps.	Transplant Center
Myeloma Tumor Cell Phenotype Characterization	3 mL Processed Myeloma Tumor Cells	***No additional sample collection needed from patient***	**N/A**	1-2 million processed myeloma tumor cells in 3 mL tumor media will be shipped at 2-8° C by priority overnight FED EX delivery to BIDMC Laboratory for tumor lysate and immunohistochemical staining.	BIDMC Central Project Laboratory
Isolation of Therapeutic Dendritic Cells	Peripheral Blood Therapeutic Cells, Apheresis Product	A therapeutic peripheral blood apheresis product will be collected following standard institutional procedures and promptly delivered to the center's cell processing facility for the isolation of dendritic cells to be used in cellular vaccine preparation.	At time of randomization to only the DC/Myeloma Vaccine arm of the study	Apheresis products will be processed and TC-Dendritic cells recovered for manufacturing the DC/Myeloma fusion cell vaccine. Processing will be performed according to protocol-specific standardized procedures.	Transplant Center

Mandatory Research Samples & Testing Associated with TC-DC/Myeloma Fusion Vaccine Production (continued)					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Cell Processing Laboratory**	**Shipping Location**
TC– DC Cell Phenotype Characterization	Processed TC-Dendritic cells	***No additional sample collection needed from patient***	N/A	2-5 x 10^6 processed dendritic cells in media will be shipped at 2-8° C by priority overnight FED EX delivery to BIDMC Laboratory for immunohistochemical staining.	BIDMC Central Project Laboratory
TC-DC/Myeloma Fusion Cell Phenotype Characterization	Processed TC-DC/Myeloma Fusion cells	***No additional sample collection needed from patient***	N/A	1-2 x 10^6 processed TC-DC/Myeloma Fusion cells in media will be shipped at 2-8° C by priority overnight FED EX delivery to BIDMC Laboratory for immunohistochemical staining.	BIDMC Central Project Laboratory
TC-DC/Myeloma Fusion Cell Vaccine Final Release Microbiological Assessment	Processed TC-DC/Myeloma Fusion cells	***No additional sample collection needed from patient***	N/A	2.0-5.0 x10^6 cells (fusion cell vaccine) in 3 mL of media will be shipped at ambient temperature by priority overnight FED EX delivery to Labs, Inc., for product release sterility testing. 1 mL of fusion cell product media will be shipped at 2-8° C by priority overnight FED EX delivery to Labs, Inc. for endotoxin testing. Two sample aliquots, each containing 0.5-1.0x10^6 cells (fusion cell vaccine) in 0.5 mL media will be shipped at 2-8° C by priority overnight FED EX delivery to Labs, Inc. for Mycoplasma screening.	Labs, Inc. Reference Laboratory

Mandatory Research Samples Associated with Immunologic Study Endpoints					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping Location**
MRD Assessment	6 mL Bone Marrow Aspirate	Collect bone marrow aspirated sample and place 3 mL into each of two 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.	Following randomization onto the study; and following the completion of cycle 9 of maintenance (~ 1 year post transplant)	One 3 mL bone marrow aspirate sample will be shipped at ambient temperature on the day of collection to RPCI by priority overnight FED EX delivery for MRD assessment.	RPCI Laboratory
				The remaining 3 mL bone marrow sample will be sent to the local pathology department for MRD assessment.	Transplant Center
Myeloma Reactive T Cells	4 mL Bone Marrow Aspirate	Collect bone marrow aspirated sample and place into a green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant.	At time of enrollment, following randomization onto the study; and just prior to the initiation of cycle 9 of lenalidomide maintenance	Bone marrow aspirate sample will be shipped at at 2-8° C on the day of collection to BIDMC by priority overnight FED EX delivery.	BIDMC Laboratory
Plasmablast Response	30 mL Peripheral Blood	Collect blood sample and place into three 10 mL fill green top plastic BD Vacutainer® tubes, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	*For all patients:* at time of randomization; and 7 days after the initiation of the 4th cycle (cycle 4+7) of maintenance therapy. *Additional collections for patients in the vaccine arm:* immediately prior the first dose of the vaccine (cycle 2) and 7 days later (cycle 2+7); and immediately prior to the third dose of vaccine (cycle 4).	Blood sample tubes will be shipped on the day of collection at ambient temperature, to the Wrammert Laboratory at Emory University by priority overnight FED EX delivery.	Emory University Laboratory
Myeloma Reactive T Cells	40 mL Peripheral Blood	Collect blood sample and place into four 10 mL fill green top plastic BD Vacutainer® tubes, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	At time of enrollment, and just prior to initiation of cycles 1, 2, 3, 4, and 9 of maintenance.	Blood sample tubes will be shipped at at 2-8° C on the day of collection to BIDMC by priority overnight FED EX delivery.	BIDMC Laboratory

