PROTOCOL SYNOPSIS – BMT CTN 1302 PROTOCOL

Multicenter Phase II, Double-blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Multiple Myeloma

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Study Design: The study is designed as a Phase II, multi-center double-blind trial that randomizes patients with high risk MM to ixazomib maintenance or placebo 60-120 days after allogeneic hematopoietic transplantation (HCT).

Primary Objective: The primary objective of this randomized trial is to compare progression free survival from randomization as a time to event endpoint between patients randomized to ixazomib maintenance or placebo.

Secondary Objectives: Secondary objectives are to describe for each treatment arm: rates of grade II-IV and III-IV acute GVHD, chronic GVHD, best disease response rates, disease progression, transplant related mortality, overall survival, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, incidence of infections, and health-related quality of life.

Eligibility Criteria: Patients aged ≥ 18.0 years and ≤ 70.0 years at the time of enrollment, with:

1) high risk multiple myeloma in partial response (PR) or better with no prior progression *and* are ≤ 24.0 months from autologous HCT (single or planned tandem), or are ≤ 24.0 months from initiation of systemic anti-myeloma therapy with no autologous HCT; *or*
2) high risk multiple myeloma in very good partial response (VGPR) or better with 1 prior progression which occurred ≤ 24.0 months after autologous HCT (single or planned tandem), or ≤ 24.0 months after initiation of systemic anti-myeloma therapy with no autologous HCT; *or*
3) standard risk multiple myeloma in VGPR or better with 1 prior progression which occurred ≤ 24.0 months from autologous HCT (single or planned tandem); *or*
4) plasma cell leukemia in VGPR or better with no prior progression *and* are ≤ 18.0 months after autologous HCT, or are

≤ 18.0 months after initiation of systemic anti-myeloma therapy with no autologous HCT

Patients must have a HLA-matched related or unrelated donor willing to donate peripheral blood progenitor cells and meet one of the following criteria:

a. A sibling donor who is a 6/6 match at HLA–A and –B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*

b. A related donor (other than sibling) who is a 8/8 match for HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*

c. An unrelated donor who is an 8/8 match at HLA–A, –B, –C, and –DRB1 (at high resolution using DNA-based typing)

Treatment Description: All patients will undergo conditioning regimen with fludarabine (120 mg/m^2), melphalan (140 mg/m^2) and bortezomib (1.3 mg/m^2) combination. GVHD prophylaxis will use the combination of tacrolimus and methotrexate. Randomization to ixazomib maintenance or placebo will occur at the time of maintenance therapy initiation (between Days 60 and 120 post-transplant). Maintenance with ixazomib will consist of 12 x 28-day cycles at a dose of 3 mg on Days 1, 8 and 15, with adjustments depending on toxicity. Ixazomib will continue for a maximum of 12 cycles (28 days/cycle). Patients randomized to placebo will follow the same treatment and dose schedule as those randomized to ixazomib maintenance.

Accrual: The sample size for this study is 110 randomized patients with a target enrollment of 138 patients to achieve that sample size.

Accrual Period: The estimated accrual period is 3 years

Study Duration: Patients will be followed for 2 years post transplant for all endpoints. In addition, patients will be followed only for second primary malignancies until all patients have completed 2 years of follow up.

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

Stopping Guidelines: The key safety endpoints to be monitored are the rate of TRM at Day 100 post-transplant in all transplanted subjects, Grade III-IV acute GVHD at Day 100 post-transplant, and Grade III-IV acute GVHD rates at Day 60 post-randomization within treatment arm. Monitoring of the key safety endpoints 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. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures (MOP).

