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

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VERSION 5.0

Study Chairpersons
Bart Scott, M.D.[1] and Mitchell Horwitz, M.D.[2]

Protocol Team

Shelly Carter, Sc.D.[1]
Joachim Deeg, M.D.[1]
Steve Devine, M.D.[4]
Iris Gersten, M.S.[3]
Sergio Giralt, M.D.[5]
Mary Horowitz, M.D., M.S.[6]
Jennifer LeRademacher, Ph.D.[6]
Brent Logan, Ph.D.[6]
Richard Maziarz, M.D.[7]
Willis Navarro, M.D.[6]
Marcelo Pasquini, M.D., M.S.[6]
Nancy Poland, M.A.[8]
David Porter, M.D.[9]
Erica Warlick, M.D.[10]

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[1]Fred Hutchinson Cancer Research Center
[2]Duke University Medical Center
[3]The EMMES Corporation
[4]Ohio State University Medical Center
[5]Memorial Sloan-Kettering Cancer Center
[6]Medical College of Wisconsin
[7]Oregon Health &Science University
[8]National Marrow Donor Program
[9]University of Pennsylvania
[10]University of Minnesota

Approval Signature (Protocol Chair/Officer

Approval Signature (Protocol Chair/Officer

Core Study Participants:

Baylor College of Medicine (Methodist)
BMT at Northside Hospital
Case Western Reserve University Consortia
- Cleveland Clinic Foundation
- Oregon Health and Science University
- University Hospitals of Cleveland

Dana Farber Cancer Institute
Duke Medical Center
Fred Hutchinson Cancer Research Center
H. Lee Moffitt Cancer Center
Ohio State University Consortia
- Ohio State
- Roswell Park Cancer Institute
- University of North Carolina/Chapel Hill

University of Florida Consortia
- Emory University
- University of Florida (Shands)

University of Minnesota
University of Nebraska Consortia
- University of Kansas Hospital
- University of Nebraska

University of Pennsylvania

Affiliate Study Participants:

Barbara Ann Karmanos Cancer Institute
Baylor University Medical Center (Dallas)
Colorado Blood Cancer Institute
Florida Hospital Cancer Institute
Fox Chase Temple University
Jewish Hospital
Mayo Clinic – Phoenix
Medical College of Wisconsin
Mount Sinai Medical Center
Texas Transplant Institute
Tufts New England Medical Center
University of California, San Diego
University of Kentucky
University of Maryland
University of Oklahoma
University of Rochester
University of Utah
University of Wisconsin
West Virginia University Hospital

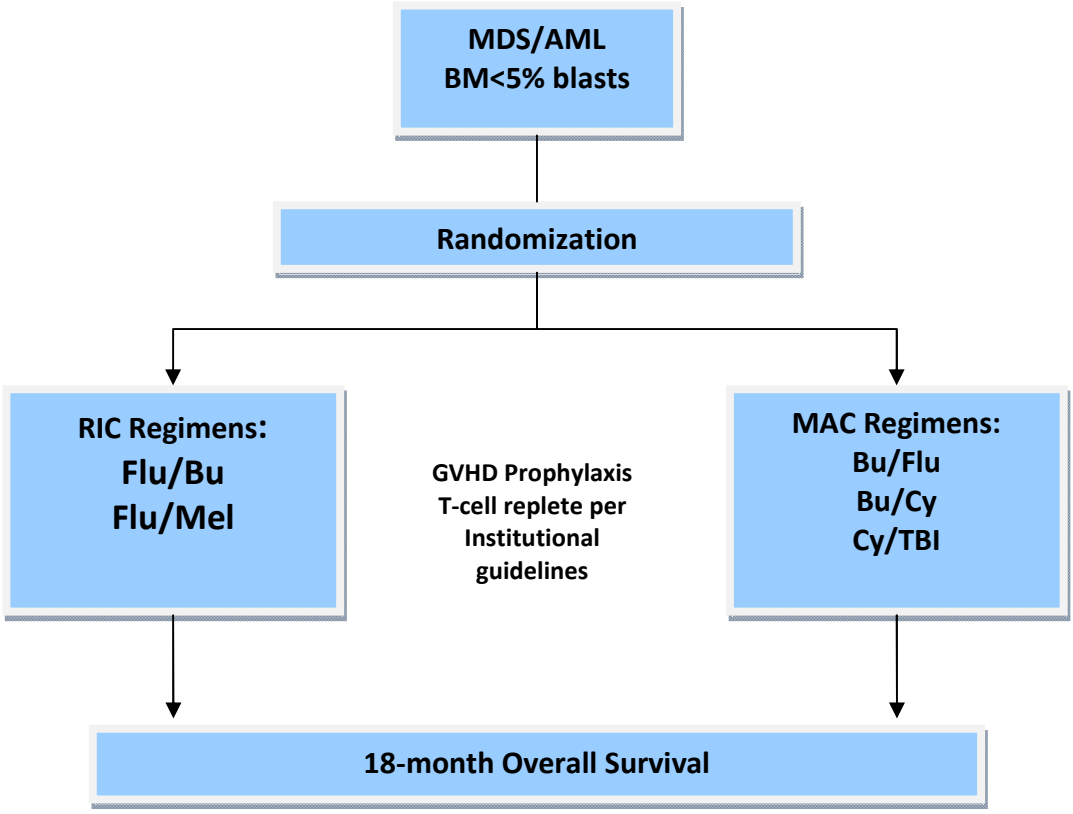
PROTOCOL SYNOPSIS – BMT CTN 0901 PROTOCOL

