PROTOCOL SYNOPSIS – BMT CTN 0603

A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies

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Study Design: This study is a Phase II, multi-center study of nonmyeloablative conditioning and transplantation of bone marrow from partially HLA-mismatched, related donors.

Primary Objective: The primary objective is to determine overall survival 180 days after HLA-haploidentical bone marrow transplantation using a nonmyeloablative preparative regimen and post-transplantation cyclophosphamide.

Secondary Objectives: Patients enrolled in this study will also be followed for the following endpoints: neutrophil and platelet recovery, graft failure, acute graft-versus-host disease (GVHD), chronic GVHD, incidence of infection, treatment-related mortality, time to relapse/progression, overall survival, and current progression-free survival.

Study Design: This study is a Phase II, multi-center study of non-myeloablative conditioning, transplantation of partially HLA-mismatched bone marrow and post-transplantation cyclophosphamide in patients with:

1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, and Burkitt's lymphoma in remission.
2) Relapsed lymphoma, including marginal zone B cell lymphoma, follicular lymphoma, and chemotherapy-sensitive large-cell or Mantle Cell Hodgkin lymphoma.

Accrual Objective: The target sample size is 50 patients

Accrual Period: The estimated accrual period is three years.

Eligibility Criteria: Patients 21-70 years of age, or 1-21 years old and ineligible for BMT CTN #0501 with the diagnosis of a hematologic malignancy and with a partially (< 5/6) HLA-mismatched donor.

Adequate organ function defined as: 1) left ventricular ejection fraction > 35%; 2) DLCO, FEV_1, FVC > 50% predicted; 3) total bilirubin ≤ 2.5 mg/dl, and ALT, AST, and alkaline phosphatase all

< 5 x upper limit of normal (ULN); 4) serum creatinine within normal range for age, or if serum creatinine outside normal range for age, then renal function (creatinine clearance or GFR by Cockroft-Gault formula) > 40 mL/min/1.73m^2; 5) Karnofsky/ Lansky performance score 60 to 100; and 6) if applicable, > 3 months since a previous autologous transplant.

Treatment Description: The preparative regimen 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 will consist of:
- Cy 50 mg/kg IV Days 3, 4
- Tacrolimus (IV or po) beginning Day 5 with dose adjusted to maintain a level of 5-15 ng/mL
- Mycophenolate mofetil (MMF) 15 mg/kg po TID beginning Day 5, maximum dose 1 g po TID
- G-CF 5 mcg/kg/day beginning Day 5 until ANC ≥ 1,000/mm^3 for 3 consecutive days

Study Duration: Patients will be followed for one year after transplantation.

TREATMENT SCHEMA*

Days –6, –5	Fludarabine 30 mg/M^2 IV daily Cyclophosphamide (Cy) 14.5 mg/kg IV daily Mesna 11.6 mg/kg IV daily** Begin antibiotic prophylaxis
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Days –4 → –2	Fludarabine 30 mg/M^2 IV daily
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Day –1	TBI 200 cGy
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Day 0	Infuse non-T cell-depleted marrow
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Days 3, 4	Cy 50 mg/kg (IBW) IV daily Mesna 40 mg/kg IV daily**
	(First dose of Cy must be administered 60-72 hour after infusion of marrow)
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Day 5	Begin tacrolimus 1mg IV qd** or 1 mg po bid** and MMF 15 mg/kg PO TID with maximum daily dose 3 gm/day Begin G-CSF 5 mcg/kg/day SC or IV, continue until ANC ≥ 1000/mm^3 x 3 days
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Day ~28	Assess chimerism in peripheral blood
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Day 35	Discontinue MMF (optional if GVHD is active)
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Day ~56	Assess chimerism in peripheral blood
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Day 180	Discontinue tacrolimus (optional if GVHD is active) Assess chimerism in peripheral blood Evaluate disease
	↓
1 yr,	Evaluate disease Assess chimerism in peripheral blood

* Refer to Section 2.5 for complete instructions on medication administration.
** Or as per institutional standards.