Mandatory Research Samples Associated with Immunologic Study Endpoints (continued)					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping Location**
NK Cell Reconstitution	30 mL Peripheral Blood	Collect blood sample and place into three 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.	Immediately prior to initiation of cycle 1 of maintenance; 7 days after initiation of cycle 2 (cycle 2+7); immediately prior to initiation of cycle 3; 7 days after initiation of cycle 4 (cycle 4+7); and just prior to the initiation of cycle 9.	Blood sample tubes will be shipped at ambient temperature on the day of collection, to MDACC by priority overnight FED EX delivery	MDACC Laboratory

OPTIONAL Undefined Future Research Sample Collections					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping /Storage Location**
OPTIONAL Future Research	3 mL bone marrow aspirate	Collect bone marrow aspirated sample and place into a 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.	At time of enrollment, following randomization onto the study, and just prior to the initiation of cycle 9 of maintenance	Bone marrow aspirate 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 marrow aliquots.	BMT CTN Research Repository
OPTIONAL Future Research	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 30-60 minutes. Centrifuge for 10 minutes. Gel barrier will form separating the serum specimen from clot.	At time of enrollment, following randomization onto the study, and just prior to the initiation of cycle 9 of maintenance	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.	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.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (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 Revlimid REMS **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**

5. **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® in the 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 1401 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 study specific prescription form.**
- **Biologics will verify the authorization number** and complete the patient counseling.

Protocol compliance and drug return

- Patients will be required to return unused drug to the study site for destruction per institutional guidelines.
- 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 Revlimid REMS® and agree to comply with the requirements of the Revlimid REMS® program
- Information about REVLIMID®(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 Revlimid REMS® 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

HUMAN SUBJECTS

APPENDIX F

HUMAN SUBJECTS

1. 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 multiple myeloma. The conference will be conducted by the Principal Investigator or other designated physician. Potential risks associated with the study interventions should be discussed as objectively as possible. Consent will be obtained using an IRB-approved consent.

The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval.

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2. 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.

3. 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.

APPENDIX G

KARNOFSKY PERFORMANCE STATUS SCALE

APPENDIX G

KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

APPENDIX H

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

APPENDIX H

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 I

VACCINE ADMINISTRATION WORKSHEET

09-061: Blockade of PD-1 In Conjunction with the Dendritic Cell/Myeloma Vaccines Following Stem Cell Transplantation