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 ≤ 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 (≤ 8 mg/kg or IV equivalent) (Fu/Bu) *or* 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 *or* 12.8 mg/kg IV) and cyclophosphamide (120 mg/kg) (Bu/Cy); *or*, busulfan (16 mg/kg PO or 12.8 mg/kg IV) and fludarabine (120-180 mg/m^2) (Bu/Flu); or, 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)** • Fludarabine (120-180 mg/m^2) • Busulfan (≤8 mg/kg PO or 6.4 mg/kg IV)	**C**	**Busulfan[1] /Fludarabine (Bu/Flu)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Fludarabine (120-180 mg/m^2)
B	**Fludarabine/Melphalan (Flu/Mel)** • Fludarabine (120-180 mg/m^2) • Melphalan (≤150 mg/m^2)	**D**	**Busulfan[1]/Cyclophosphamide (Bu/Cy)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Cyclophosphamide (120 mg/kg)
		E	**Cyclophosphamide/Total Body Irradiation (Cy/TBI)** • 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.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Introduction

MDS and AML are predominantly diseases of older patients. For patients with advanced or chemotherapy refractory disease allogeneic hematopoietic cell transplantation (HCT) is currently the only strategy that offers cure. Unfortunately, this modality is currently available only to a small proportion of patients. Many patients do not undergo HCT either because of advanced age, because no suitable donor is available, or because of unacceptable risks currently associated with HCT.

One major cause of mortality after HCT is toxicity from pretransplant conditioning which historically has included high, myeloablative doses of cytotoxic chemotherapy with or without radiation. In recent years, reduced intensity conditioning regimens were introduced in an attempt to reduce non-relapse mortality (NRM) so that HCT could be offered to patients who otherwise would not be considered candidates. The encouraging results of initial studies with these regimens are of particular interest for patients with MDS or AML diseases that increase in frequency with age (Figure 1.1)[1], since older patients are at highest risk of severe complications from intensive conditioning.

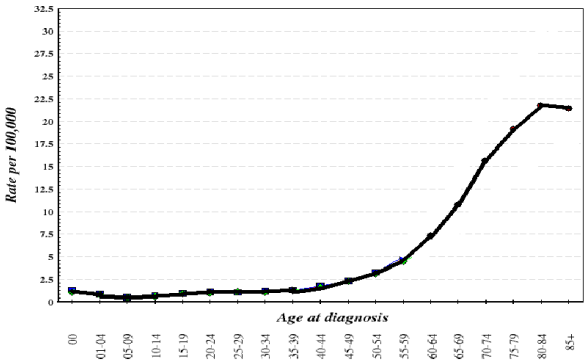


Figure 1.1: Incidence of AML by age

Here we propose a phase III multi-center trial to compare outcomes with myeloablative (MAC) and reduced intensity (RIC) conditioning regimens in patients undergoing allogeneic HCT for MDS and AML.

1.2. Diagnostic and Prognostic Criteria

In the past, MDS and AML were classified by the FAB Classification.[2] Some modifications were introduced by the World Health Organization (WHO) (Appendix A) which currently sets 20% myeloblasts by marrow morphology as the upper threshold for the diagnosis of MDS.[3] This classification has eliminated the MDS category RAEB-T, reclassifying these patients as having

AML with multilineage dysplasia transformed from MDS (tAML). The WHO classification system also incorporated clinical and biological subgroups of AML on the basis of cytogenetic results and presumed etiology (Appendix A).

The International Prognostic Scoring System (IPSS) for patients with MDS (Appendix D) was developed on the basis of a retrospective review of 816 patients with primary MDS in an attempt to offer prognostic guidance.[4] Three parameters were identified as having prognostic significance: number of cell lines showing peripheral blood cytopenias, number of bone marrow myeloblasts, and karyotype. Based on the values for these three parameters, patients were assigned to four risk groups: low, intermediate-1 (int-1), int-2 and high risk with median life expectancies of 5.7, 3.5, 1.2 and 0.4 years respectively. These prognostic categories are helpful in counseling patients regarding the suggested time and type of therapeutic interventions, including HCT.[5]

The single most valuable prognostic factor in patients with AML is the karyotype at the time of diagnosis. The results of cytogenetic testing impact the choice of post-induction chemotherapy consolidation, and patients considered at high risk for relapse are frequently offered HCT in first complete remission. The Southwest Oncology Group (SWOG) has defined a set of cytogenetic criteria that predict clinical outcomes (Appendix E).[6] The chances of obtaining a complete remission with induction chemotherapy differ by SWOG cytogenetic risk group (84%, 76%, and 55% for favorable, intermediate, and unfavorable risk, respectively). The relative risks of death from any cause for patients with intermediate and unfavorable cytogenetics, as compared to those with favorable cytogenetics, were 1.5 and 3.33, respectively. These advances in the classification schemes of both MDS and AML allow improved prediction of relapse risk, and subsequently improved selection of appropriate therapy.

1.3. Conditioning Regimen Intensity

As discussed above, a major problem with MAC is regimen-related toxicity and resulting NRM. Therefore, there are many efforts directed at reducing NRM by reducing conditioning intensity. However, conditioning intensity is also considered important in preventing post-HCT relapse leading to concern that decreasing the intensity too much may increase the risk of disease recurrence.[7] Different investigators have taken diverse approaches to modifying conditioning regimens to minimize toxicity while maintaining anti-tumor efficacy.[8] Consequently, there are currently a variety of conditioning regimens in use, ranging from low to high intensity.

1.3.1. Myeloablative Conditioning for MDS/AML

Busulfan (Bu)/Cyclophosphamide (Cy) Regimen:
Traditionally, myeloablative doses of chemotherapy were given to eradicate clonal stem cells, and donor stem cells were necessary to rescue patients from marrow failure. The FHCRC team reported results for 109 patients with MDS conditioned with oral Bu (16 mg/kg), dose adjusted to maintain plasma concentrations at steady state (Css) levels of 800-900 ng/mL (targeted Bu [tBu]), and cyclophosphamide (Cy) (120 mg/kg)—oral tBu/Cy.[9] Patients were 6-66 (median 46) years of age. The Bu Css levels reached were 635-1,140 (median, 883) ng/mL. Sixty percent of patients were in the prescribed target range. Pre-HCT marrow myeloblast percentage and IPSS

