

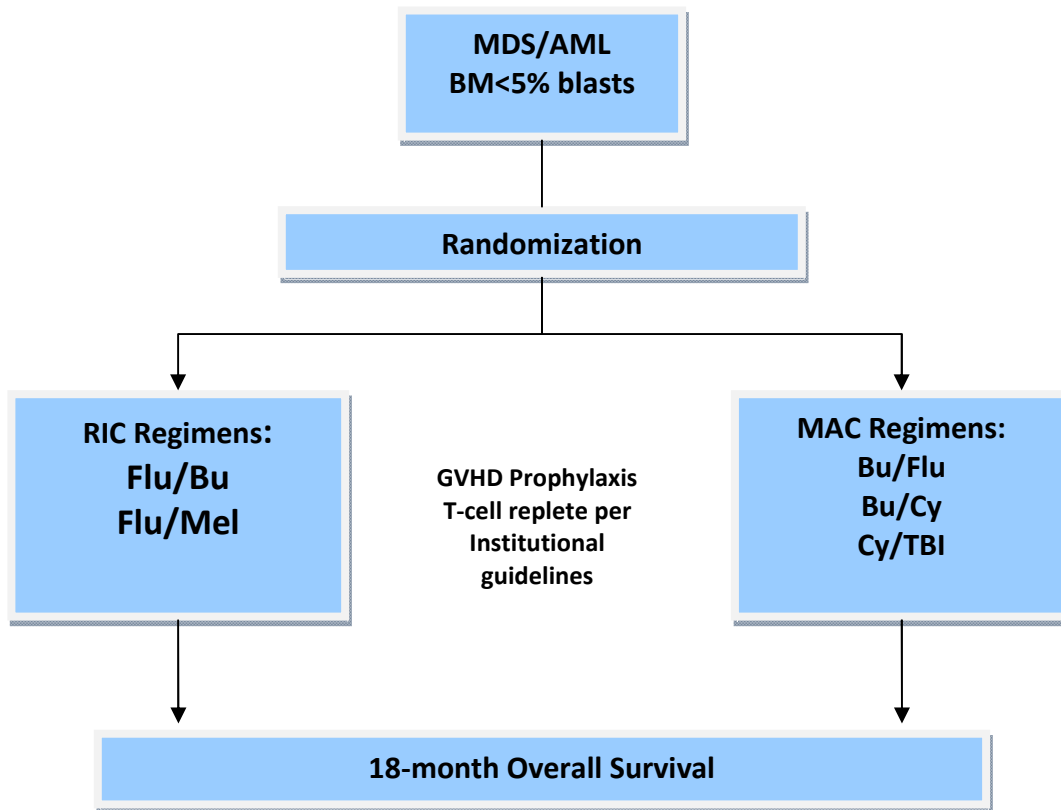
PROTOCOL SYNOPSIS – BMT CTN 0901 PROTOCOL

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

- Co-Principal Investigators:** Bart Scott, MD and Mitchell Horwitz, MD
- Study Design:** The study is designed as a Phase III, multicenter trial comparing outcomes after allogeneic hematopoietic stem cell transplantation (HCT) for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) between patients receiving myeloablative conditioning (MAC) versus reduced intensity conditioning (RIC) regimens.
- Primary Objective:** The primary objective of the randomized trial is to compare 18-month overall survival (OS) rates between the two groups. The hypothesis to be tested is that reducing the intensity of the conditioning regimen will decrease treatment-related mortality without increasing relapse so that overall survival will be improved.
- Secondary Objectives:** Secondary objectives include comparisons of disease-free survival rates after transplantation, rates of transplant-related mortality, incidence of relapse, hematologic recovery, kinetics of donor cell engraftment, incidence of graft failure, incidence and severity of acute and chronic graft-versus-host disease (GVHD), quality of life, rates of infectious complications, rates of \geq grade 3 toxicities according to the CTCAE criteria, immune reconstitution and quality of life.
- Eligibility Criteria:** Patients 18-65 years with the diagnosis of acute myeloid leukemia or myelodysplasia with less than 5% bone marrow blasts by morphology and no circulating leukemic myeloblasts, with HCT-specific comorbidity index score \leq 4 and an available related or unrelated bone marrow or peripheral blood donor. Sibling donor must be a 6/6 match at HLA-A and -B (intermediate or higher resolution) and -DRB1 (at high resolution using DNA-based typing). Related donor other than sibling must be a 7/8 or 8/8 match for HLA-A, -B, -C (at intermediate typing or higher resolution) and -DRB1 (at high resolution using DNA-based typing). Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C and -DRB1 at high resolution using DNA-based typing. There must be at least 30 days between the start of the most recent cycle of cytotoxic therapy for the malignancy and enrollment or, for patients treated with hypomethylating agents, at least 10 days between completion of therapy and enrollment.

Treatment Description:	Patients randomized to RIC will receive one of two regimen types: the combination of fludarabine (120-180 mg/m ²) and busulfan (\leq 8 mg/kg or IV equivalent) (Fu/Bu) <i>or</i> fludarabine (120-180 mg/m ²) and melphalan (< 150 mg/m ²) (Flu/Mel). Patient randomized to MAC will receive one of three regimens: busulfan (16 mg/kg oral <i>or</i> 12.8 mg/kg IV) and cyclophosphamide (120 mg/kg) (Bu/Cy); <i>or</i> , busulfan (16 mg/kg PO or 12.8 mg/kg IV) and fludarabine (120-180 mg/m ²) (Bu/Flu); <i>or</i> , cyclophosphamide (120 mg/kg) and total body irradiation (> 1200-1420cGy) (CyTBI).
Accrual Objective:	356 patients, 178 to each arm.
Accrual Period:	The estimated accrual period is four years.
Study Duration:	Patients will be followed for up to 18 months from transplantation.

Outline of Treatment Plan



Reduced Intensity Conditioning (RIC)		Myeloablative Conditioning (MAC)	
A	Fludarabine/Busulfan (Flu/Bu) <ul style="list-style-type: none"> Fludarabine (120-180 mg/m²) Busulfan (≤8 mg/kg PO or 6.4 mg/kg IV) 	C	Busulfan¹/Fludarabine (Bu/Flu) <ul style="list-style-type: none"> Busulfan (16 mg/kg PO or 12.8 mg/kg IV) Fludarabine (120-180 mg/m²)
B	Fludarabine/Melphalan (Flu/Mel) <ul style="list-style-type: none"> Fludarabine (120-180 mg/m²) Melphalan (≤150 mg/m²) 	D	Busulfan¹/Cyclophosphamide (Bu/Cy) <ul style="list-style-type: none"> Busulfan (16 mg/kg PO or 12.8 mg/kg IV) Cyclophosphamide (120 mg/kg)
		E	Cyclophosphamide/Total Body Irradiation (Cy/TBI) <ul style="list-style-type: none"> Cyclophosphamide (120 mg/kg) TBI (1200-1420 cGy)

¹ Bu = PO doses will be adjusted to maintain Bu steady state concentration at 900±100 ng/mL.