DAY 0-DAY OF DC/FUSION VACCINE

DC/FUSION VACCINE

- ☐ **DATE:** **TIME:**
- ☐ **LOCATION:**
  - ☐ Right Thigh ☐ Left Thigh

DAY 0-GM-CSF ADMINISTRATION

- ☐ **DATE:** **TIME:**
- ☐ **LOCATION:**
  - ☐ Right Thigh ☐ Left Thigh

DC/FUSION VACCINE CHART:
VACCINE #1

DAY 1
GM-CSF ADMINISTRATION

- ☐ **DATE:** **TIME:**
- ☐ **LOCATION:**
  - ☐ Right Thigh ☐ Left Thigh

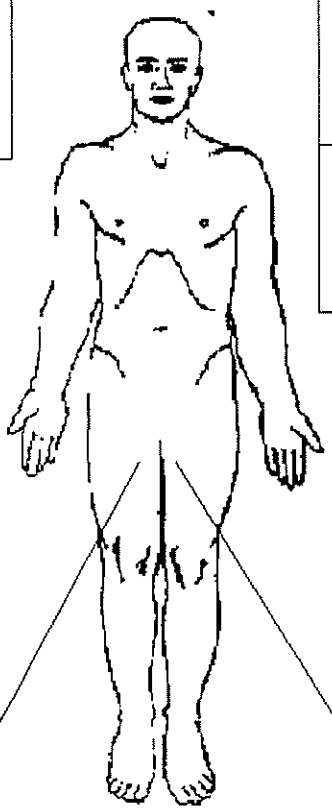
DAY 2
GM-CSF ADMINISTRATION

- ☐ **DATE:** **TIME:**
- ☐ **LOCATION:**
  - ☐ Right Thigh ☐ Left Thigh

DAY 3
GM-CSF ADMINISTRATION

- ☐ **DATE:** **TIME:**
- ☐ **LOCATION:**
  - ☐ Right Thigh ☐ Left Thigh

Patient Name:
Hospital ID:
DOB:
Study ID:



Right Upper Thigh

Left Upper Thigh

APPENDIX J

ADVERSE EVENTS

APPENDIX J

ADVERSE EVENTS

J.1. Adverse Event Reporting

Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms in AdvantageEDC..

The calendar-driven forms are those that appear in the AdvantageEDC Forms grid for each enrolled patient at designated timepoints (e.g. Day 28 post transplant) throughout the course of the study. Completion of calendar-driven forms is expected by the target date for the given assessment period.

Calendar Driven forms for the BMT CTN 1401 study are as follows:

- Toxicity Form: this form documents all expected toxicities for the BMT CTN 1302 study; each toxicity is also assigned a grade, based on the NCI CTCAE Version 4.0.
- Follow Up Status Form: this form documents the status of each patient at various intervals on the study.

Event-driven forms must be completed when a certain event triggers the appearance of the form in the AdvantageEDC Forms Grid. Most often the event-driven form is triggered by information entered on the Follow-up Status Form. Event-driven forms for the BMT CTN 1401 study are as follows:

- **Re-Admission/Hospitalization Form**: this form documents all hospital admissions, *including* the admission for transplant for this study.
- **Infection Form**: this form documents infections from Day 0 (date of transplant) through the 1-year post-transplant follow-up period.
- **Progression/Relapse Form**: the form captures detailed information associated with progression or relapse of the primary disease. DO NOT report progression or relapse as an Unexpected, Grade 3-5 Adverse Event.
- **Death Form**: this form documents the death of a patient from the time of study enrollment and randomization through the 1-year post-transplant follow-up period.
- **Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, **regardless of attribution** to any of the study interventions. These forms are also used to collect information on any SAE event required by the additional adverse event reporting requirements. These events require expedited reporting and will be reviewed by the Medical Monitor associated with the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.

J.2 Reporting Expected Toxicities

Expected toxicities for all patients enrolled on BMT CTN 1401 will be collected on the BMT CTN 1401 Calendar-Driven Toxicity Form and some of the event-driven forms (Infection, Readmission/Hospitalization, Progression/Relapse, Graft Failure and Death forms). Any grade 4 expected event not collected on the calendar-driven toxicity or specified event- driven form must be reported through the expedited AE reporting system in AdvantageEDC.

J.3 Reporting Unexpected, Grade 3-5 Adverse Events

All Unexpected, Grade 3-5 Adverse Events should be reported for every patient enrolled on the study from the time of randomization until 3 years post maintenance initiation.