score were the most significant predictors of relapse-free survival (RFS) (Figure 1.3.1a). NRM at 100-days and 3-years was 16% and 31%, respectively. The 3-year RFS was 56% with related and 59% with unrelated donors. The cumulative incidence of acute GVHD was 64% with HLA-matched related, and 68% for HLA-matched unrelated donors. Oral tBu/Cy was an effective regimen in patients with MDS, particularly those with early stage disease, but with considerable NRM. Similar results have been reported in AML patients. In a prospective study performed by SWOG/ECOG, 233 patients who obtained complete remissions following 2 cycles of induction chemotherapy were randomized to autologous HCT (n=116) or high-dose cytarabine (n=117). Patients who had achieved complete remissions and had an HLA-matched or single antigen mismatch related donor were offered allogeneic HCT (n=116). The conditioning regimen for allogeneic HCT was oral Bu, 16 mg/kg, and Cy 50 mg/kg x 4 days (oral Bu/Cy).[10] Among the 116 first complete remission patients who received related donor allografts following myeloablative conditioning, the median relapse-free survival was 32 months with an estimated 4-year relapse-free survival of 43%. The median overall survival (OS) was approximately 35 months, and the estimated 4-year overall survival was 45% (Figure 1.3.1b**)**. The 100-day NRM among patients who did not relapse was 21%.

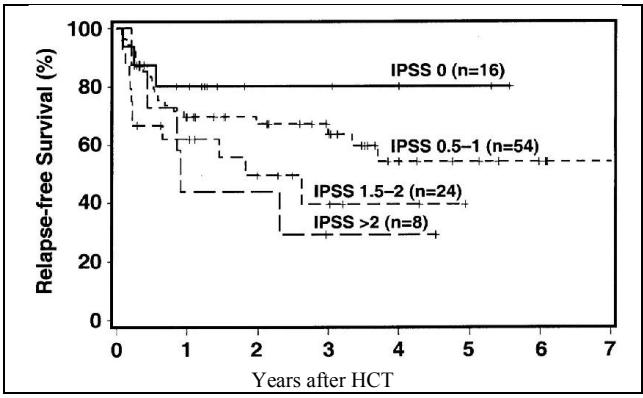


Figure 1.3.1a: RFS by IPSS grouping after oral tBu/Cy conditioning.

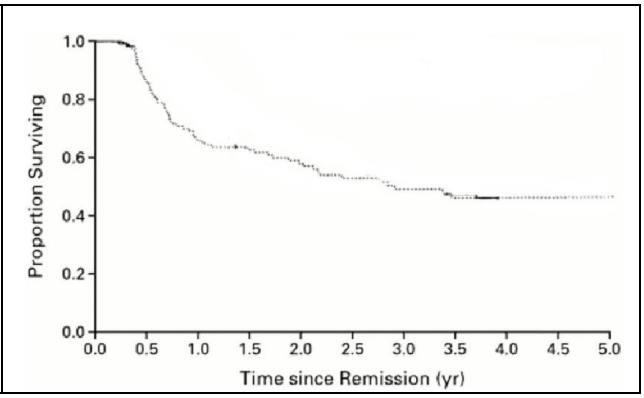


Figure 1.3.1b: Relapse-free survival following myeloablative conditioning and related donor allografting in 116 patients in first complete remission.

Fludarabine (Flu)/Bu Regimen:
In a subsequent trial, Cy was replaced with fludarabine (Flu) (120 mg/m^2) followed by oral tBu (16 mg/kg) to Css levels of 900±100 ng/mL—Flu/oral tBu. Forty-two patients (38 with high risk MDS and 4 with advanced chronic myeloid leukemia) were enrolled.[11] Engraftment was achieved in all patients. The day-100 NRM was 7%. After a median follow-up of 18 months, overall survival, NRM, and RFS were 42%, 24%, and 35%, respectively (Figure 1.3.1c). The Bu Css levels were 774-1,188 (median, 908) ng/mL. Fifteen patients had an average Bu exposure <900 ng/mL, with 7 relapses and 4 NRM. Twelve patients had an average Bu exposure of >900 ng/mL with 2 relapses and 5 NRM. The use of Flu instead of Cy appeared to permit higher average Bu exposure before equivalent toxicity developed. This might have resulted in greater anti-leukemic efficacy. Thus, myeloablative HCT was effective and potentially curative in patients with MDS, but had significant toxicity as evidenced by a NRM of 20-30%.

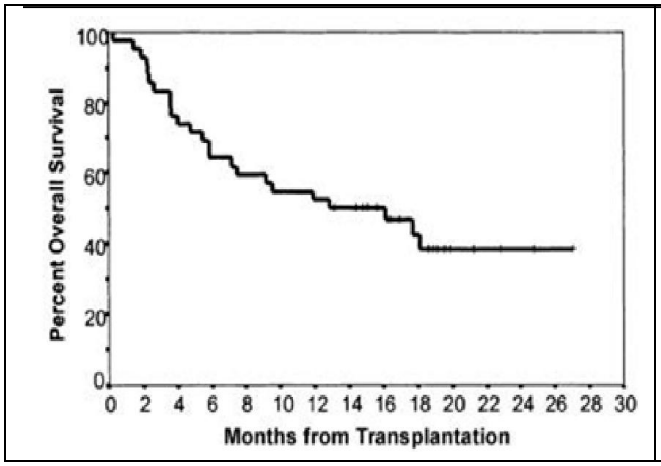


Figure 1.3.1c: OS in patients receiving Flu/Bu

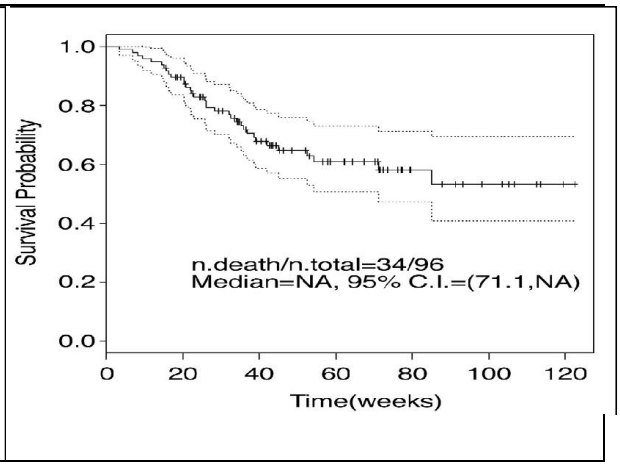


Figure 1.3.1d: OS for patients with MDS/AML after Flu/IV Bu conditioning and allogeneic HCT (Dotted lines indicate the confidence interval.)

