PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0303

A Single Arm, Multicenter Phase II Trial of Transplants of HLA-Matched, CD34$^+$ Enriched, T cell Depleted Peripheral Blood Stem Cells Isolated by the CliniMACS System in the Treatment of Patients with AML in First or Second Morphologic Complete Remission

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Primary Objective: The primary objective is to assess disease-free survival (DFS) at 6 months post-transplant. Death or relapse will be considered events for this endpoint.

Secondary Objectives: Secondary objectives are to assess infusional toxicity, the time to neutrophil and platelet engraftment, the incidence and severity of acute and chronic GVHD, the incidence of transplant-related mortality, the incidence of EBV post-transplant lymphoproliferative disorder, the time to leukemia relapse, the probability of survival and disease-free survival at 2 years post-transplant and the proportion of grafts with both > 5 x 10^6 /kg CD34 cells and < 1 x 10^5 /kg CD3 cells.

Study Design: The study is a single arm Phase II, multicenter trial. It is designed to determine whether the anticipated endpoints for a T cell depleted transplant arm of a planned prospective randomized trial comparing T cell depleted and unmodified hematopoietic allografts are likely to be achieved in a multicenter study conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN or Network). The study population is patients with acute myeloid leukemia (AML) in first or second morphologic complete remission. The enrollment is 45 patients.

Based on published results of unmodified transplants from HLA-matched siblings applied to patients with AML in first or second morphologic complete remission, a significant improvement in results with a graft modified as specified in this protocol would be expected if DFS at 6 months was > 75%, the true incidence of transplant-related mortality at 1 year was < 30% and the DFS rate at 2 years was ≥ 70% for patients transplanted in first remission and > 60% for patients transplanted in second remission. Additional secondary endpoints include: graft failure rate, incidences of acute grade II-IV and chronic graft-versus-host disease (GVHD). Additionally, the trial will have target specific doses of CD34$^+$ progenitors and CD3$^+$ T cells to be obtained following fractionation with the CliniMACS system. Based on the results of this trial, a Phase III trial comparing T cell depleted peripheral blood stem cell transplants (PBSCT) with unmanipulated bone marrow or unmanipulated PBSCT will be designed.

Eligibility Criteria: Patients from 18 to 65 years of age with AML in first or second morphologic complete remission with an HLA-identical sibling donor are eligible. The donor must be healthy and willing to undergo G-CSF-based stem cell mobilization. Patients must have a Karnofsky performance status ≥ 70%. Patients must be in good clinical condition without coexisting medical problems that would significantly increase the risk of the transplant procedure. Patients must be free of active infections at the time of transplantation.

Treatment Description: Following screening and enrollment, the donor will receive mobilization therapy with daily G-CSF at a dose of 16 µg/kg/day subcutaneously. Leukapheresis will be performed on a continuous flow cell separator according to institutional standards commencing on Day 5 of G-CSF treatment. Daily leukapheresis of the donor with subsequent $CD34^+$ cell selection using the Miltenyi CliniMACS device will continue until a post-selection target of > 5.0 x 10^6 $CD34^+$ cells /kg recipient body weight and < 1.0 x 10^5 $CD3^+$ cells /kg recipient body weight is reached following at least two but not more than three leukapheresis procedures. There is no limit to the number of $CD34^+$ progenitors that can be administered.

The conditioning regimen will include total body radiation (TBI), thiotepa, cyclophosphamide, and rabbit antithymocyte globulin (ATG, thymoglobulin). The $CD34^+$ selected cells will be infused within 48-72 hours after the last dose of the conditioning regimen. Hyperfractionated TBI is administered at a dose rate of 8-20 cGy/minute. Doses of 125 cGy/fraction are administered at 4-hour intervals three times/day for a total of 11 doses (1375 cGy) over 4 days (Day -9, -8, -7, and -6).

Thiotepa will be administered at a dose of 5mg/kg/day IV for two consecutive days (Day -5, and -4). **Cyclophosphamide** will be administered at a dose of 60 mg/kg/day IV for two consecutive days (Day -3, and -2). **Rabbit Antithymocyte Globulin** (Thymoglobulin, Genzyme) will be administered as a single intravenous dose on Day -4 at 2.5mg/kg over 6-8 hours.

No additional GVHD prophylaxis will be administered. Due to stringent T cell depletion, no significant GVHD is anticipated. Should GVHD occur, the appropriate treatment schedule and dose will be initiated.

Accrual Objective: The sample size is 45 patients for this trial.

Accrual Period: It is anticipated that the accrual will last one year.

Study Duration: Patients will be followed for at least two years following transplantation.

Schema of Conditioning Regimen

-9	-8	-7	-6	-5	-4	-3	-2	-1	0	+1
TBI	TBI	TBI	TBI							
				THIO	THIO					
					rATG	CTX	CTX			
									$CD34^+$ PBSC Transplant	$CD34^+$ PBSC Transplant
Donor Mobiliza-tion				X	X	X	X	X Begin Leu-kapheresis	X Continue Leu-kapheresis	X Continue Leu-kapheresis, if necessary

TBI=total body irradiation; THIO=Thiotepa; rATG=rabbit antithymocyte globulin; CTX=cyclophosphamide