J.4 Reporting Secondary Malignancies

All secondary primary malignancies (SPMs), excluding non-melanoma skin cancers, experienced by participants from the time of enrollment until 3 years post maintenance initiation 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.

J.5 Reporting Adverse Events from enrollment until randomization

No adverse event reporting is required from the time of enrollment until randomization. All patient deaths, SPMs, and progressions must still be reported during this time.

J.6 Reporting Adverse Events after the start of Lenalidomide

Additional Adverse Event reporting applies to patients who receive lenalidomide. Refer to Chapter 4 for additional instructions for reporting of Second Primary Malignancies and other special events of interest. Determination of the expectedness of adverse events should be differentiated between the initial transplant, maintenance, or vaccine therapy at the discretion of the investigator. For example, oral mucositis would be an expected risk associated with transplantation, but the investigator should assess the expectedness for oral mucositis during maintenance with or without vaccine therapy.

TABLE J-1: ADVERSE EVENTS FOR BMT CTN 1401 FROM FIRST DOSE OF LENALIDOMIDE THROUGH 28 DAYS AFTER LAST DOSE[1] BY ORGAN SYSTEM

Adverse Event	Collection Type	Collection Form[2]
AUDITORY DISORDERS		
Hearing loss	Calendar-Driven	Toxicity
BLOOD AND LYMPHATIC DISORDERS		
Anemia	Calendar-Driven	Toxicity

Adverse Event	Collection Type	Collection Form[2]
Disseminated intravascular coagulation[3]	Event-Driven	Adverse Event Form
Febrile neutropenia[5]	Event-Driven	Adverse Event Form
Lymphopenia	Calendar-Drive	Toxicity
Neutropenia	Calendar-Driven	Toxicity
Thrombocytopenia	Calendar-Driven	Toxicity
Thrombotic thrombocytopenic purpura/ Thrombotic microangiopathy	Calendar-Driven	Toxicity
CARDIAC DISORDERS		
Asystole[3]	Event-Driven	Adverse Event Form
Atrial fibrillation[3]	Event-Driven	Adverse Event Form
Atrial flutter[3]	Event-Driven	Adverse Event Form
Atrioventricular block[3]	Event-Driven	Adverse Event Form
Left ventricular systolic dysfunction	Calendar-Driven	Toxicity
Myocardial infarction[3]	Event-Driven	Adverse Event Form
New or worsening heart failure[3]	Event-Driven	Adverse Event Form
Pericardial effusion[3]	Event-Driven	Adverse Event Form
Pericarditis[3]	Event-Driven	Adverse Event Form
Sinus bradycardia[3]	Event-Driven	Adverse Event Form
Ventricular arrhythmia	Calendar-Driven	Toxicity
Ventricular tachycardia[3]	Event-Driven	Adverse Event Form
ENDOCRINE DISORDERS		
Hyperthyroidism[3]	Event-Driven	Adverse Event Form
Hypothyroidism	Calendar-Driven	Toxicity
GASTROINTESTINAL DISORDERS		
Abdominal pain	Calendar-Driven	Toxicity
Anorexia	Calendar-Driven	Toxicity
Constipation	Calendar-Driven	Toxicity
Diarrhea	Calendar-Driven	Toxicity
Diverticulitis[3]	Event-Driven	Adverse Event Form
Dry mouth	Calendar-Driven	Toxicity
Dysgeusia (taste alteration)	Calendar-Driven	Toxicity
Dyspepsia (heartburn)	Calendar-Driven	Toxicity
GI perforation[3]	Event-Driven	Adverse Event Form
Intestinal obstruction[3]	Event-Driven	Adverse Event Form
Ischemic bowel[3]	Event-Driven	Adverse Event Form
Nausea	Calendar-Driven	Toxicity
Oral mucositis	Calendar-Driven	Toxicity
Vomiting	Calendar-Driven	Toxicity
GENERAL DISORDERS		