The M.D. Anderson Cancer Center (MDACC) has also reported results using a Flu/Bu regimen. regimen consisting of IV fludarabine 40 mg/m^2/day and IV busulfan 130 mg/m^2/day on Day -6 to -3 (Flu 160 mg/m^2, Bu 520 mg/m^2).[12] There were a total of 96 patients with MDS or AML conditioned with this regimen. Patients were 19-66 (median 45) years of age. The regimen results in a 1-year overall survival of (65%), NRM of (3%), and RFS of (52%) (Figure 1.3.1d). Also, NRM was lower with the Flu/IV Bu regimen when compared to the Flu/oral tBu regimen reported above (3% *vs*.15%, respectively). The mean and median area under the curve (AUC) of IV Bu was 4,891 µmol/min and 4,871 µmol-min, respectively. This corresponds to a Bu Css of 836.6 ng/mL, which was only slightly lower than the median level of 908 ng/mL in the Flu/oral tBu regimen.[13] Consequently, it appears unlikely that the lower NRM observed with Flu/IV Bu was attributable solely to a lower Css of Bu. The route (IV *vs*. oral) of Bu administration may have also been important.

Cy/TBI Regimen:
Between 1985 and 1998, 161 patients with de novo AML were transplanted at the FHCRC with unrelated donor allografts either HLA-matched (n=102) or mismatched (n=59).[14] The majority of patients (154, 96%) were conditioned with Cy 120 mg/kg and TBI 13.2-15.75 Gy (Cy/TBI). Leukemia-free survival was 50% for patients in first complete remission, 28% for patients in second complete remission, and 7% for patients in relapse (Figure 1.3.1e). The 5-year cumulative NRM in this cohort was 43%.

A retrospective matched cohort study was performed by the EBMT comparing Bu/Cy vs. Cy/TBI MAC allograft HCT performed between 1987 and 1993.[15] Matching parameters included disease stage, age, and GVHD prevention. There were 268 patients with AML who received Bu/Cy conditioning matched to 268 patients with AML who received Cy/TBI conditioning. There were no significant differences in NRM, relapse, or RFS between the Bu/Cy cohort compared to the Cy/TBI cohort (Figure 1.3.1f). Based on these results it appears that the Cy/TBI regimen offers equivalent relapse free survival in comparison to the Bu/Cy regimen. However, this was not a randomized study and while matching was performed to remove some of the inherent bias present this does not completely remove the selection bias that may be

present when patients are offered MAC. In addition, there was no control for center effects in this large non-randomized retrospective EBMT study. Similar findings from a retrospective study at the FHCRC were reported in an MDS population.[16]

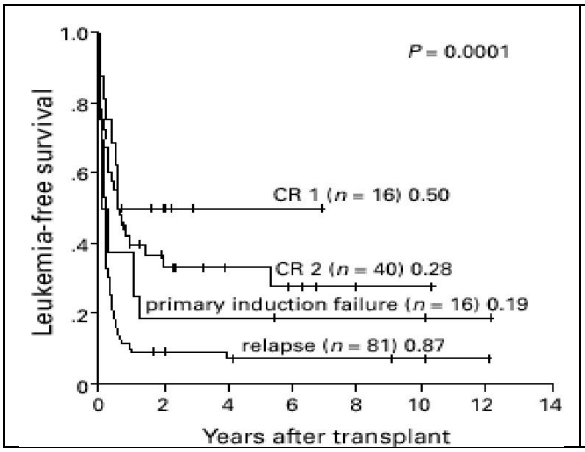


Figure 1.3.1e: Leukemia-free survival following MAC and unrelated donor allografting by disease state at time of HCT

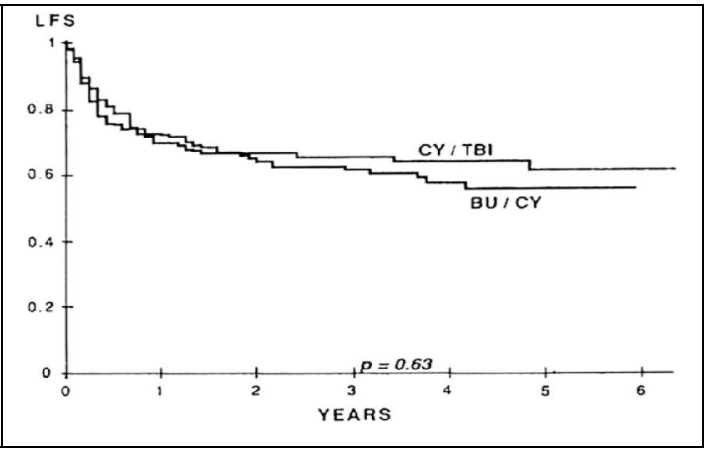


Figure 1.3.1f: LFS in AML patients in CR-1 conditioned with Bu/Cy vs. Cy/TBI

1.3.1.1.Busulfan dosing in myeloablative regimens

Several studies demonstrate that Bu dose adjustments to achieve narrowly defined plasma levels may reduce regimen-related toxicity and NRM; most of those studies were carried out with oral Bu. Since its FDA approval in 1999, IV Bu is increasingly used in combination with Cy or Flu.[17, 18, 19, 20] The use of IV Bu may lead to a lower incidence of toxicity compared to oral Bu, particularly mucositis and hepatic veno-occlusive-disease (VOD). One advantage of IV over oral Bu is more predictable bioavailability since it avoids the variable gastrointestinal absorption and first-pass metabolism rates contributing to high inter-patient variability of Bu levels with the oral drug.[21] It also eliminates the need for re-dosing after vomiting. IV Bu was initially administered every 6-hours, similar to oral Bu regimens, but recent studies have used the drug with once or twice daily administration. The IV formulation at a dose of 0.8 mg/kg IV every 6 hours is considered equivalent to the oral formulation at a dose of 1 mg/kg PO every 6 hours. On this basis a regimen using 4 x 0.8 mg/kg=3.2 mg/kg of IV Bu as a single daily dose was developed.[19, 22]

