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

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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 (or approximately 10 months post randomization) 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 ≥18.00 and < 71.00 years of age with symptomatic multiple myeloma requiring treatment, without history of prior disease progression or prior HCT, Karnofsky performance score ≥70%, evidence of at least 20% plasma cells in a bone marrow differential within 60 days of enrollment, and have received ≤1 cycle of systemic anti-myeloma therapy. If patient receives anti-myeloma therapy treatment after bone marrow aspirate to assess eligibility and before bone marrow aspirate for tumor cell collection, a repeat bone marrow evaluation will be required to confirm ≥ 20% plasma cells in the bone marrow aspirate differential prior to enrollment and tumor cell collection. 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 per the BMT CTN 1401 Manufacturing SOPs. 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 per the BMT CTN 1401 Manufacturing SOPs:

1) Bone marrow aspiration of 30 mL, isolation of mononuclear cells by ficoll centrifugation, quantification of CD138+ or 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 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) At least 20% of tumor cell prep must express CD38 or CD138 by staining
2) Tumor cell prep must yield $\geq$10 million plasma cells[1]
3) 50% of DC prep express CD86
4) Viability of DC prep > 50%
5) Fusion efficiency > 15%
6) Fusion viability > 50%
7) Sterility, mycoplasma, and endotoxin assays are negative

[1] Plasma cell count is determined by multiplying the total mononuclear cell yield by the percent of CD38 and CD138 staining reported on the Immunohistochemistry Report

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
Interim Analysis:	There will be no interim analysis for efficacy or futility.

STUDY SCHEMA

Initial Inclusion Criteria

1. Transplant Eligible
2. Meet criteria for symptomatic multiple myeloma (Appendix A)
3. Age ≥18.00 – < 71.00
4. Karnofsky Performance of ≥ 70%
5. 20% plasma cells in the bone marrow ≤ 60 days prior to enrollment[1]
6. Received ≤ 1 cycles of systemic anti-myeloma therapy[2]
7. Creatinine clearance ≥ 40 mL/min (estimated or calculated)

[1] If patient receives anti-myeloma therapy treatment after bone marrow aspirate to assess eligibility and before bone marrow aspirate for tumor cell collection, a repeat bone marrow evaluation will be required to confirm ≥ 20% plasma cells in the bone marrow aspirate differential prior to enrollment and tumor cell collection.

[2] Anti-myeloma therapy is defined as systemic treatment intended to treat the underlying myeloma disease. Treatments intended to alleviate pain and other symptoms of disease and/or administration of ≤160mg of dexamethasone or equivalent alternative steroid dose within a 30 day period are not considered anti-myeloma therapy.

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 a history of Plasma Cell Leukemia at any time prior to enrollment
4. Patients with prior disease progression at any time prior to enrollment
5. Patients seropositive for the human immunodeficiency virus (HIV).
6. Patients receiving treatment with Daratumumab or other CD38 Monoclonal Antibodies.
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 section 2.3.2

Inclusion Criteria for Randomization

1. No disease progression since initiation of systemic anti-myeloma therapy
2. Received autologous transplant with melphalan 200mg/m^2 with a minimum cell dose of 2x10^6 CD34+ cells/kg ≤12 months from enrollment onto BMT CTN 1401Tumor cell preparation must (1) Express ≥ 20% CD38 or CD138 by staining (2) yield ≥ 10 million plasma cells (*Plasma cell count is determined by multiplying the total mononuclear cell yield by the percent of CD38 and CD138 staining reported on the Immunohistochemistry Report)* (3) Have a negative microbiology assessment
3. No evidence of uncontrolled infection requiring systemic therapy
4. Platelet count ≥75,000/mm^3 (without transfusion in previous 7 days).
5. Absolute neutrophil count (ANC) ≥ 1,500/mm^3 without filgrastim administration within 7 days, or pegfilgrastim within 14 days of measurement.
6. Bilirubin < 2x the upper limit of normal
7. ALT and AST < 2.5x the upper limit of normal
8. 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
9. Patients must be willing to receive DVT prophylaxis
10. Patient must be willing to follow birth control and pregnancy testing 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:

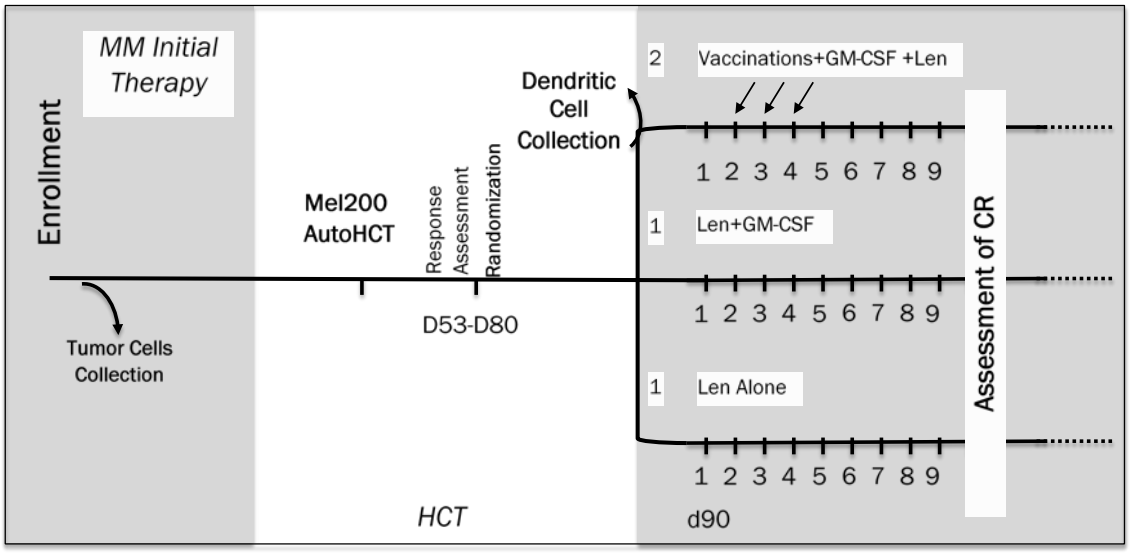
Treatment-induced expansion of myeloma-specific T cells as defined by the 2.4-fold increase from pre-therapy to peak post-treatment levels comparing the vaccine arm with patients receiving lenalidomide maintenance therapy with and without GM-CSF.

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 lenalidomide + 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.