Adverse Event	Collection Type	Collection Form[2]
Chest pain- non-cardiac	Calendar-Driven	Toxicity
Chills	Calendar-Driven	Toxicity
Edema- generalized	Calendar-Driven	Toxicity
Fatigue	Calendar-Driven	Toxicity
Fever	Calendar-Driven	Toxicity
Sudden death[3]	Event-Driven	Adverse Event Form
HEPATOBILIARY/PANCREAS DISORDERS		
Abnormal liver function tests	Calendar-Driven	Toxicity
Hepatitis[3]	Event-Driven	Adverse Event Form
Liver failure[3]	Event-Driven	Adverse Event Form
Pancreatitis[3]	Event-Driven	Adverse Event Form
HEMORRHAGIC DISORDERS		
Intracranial[3]	Event-Driven	Adverse Event Form
Gastrointestinal[3]	Event-Driven	Adverse Event Form
Genitourinary	Calendar-Driven	Toxicity
Pulmonary/Upper respiratory[3]	Event-Driven	Adverse Event Form
IMMUNE SYSTEM DISORDERS		
Allergic reaction[3]	Event-Driven	Adverse Event Form
Anaphylaxis (swelling of the skin and/or swelling of the face or throat)[3]	Event-Driven	Adverse Event Form
INFECTIONS		
Infections/ Sepsis	Event-Driven	Infection
INVESTIGATIONS		
Increased ALT $\geq$ 3.0 x ULN[4]	Event-Driven	Adverse Event Form
Increased AST $\geq$ 3.0 x ULN[4]	Event-Driven	Adverse Event Form
Increased bilirubin $\geq$ 3.0 x ULN[4]	Event-Driven	Adverse Event Form
Increased creatinine	Calendar-Driven	Toxicity
Prolongation of QTc interval[4]	Event-Driven	Adverse Event Form
Weight loss	Calendar-Driven	Toxicity
METABOLISM AND NUTRITION DISORDERS		
Dehydration	Calendar-Driven	Toxicity
Hypercalcemia	Calendar-Driven	Toxicity
Hyperglycemia	Calendar-Driven	Toxicity
Hypoglycemia	Calendar-Driven	Toxicity
Hypokalemia	Calendar-Driven	Toxicity
Hyponatremia	Calendar-Driven	Toxicity
Tumor lysis syndrome[3]	Event-Driven	Adverse Event Form
MUSCULOSKELETAL AND TISSUE DISORDERS		
Arthralgia	Calendar-Driven	Toxicity
Myalgia	Calendar-Driven	Toxicity

Adverse Event	Collection Type	Collection Form[2]
Muscle weakness (generalized or specific area)	Calendar-Driven	Toxicity
Musculoskeletal pain	Calendar-Drive	Toxicity
NERVOUS SYSTEM DISORDERS		
Anxiety	Calendar-Driven	Toxicity
Ataxia	Calendar-Driver	Toxicity
Confusion	Calendar-Driven	Toxicity
Cranial palsy[3]	Event-Driven	Adverse Event Form
Depression	Calendar-Driven	Toxicity
Depressed level of consciousness[3]	Event-Driven	Adverse Event Form
Dizziness	Calendar-Driven	Toxicity
Edema cerebral[3]	Event-Driven	Adverse Event Form
Encephalopathy[3]	Event-Driven	Adverse Event Form
Headache	Calendar-Driven	Toxicity
Insomnia	Calendar-Driven	Toxicity
Neuralgia[3]	Event-Driven	Adverse Event Form
Neuropathy[3]	Event-Driven	Adverse Event Form
Reversible posterior leukoencephalopathy syndrome (PRES)[3]	Event-Driven	Adverse Event Form
Seizure[3]	Event-Driven	Adverse Event Form
Severe muscle weakness/paralysis[3]	Event-Driven	Adverse Event Form
Somnolence	Calendar-Driven	Toxicity
Spinal cord compression (non-malignant)[3]	Event-Driven	Adverse Event Form
Stroke	Calendar-Driver	Toxicity
Syncope (fainting)[3]	Event-Driven	Adverse Event Form
Tremor	Calendar-Drive	Toxicity
OCULAR/VISUAL DISORDERS		
Blurred vision[3]	Event-Driven	Adverse Event Form
Conjunctivitis	Calendar-Driven	Toxicity
Sudden loss of vision[3]	Event-Driven	Adverse Event Form
RENAL DISORDERS		
Cystitis Non-infective	Calendar-Driven	Toxicity
Acute kidney injury[3]	Event-Driven	Adverse Event Form
Chronic kidney disease[3]	Event-Driven	Adverse Event Form
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Adult respiratory distress syndrome[3]	Event-Driven	Adverse Event Form
Bronchitis	Calendar-Driven	Infection
Bronchopulmonary hemorrhage[3]	Event-Driven	Adverse Event Form
Cough	Calendar-Driven	Toxicity