While differences in absorption and, hence, bioavailability, between patients were eliminated with IV Bu, the inter-patient variability in the clearance of IV Bu is similar to that with oral Bu. After oral Bu, PK sampling at 7 time points over 6-hours after dose 1, and 5 time points after doses 5 and 9 allows a predetermined target Css to be achieved reliably. Results in 10 patients who were conditioned with once a day dosing of IV Bu (3.2 mg/kg/day x 4 days) with concomitant Flu have been reported. Virtually no intra-patient variability in the clearance of IV Bu, (106.8 ± 16.7 mL/min/m^2) after dose 1 vs. after dose 4 (106.9 ± 21.6 mL/min/m^2) was present.[19] Thus, less frequent blood sampling might be sufficient for consistent targeting with IV Bu in that (i) more predictable PK parameters are achieved with IV than with the oral

administration, and (ii) less intra-patient variability is expected. These results have been confirmed by additional PK analyses performed by the group at MDACC.[22] The use of IV Bu is one approach to reducing toxicity associated with HCT conditioning.

1.3.2. RIC regimens for MDS and AML

Another approach to reduce NRM associated pre-transplant conditioning is to reduce the overall intensity of the conditioning regimen. The definition of *reduced intensity* conditioning is related to the dose of the agent and specific combination. The consensus criteria were utilized for the threshold definition of a reduced intensity conditioning[23]. Busulfan dose of less than 9 mg/kg, melphalan dose of less than 150 mg/m^2 and irradiation dose of less than 500 cGy unfractionated or less than 800 cGy fractionated are defined as RIC. The major concern with RIC regimens are an increased probability of relapse.

Flu/Bu Regimen:
A RIC regimen consisting of fludarabine and busulfan was first reported by Slavin et al. The authors treated 26 consecutive patients with a variety of malignant and nonmalignant conditions with fludarabine 180 mg/m^2 and oral busulfan 8 mg/kg. The overall survival, after a median follow-up of 8 months, was 85% and 81% of patients were disease-free. Since then several investigators have further explored this regimen in myeloid malignancies.[24] For example, a conditioning regimen of Flu (150 mg/m^2), oral Bu (8 mg/kg), and anti-CD52 antibody-alemtuzumab (100 mg) was used in 62 patients with MDS (all WHO categories), chronic myelomonocytic leukemia, or tAML.[25] Patients were 22-70 (median 53) years of age. The predicted 1-year overall survival (74%), NRM (15%), and RFS (62%) were encouraging and suggest that reduced-intensity regimens should be explored further. Importantly, however, a large proportion of these patients required donor lymphocyte infusion (DLI) to achieve complete chimerism and remissions post-HCT. The plasma Bu concentrations were not reported in this analysis. Investigators in France published results using a Flu (180 mg/m^2) and oral Bu (8 mg/kg) with ATG in 101 patients undergoing HCT.[26] DLI was given to 4 patients to establish full donor chimerism and to 33 patients secondary to relapse. In patients who received HCT for hematologic malignancies the RFS at 2 years was 57%.

Long-term results of a Flu/Bu RIC regimen in 59 patients with AML and 34 patients with MDS were recently reported.[27] The conditioning regimen consisted of Flu 150 mg/m^2 and Bu 8-10 mg/kg. Patients were 21-70 (median 56) years of age. Forty-nine percent of the patients were in complete remission at the time of transplant. The 4-year probability of survival was 47% in the entire cohort, 42 % for AML patients, and 49% for MDS patients (Figure 1.3.2a). Eighteen patients died secondary to NRM at a median of 4.3 months post-transplant. The 1 year cumulative incidence of NRM was 16%. In multivariate analysis only the presence of chronic GVHD improved overall survival. The authors demonstrated that the RIC Flu/Bu regimen resulted in long-term remission with relatively low NRM. Further the development of chronic GVHD was important in reducing relapse and improving overall survival[28].

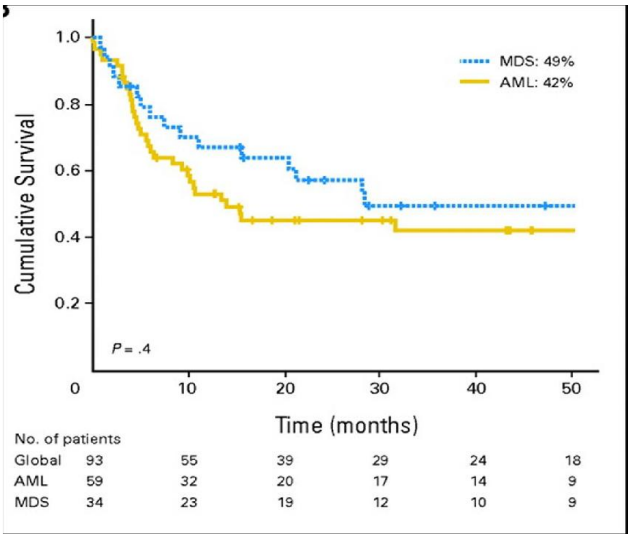


Figure 1.3.2a: Overall survival in MDS and AML patients treated with a RIC regimen of Flu/Bu

Flu/Mel Regimen:
Investigators at MDACC first reported results with a RIC regimen consisting of Flu 125 mg/m^2 and melphalan (Mel) 100-140 mg/m^2 in 78 patients with a variety of hematologic malignancies. The Day 100 NRM was 37.4%. The RFS was 57% for patients in first remission or chronic phase disease. This regimen has subsequently been investigated at other centers yielding similar results [29].