STUDY SCHEMA

Aim: To determine the impact of maintenance and allogeneic transplant in high risk multiple myeloma

Inclusion Criteria	**Exclusion Criteria**
1. Age ≥ 18.0 and ≤ 70.0 years at the time of enrollment 2. Patient must meet ONE of the disease criteria outlined in table 1 below. 3. Patients must have a HLA-matched related or unrelated peripheral blood stem cell donor that meet one of the following criteria: A sibling donor who is a 6/6 match at HLA–A and–B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR* a related donor (other than sibling) who is a 8/8 match for HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR* an unrelated donor who is an 8/8 match at HLA–A, –B, –C, and –DRB1 (at high resolution using DNA-based typing). 4. Cardiac function: Ejection fraction > 40% 5. Estimated creatinine clearance greater than 40 mL/minute 6. Pulmonary function: DLCO ≥ 40% (adjusted for hemoglobin) and FEV1 ≥ 50% 7. Liver function: total bilirubin < 2x the upper limit of normal and ALT/AST < 2.5x the upper normal limit 8. Effective methods of birth control as described in the protocol 9. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.	1. Karnofsky Performance Score < 70% 2. Prior allogeneic HCT 3. Non secretory multiple myeloma (defined as normal serum and urine immunofixation and normal serum free light chain assay). 4. Uncontrolled bacterial, viral or fungal infections (undergoing appropriate treatment and with progression of clinical symptoms). 5. Seropositive for the human immunodeficiency virus (HIV). 6. Active Hepatitis B or C determined by serology and/or NAAT. 7. Hypersensitivity to bortezomib, boron or mannitol. 8. Grade 2 or higher sensory peripheral neuropathy. 9. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D), 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 must be documented by the investigator as not medically relevant. 10. Pre-planned pre-emptive or prophylactic administration of donor lymphocytes. 11. CNS involvement with MM (CSF positivity for plasma cells or a parenchymal CNS plasmacytoma 12. Presence of fluid collection that interferes with methotrexate clearance. 13. Known GI disease or GI procedure that could interfere with the oral absorption of MLN9708 (ixazomib). 14. Prior cancers except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years, which is in remission, will be reviewed on a case-by-case basis by the Protocol Officer or one of the Protocol Chairs 15. Multi-organ involvement by amyloidosis or evidence of amyloidosis-related organ dysfunction. 16. Received radiation therapy within ≤ 3.0 weeks before transplant

Table 1: Disease Criteria for Eligible Patients

Disease	Disease Status	Prior Progression	Prior Therapy/Auto HCT
High Risk[1] Multiple Myeloma	**≥ PR**	**None**	≤ 24.0 months after autologous HCT (single or planned tandem), or after initiation of systemic anti-myeloma therapy with no autologous HCT
High Risk[1] Multiple Myeloma	**≥ VGPR[2]**	**1**	progression or relapse ≤ 24.0 months after autologous HCT (single or planned tandem), or after initiation of systemic anti-myeloma therapy with no autologous HCT
Standard Risk Multiple Myeloma	**≥ VGPR[2]**	**1**	progression or relapse ≤ 24.0 months after single or planned tandem autologous HCT
Plasma Cell Leukemia	**≥ VGPR**	**None**	≤ 18.0 months after autologous HCT, or after initiation of systemic anti-myeloma therapy

***Immune Suppression Taper*:**
Patients without GVHD
Tacrolimus
- Taper to initiate at least Day 90 and completely off at Day 180.

Primary endpoint:
- Progression free survival as a time to event endpoint from randomization

Secondary endpoints:
- Grades II-IV and III-IV acute GVHD
- Chronic GVHD
- Best response
- Disease progression
- Treatment-related mortality
- Toxicity
- Rates of infections
- Overall survival
- Rate of non-randomization
- Health-Related Quality of Life

[1]High Risk is defined as one or more of the following detected at any time prior to enrollment: del13 by conv. karyotyping only; hypodiploidy, 1q amplification or 1p deletion, t(4;14), t(14;16), t(14;20) or deletion of 17p by FISH or conv. karyotyping; or high risk criteria based on GEP.

[2]Patients with one prior progression without measurable monoclonal paraprotein at the time of disease progression or relapse (< 1.0 g/dl in serum or < 200 mg/24 hrs in urine) may be considered to have met VGPR criteria if < 5% plasma cells in bone marrow *and* ≥ 90% decline in the difference between involved and uninvolved FLC levels from baseline (time of progression/relapse).

Patients with IgG kappa multiple myeloma receiving daratumumab: International Myeloma Working Group criteria for VGPR may not be achieved since daratumumab is known to increase the IgG kappa spike. In such cases the FLC and marrow may be used to establish VGPR, as above, with prior approval from the protocol co-chairs.

OUTLINE OF TREATMENT PLAN