PROTOCOL SYNOPSIS – BMT CTN 0702 PROTOCOL

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

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

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

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

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

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

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

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

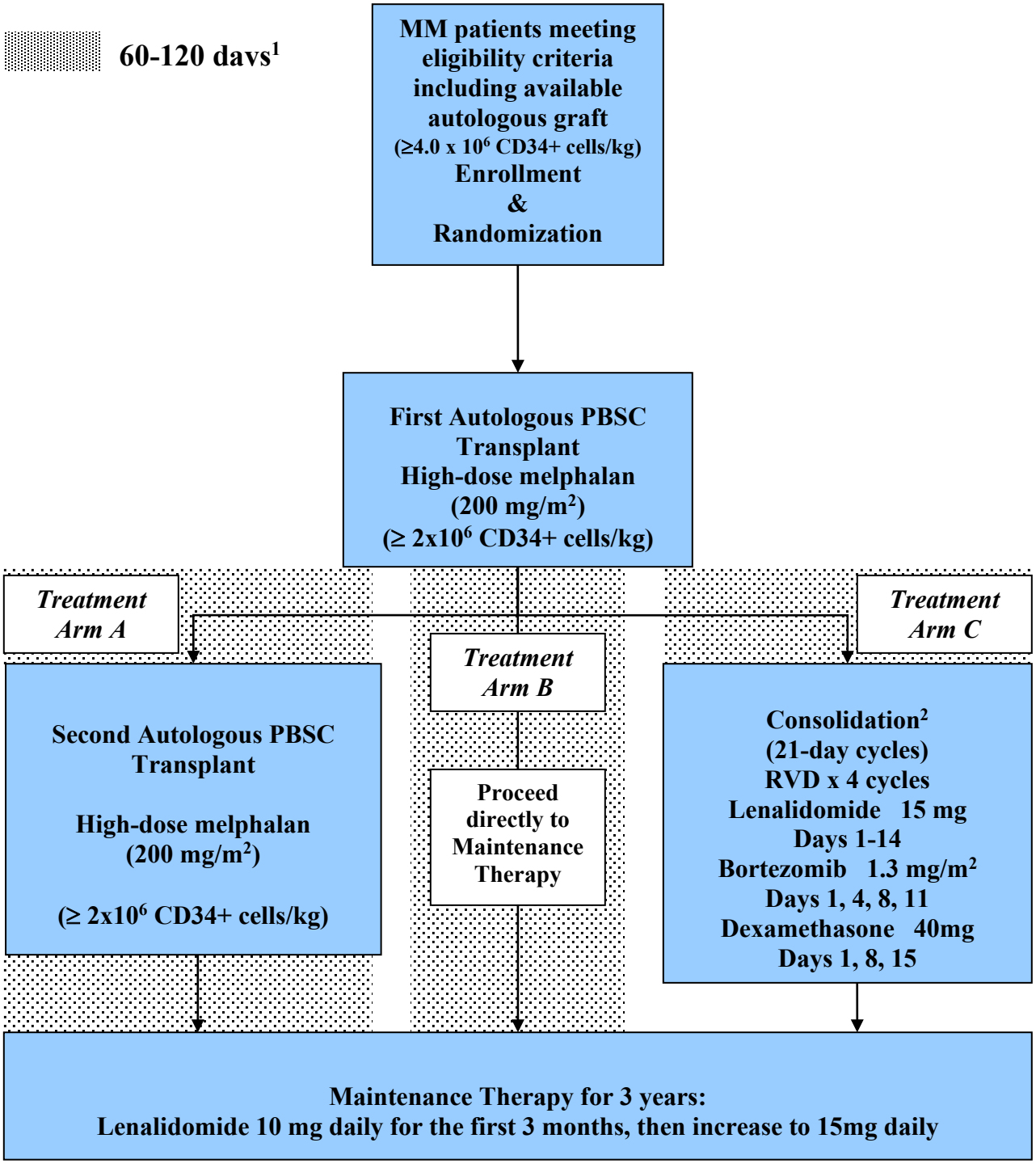
Quality of Life: The FACT-BMT and MOS SF-36 instruments will be used to describe the health-related quality of life (HQL) of patients. A secondary analysis will compare the HQL between the treatment arms. The self-report questionnaires will be performed prior to first and second transplants, consolidation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

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

Accrual Period: The estimated accrual period is three years.

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

Outline of Treatment Plan



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