Long-term results of the Flu/Mel regimen in patients with AML or MDS have been reported. One hundred twelve patients with AML or MDS were conditioned with Flu 100-150 mg/m^2 and Mel 100-180 mg/m^2. The majority of patients were not in remission at the time of HCT and the median age was 55 (range, 22-74) years. The median follow-up was 29.4 (range, 22-74) months. There were no differences in survival or risk of progression between patients who received Mel 140 mg/m^2 vs. Mel 180 mg/m^2. The cumulative incidence of Day 100 and 2-year NRM was 0% and 20%, respectively. The estimated 2-year survival was 66% for patients in remission at time of transplant and 40% for patients with active disease but without circulating blasts (Figure 1.3.2b).[30] Results using a RIC regimen of Flu/Mel have also been reported from the City of Hope Comprehensive Cancer Center. Investigators conditioned 43 MDS patients with Flu 125 mg/m^2 and Mel 140 mg/m^2. The median age was 58 (range, 30-71) years and the majority of patients had int-2 or high risk MDS. The 2-year overall survival and NRM was 53.5% and 35.2%, respectively.[31] The results of these studies demonstrate reliable engraftment following a RIC regimen of Flu/Mel and that the NRM and overall survival are comparable to the historical results of MAC regimens.

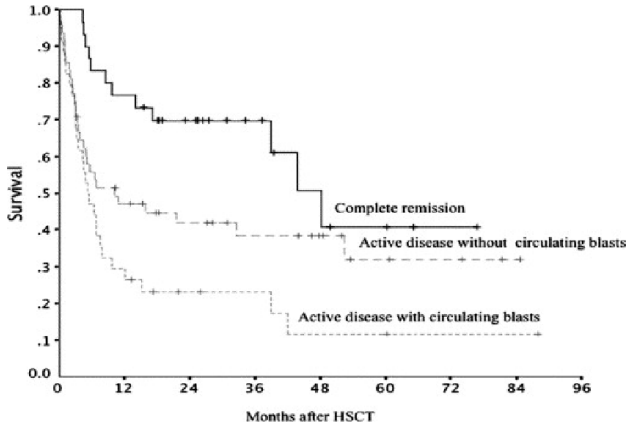


Fig. 1.3.2b: Overall survival by disease status at time of HCT using a RIC of Flu/Mel.

1.3.3. Comparative Studies

Retrospective Studies:

Despite the above studies, the benefits of reduced intensity conditioning regimens in comparison to standard myeloablative regimens remain undetermined. A retrospective analysis from the Dana-Farber Cancer Institute compared outcomes with nonmyeloablative and myeloablative conditioning regimens in patients over the age of 50 years, transplanted for various diagnoses (non-Hodgkin lymphoma, AML, acute lymphocytic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, MDS, CMML).[32] The RIC regimen was used in 71 patients and consisted of Flu 120 mg/m^2, and IV Bu 3.2 mg/kg, and the MAC regimen used in 81 patients consisted of either Cy, 1800 mg/m^2 given over 2 days with either 14 Gy fractionated TBI or oral Bu, 16 mg/kg over 4 days, and Cy 1800 mg/m^2. The analysis showed a trend towards improvement in overall survival with RIC *vs.* MAC (39% *vs.* 29%, *P*=0.056) at 2 years, but no significant differences were seen in relapse-free survivals (27% *vs.* 25%, *P*=0.24) or incidences of grades II-IV GVHD (28% *vs.* 27%). Furthermore, while NRM was significantly reduced with RIC conditioning (32% *vs.* 50%, *P*=0.01), there was an increase in relapse incidence (46% *vs.* 30%, *P*=0.052). As a result, relapse-free survival was identical for the two groups. Because of many patient and disease related variables in that study, conclusions in regards to outcomes among patients with specific diagnoses could not be drawn. The same investigators subsequently published a similar retrospective review focused on patients with AML or MDS conditioned with the same RIC and MAC as detailed above.[33] Ninety-seven patients received a MAC regimen and 39 patients received a RIC regimen. Patients who received a RIC regimen were more likely to be older and to have received a previous HCT compared to the patients who received a MAC regimen. There were no significant differences between the cohorts in regards to disease type, stage of disease, type of donor, or stem cell source. There were no differences between the cohorts in regards to the incidence of acute GVHD; however, the RIC cohort was more likely to develop extensive chronic GVHD compared to the MAC cohort. The cumulative incidence for NRM was 26% and 33% in patient transplanted with a RIC regimen and MAC regimen, respectively. There was a significantly increased cumulative incidence in relapse among patients who received a RIC regimen (61%) compared to patients who received a MAC

regimen (38%). There was no difference in overall survival or RFS between the 2 cohorts (Figure 1.3.3a). The 2-year estimated overall survival was 28% for the RIC cohort and 34% for the MAC cohort. Among patients who received a RIC regimen, donor chimerism ≥ 90% was associated with improved survival. In this retrospective review, there was no significant difference in NRM but the relapse rate was significantly higher in the RIC cohort. Despite this the overall survival was similar between the RIC and MAC regimens. This finding was remarkable given that patients who received a RIC regimen were older and more likely to have received a prior HCT.

