PROTOCOL SYNOPSIS – BMT CTN 0604

A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning (NST) and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors for Patients with Hematologic Malignancies

Study Chairperson:	Claudio Brunstein, MD
Primary Objective:	The primary objective is to determine overall survival 180 days after double cord blood transplantation using a non-myeloablative preparative regimen.
Secondary Objectives:	Patients enrolled in this study will 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 prospective study of non-myeloablative conditioning and transplantation of double UCBs from unrelated donors 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 large-cell lymphoma, Hodgkin's 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 < 21 years old and ineligible for BMT CTN #0501 with the diagnosis of a hematologic malignancy and with two partially HLA-matched UCB units. Units must be HLA-matched at 4 of 6 HLA-A and B (intermediate resolution molecular typing) and DRB1 (high resolution molecular typing) with each other and 4 of 6 with the recipient. Each unit must contain a minimum pre-cryopreserved, nucleated cell dose of 1.5×10^7 per kilogram. Patients may not have an available HLA 6/6- or 5/6-matched sibling.

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 40 mg/m^2 IV Days –6, -5, -4,-3, -2
- Cyclophosphamide 50 mg/kg IV Day -6
- Total Body Irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of the double UCB transplant

The GVHD prophylaxis regimen will consist of:
- Cyclosporine beginning Day –3 with dose adjusted to maintain a level of 200-400 ng/mL
- Mycophenolate mofetil (MMF) 1 gram IV TID if > 50 kg or 15 mg/kg IV TID if < 50 kg beginning Day-3 until Day 30 or 7 days after engraftment whichever day is later.

Study Duration:

Patients will be followed for one year post-transplant.

TREATMENT SCHEMA*

Days –6	Fludarabine 40 mg/M^2 IV daily Cyclophosphamide (Cy) 50 mg/kg IV daily Mesna 50 mg/kg IV daily**
	↓
Days –5	Fludarabine 40 mg/M^2 IV daily
	↓
Days –4	Fludarabine 40 mg/M^2 IV daily
	↓
Days –3	Fludarabine 40 mg/M^2 IV daily Start cyclosporine A (or tacrolimus) Start cyclosporine mycophenolate mofetil
	↓
Days –2	Fludarabine 40 mg/M^2 IV daily
	↓
Day –1	TBI 200 cGy
	↓
Day 0	Infuse umbilical cord blood graft units
	↓
Day +1	Start filgrastim 5 mcg/kg/day
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Day 21 (±2)	Assess chimerism in peripheral blood Bone marrow biopsy to assess cellularity
	↓
Day +30	Discontinue MMF if neutrophil engraftment and no acute GVHD
	↓
Day +56	Assess chimerism in peripheral blood
	↓
Day +180	Discontinue cyclosporine A (or 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 2.6 for complete instructions on medication administration.
** Or as per institutional standards.