Adverse Event	Collection Type	Collection Form[2]
Dyspnea	Calendar-Driven	Toxicity
Hypoxia	Calendar-Driven	Toxicity
Pleural effusion (non-malignant)[3]	Event-Driven	Adverse Event Form
Pneumonia	Calendar-Driven	Infection
Pneumonitis[3]	Event-Driven	Adverse Event Form
Pulmonary Hypertension[3]	Event-Driven	Adverse Event Form
Sinusitis	Calendar-Driven	Toxicity
Sore throat	Calendar-Driven	Toxicity
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Dry skin	Calendar-Driven	Toxicity
Erythema multiforme[3]	Event-Driven	Adverse Event Form
Pruritis	Calendar-Driven	Toxicity
Pyoderma gangrenosum[3]	Event-Driven	Adverse Event Form
Rash	Calendar-Driven	Toxicity
Sweet's syndrome (acute neutrophilic dermatosis)[3]	Event-Driven	Adverse Event Form
VASCULAR DISORDERS		
Capillary leak syndrome[3]	Event-Driven	Adverse Event Form
Edema	Calendar-Driven	Toxicity
Hypertension	Calendar-Drive	Toxicity
Hypotension	Calendar-Driven	Toxicity
Thromboembolic event (DVT, pulmonary emboli)[3]	Event-Driven	Adverse Event Form
Vasculitis[3]	Event-Driven	Adverse Event Form
OTHER		
Pregnancy[3]	Event-Driven	Adverse Event Form
Secondary malignancies[6]	Event-Driven	Adverse Event Form
Other unexpected grade 3-5 AE	Event-Driven	Adverse Event Form

[1]Last dose of lenalidomide refers to the last dose prior to permanent discontinuation of study lenalidomide.

[2]The form listed for collection may not be the only form that the toxicity should be reported on, but the lists the highest/most expeditious level of reporting.

[3]Any AEs that meets one of the criteria of a serious adverse event (SAE) as defined by the 21 CFR (312.32) and occurs from the first dose through 28 days after the last dose of lenalidomide, the Adverse Event Forms are required to be submitted.

[4]Any elevation in AST, ALT or bilirubin $\geq$ 3.0 times the upper limit of normal (ULN) and occurs from the first dose through 28 days after the last dose of lenalidomide, requires completion of the Adverse Event forms regardless of whether the event meets one of the seriousness criteria as defined by 21 CFR (312.32).

[5]Febrile neutropenia will be collected on the event-driven Infection Form. If febrile neutropenia meets one of the criteria of a serious adverse event (SAE) as defined by the 21 CFR (312.32) and occurs from the first dose through 28 days after the last dose of lenalidomide, the Adverse Event Forms are required to be submitted.

[6] Secondary malignancies will be collected on the adverse event forms at any time from study enrollment through 3 years post-maintenance.

APPENDIX K

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