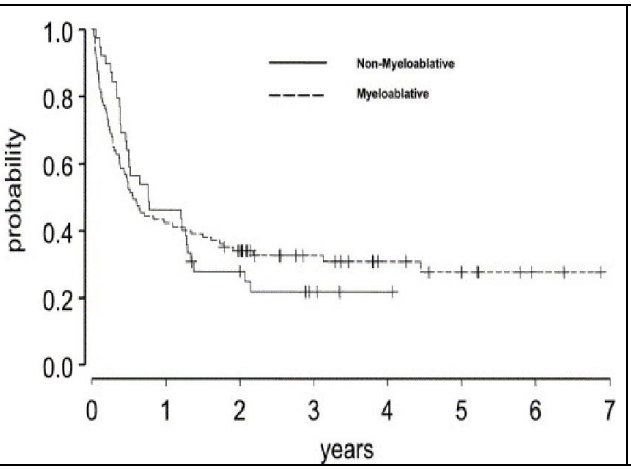


Figure 1.3.3a: Probability of overall survival in patients with AML or MDS who underwent HCT with RIC (n=39) or MAC (n=97) regimens

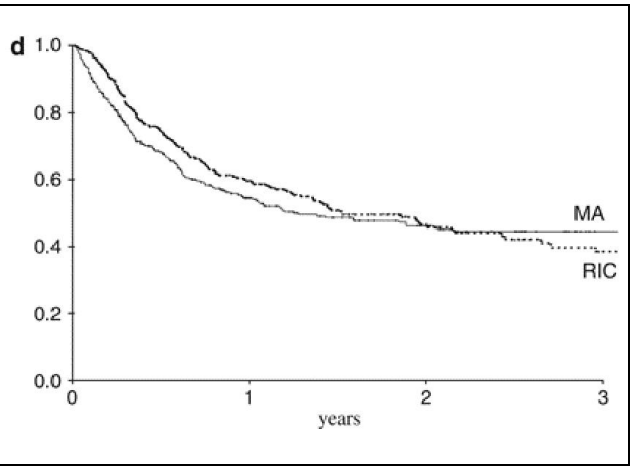


Fig. 1.3.3b: Overall survival in AML patients ≥ 50 years conditioned with MA (n=407) or RIC (n=315)

A large retrospective study by the EBMT compared outcomes in patients with AML aged ≥ 50 years at time of HCT and who where conditioned with MAC vs. RIC regimens[34]. MAC regimens consisted of TBI ≥ 10 Gy or Bu > 8 mg/kg; RIC regimens consisted of TBI < 3 Gy or Bu ≤ 8 mg/kg. A total of 407 patients received MAC regimens and 315 patients received RIC regimens. Patients who received a RIC regimen were more likely to be older, have older donors, to be male and have a later date of HCT in comparison to patients who received a MAC regimen. There were no significant differences between the two groups in regards to FAB classification, disease status at time of HCT, and cytogenetic risk. The cumulative incidence of 2-year NRM was 32% and 18% for MAC and RIC HCT, respectively. However, the cumulative incidence of relapse was higher for the RIC (41%) compared to the MAC regimen (24%). Therefore, there was no significant difference in 2-year overall survival (40% vs. 47%) or RFS (44% vs. 46%) between the RIC and MAC cohorts, respectively (Figure 1.3.3b). The EBMT performed a similar retrospective analysis in patients with MDS[35]. There were no age restrictions placed on this analysis and the definition of RIC and MAC regimens was slightly different. RIC regimens consisted of TBI 2-4 Gy, oral Bu 8-10 mg/kg, Mel 80-140 mg/m^2, Cy 60-120 mg/m^2 or thiotepa 5-10 mg/kg. MAC regimens consisted of TBI ≥ 8 Gy, oral Bu 16 mg/kg or "equivalent" IV Bu. A total of 621 patients received a MAC regimen and 215 patients received a RIC regimen. Patients who received a RIC regimen were more likely to be older, have secondary AML, have untreated disease, have received a prior auto HCT, and to have received PBSCT grafts. Clearly there was an intrinsic disadvantage in the RIC cohort compared to the MAC cohort. The 3-year relapse rate was significantly increased in the RIC cohort (HR=1.64, p=0.001), but the 3-year

NRM rate was decreased (HR=0.61, p=0.015). There was no difference in 3-year probability of RFS or overall survival (39% vs. 34% and 45% vs. 41%) between the MAC and RIC regimens, respectively (Figure 1.3.3c).

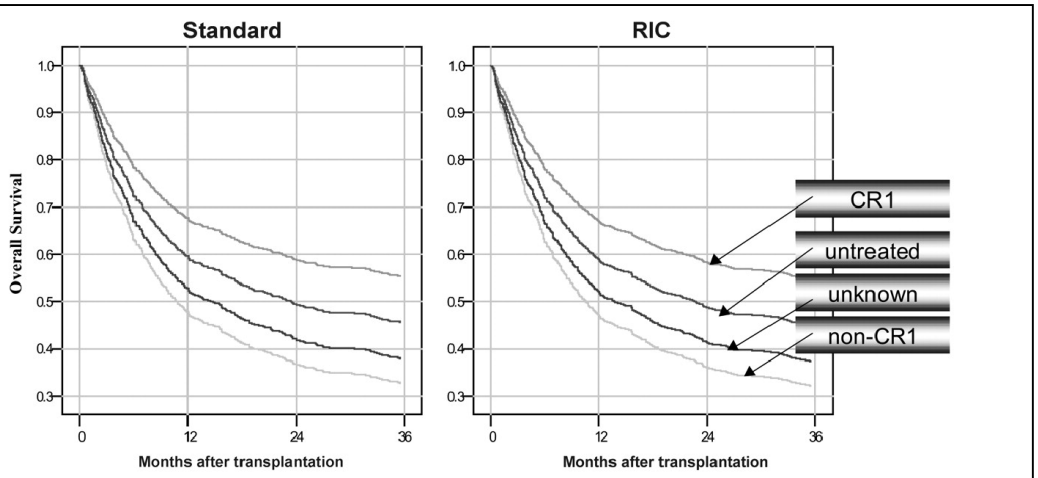


Figure 1.3.3c: Overall survival with MAC and RIC regimens by disease status at time of HCT.

