PROTOCOL SYNOPSIS – BMT CTN 1101

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow (haplo-BM) for Patients with Hematologic Malignancies

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Study Design: This study is a multi-center, Phase III, randomized trial of reduced intensity conditioning followed by transplantation of two unrelated cord blood units with calcineurin inhibitor and mycophenolate mofetil (MMF) for GVHD prophylaxis versus HLA-haploidentical related bone marrow with posttransplant cyclophosphamide, calcineurin inhibitor, and MMF for GVHD prophylaxis in patients with:

1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, dendritic cell leukemias, natural killer cell malignancies or Burkitt's lymphoma in remission.
2) Lymphoma, including marginal zone lymphoma, follicular lymphoma, or chemotherapy-sensitive large-cell, Hodgkin or mantle cell lymphoma, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma.

Primary Objective: The primary objective is to compare progression-free-survival at 2 years post-randomization between patients who receive unrelated double cord blood unit transplantation versus HLA-haploidentical related bone marrow transplantation.

Secondary Objectives: Patients enrolled in this study will also be followed for the following endpoints: neutrophil recovery, graft failure, platelet recovery, donor cell engraftment, acute graft-versus-host-disease (GVHD) and chronic GVHD, overall survival, treatment-related mortality, infections, hospital admission and length of stay, health related quality of life, relapse/progression, and cost effectiveness (see companion 1101 study document for ancillary cost effectiveness protocol).

Accrual Objective: The target sample size is 410 patients.

Accrual Period: The target accrual period is 4 years.

Eligibility Criteria: Patients $\geq$ 18 and $\leq$ 70 years of age with a diagnosis of a hematologic malignancy with two partially HLA-matched UCB

units, each with a minimum of 1.5 x 10^7/kg pre-cryopreserved total nucleated cell dose (for non-red blood cell depleted units, the minimum cryopreserved total nucleated cell dose of each unit must be at least 2.0 x 10^7/kg), and a partially HLA-mismatched related donor.

Adequate organ function defined as: 1) left ventricular ejection fraction ≥ 40%; 2) DLCO, FEV_1, FVC > 50% predicted; 3) total bilirubin ≤ 2.5 mg/dL except for patients with Gilbert's syndrome or hemolysis, and ALT, AST, and alkaline phosphatase all < 5 x upper limit of normal (ULN); 4) serum creatinine within normal range, or if serum creatinine outside normal range, must have measured or estimated creatinine clearance > 40 mL/min/1.73m^2; 5) Karnofsky performance score ≥ 70; and 6) if applicable, > 6 months since a previous autologous transplant.

Treatment Description: Eligible patients will be randomized to dUCB or haplo-BM transplantation:

The preparative regimen for haplo-BM transplantation will consist of:

- Fludarabine 30 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide (Cy) 14.5 mg/kg IV Days –6, –5
- Total body irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of infusion of non-T-cell depleted bone marrow

The GVHD prophylaxis regimen for haplo-BM transplantation will consist of:

- Cy 50 mg/kg IV Days 3, 4
- Tacrolimus (IV or po) beginning Day 5 with dose adjusted to maintain a trough level of 5-15 ng/mL. Cyclosporine (trough level of 200-400 ng/mL) may be substituted for tacrolimus if the patient is intolerant of tacrolimus or per institutional practice.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID, maximum dose 1 g po TID beginning Day 5 until Day 35

Supportive care for haplo-BM transplantation includes:

- Filgrastim (G-CSF) 5 mcg/kg/day beginning Day 5 until ANC ≥1500/mm^3 for 3 consecutive measurements on at least two different days

The preparative regimen for dUCB transplantation will consist of:

- Fludarabine 40 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide 50 mg/kg IV Day –6
- Total Body Irradiation (TBI)
  - 200 cGy Day –1 for patients who have received cytotoxic

chemotherapy within the last 3 months or an autologous transplant within 24 months of enrollment
- 300 cGY Day -1 for patients who have not received cytotoxic chemotherapy within 3 months of enrollment or an autologous transplant within 24 months of enrollment
- Day 0 will be the day of the double UCB transplant

The GVHD prophylaxis regimen for dUCB transplantation will consist of:

- Cyclosporine beginning Day –3 with dose adjusted to maintain a trough level of 200-400 ng/mL. Tacrolimus (trough level of 5-15 ng/mL) may be substituted for cyclosporine if the patient is intolerant of cyclosporine or per institutional practice.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID, maximum dose 1 g po TID beginning Day-3 until Day 35.

Supportive care for dUCB transplantation includes:

- Filgrastim (G-CSF) 5 mcg/kg/day beginning Day 1 until ANC $\geq$1500/mm^3 for 3 consecutive measurements on at least two different days

Study Duration: Patients will be followed for three years after transplantation.