Specific doses of Bu have been compared by investigators at the Chaim Sheba Medical Center.[36] In this retrospective review 112 consecutive patients with AML/ MDS were conditioned with a MAC regimen of IV Bu 12.8 mg/kg and Cy 120 mg/kg (BuCy n=45), a MAC regimen of IV Bu 12.8 mg/kg and Flu150-160 mg/m^2 (FB_4 n=26), or a RIC regimen of IV Bu 6.4 mg/kg and Flu 150-160 mg/m^2 (FB_2 n=41). The patients who received the RIC regimen were more likely to be older, to have unrelated grafts, and to be in remission at time of HCT in comparison to patients who received the MAC regimens. In agreement with the previous retrospective studies the investigators found that the MAC regimens were associated with a higher NRM but a lower relapse rate. The overall survival at 2 years was 50, 49, and 47% for BuCy, FB_4 and FB_2 regimens, respectively. However if patients had active disease at time of HCT, there was a difference in overall survival between the MAC and RIC regimens (Figure 1.33d).

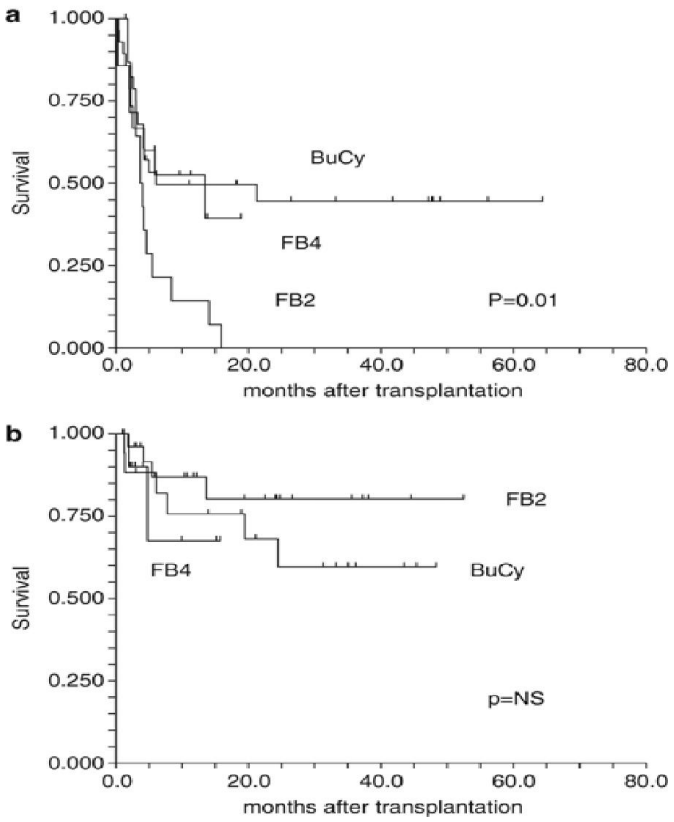


Figure 1.3.3d: Overall survival by conditioning regimen for patients with (a) active disease at time of HCT (n=58) or with (b) remission at time of HCT (n=54)

Another study from the same group at Chaim Sheba Medical Center compared outcomes between different RIC regimens.[37] The authors compared the Flu 150 mg/m^2 + Mel 100-140 mg/m^2 regimen to the Flu 150 mg/m^2 + IV Bu 6.4 mg/kg regimen. There were 72 patients conditioned with Flu/Bu and 79 patients conditioned with Flu/Mel. All patients had hematologic malignancies. The patients who received Flu/Mel were younger, more likely to have multiple myeloma rather than AML, more likely to have received a prior auto HCT, and more likely to have received a related donor graft in comparison to patients who received the Flu/Bu regimen. While the NRM was significantly higher with the Flu/Mel regimen (40% vs. 16%, p=0.003), (Figure 1.3.3e) there was no difference in overall survival between the two regimens. For patients in remission, there was a survival advantage with the FB regimen compared to the FM regimen (72% vs. 36%, p=0.03), respectively. The survival advantage with the FB regimen in patients in remission at time of HCT was chiefly related to a reduced NRM. While these observations are intriguing they could be explained by selection bias at time of HCT; therefore, these observations should be confirmed in a prospective randomized study.

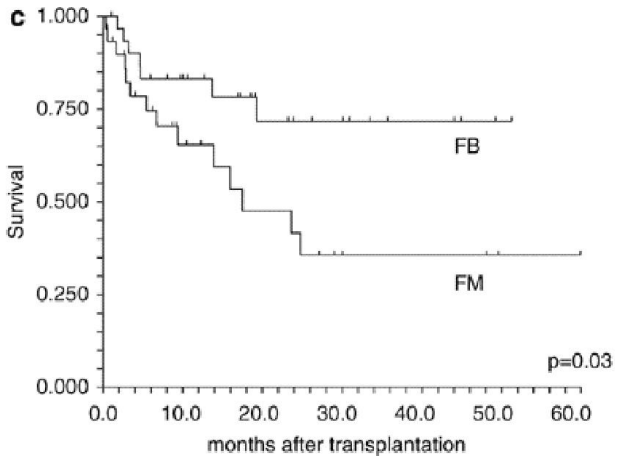


Fig 1.3.3e: OS in patients in remission at time of HCT

Prospective Studies:
A prospective study comparing RIC vs. MAC consecutively enrolled patients with AML/MDS who underwent HLA-identical sibling HCT has been completed.[38] Patients ≤ 50 years of age were schedule to receive a MAC regimen, and patients > 50 years of age were scheduled to receive a RIC regimen. Forty patients were scheduled to receive a MAC regimen of Cy/TBI and 47 patients were scheduled to receive a RIC regimen of Flu/Bu (10 mg/kg). The choice of conditioning intensity was not randomized, but as stated was based on age. Patients who received a RIC regimen were more likely to be older, have MDS as opposed to AML, have poor risk cytogenetics, and have a higher co-morbidity index in comparison to patients who received a MAC regimen. The 4-year NRM was 19 and 20% for the MAC and RIC regimens, respectively. There was no difference in relapse or overall survival between the MAC and RIC regimens. The major limitation of this analysis is that the choice of conditioning regimen was based on age and that this decision was made prior to the administration of induction chemotherapy. Thus, there were some dropouts between the decision to proceed to HCT and the start of conditioning. Despite these limitations this was one of the first prospective studies conducted, and the results confirm the findings of the retrospective studies presented above.

1.4. Quality of Life associated with RIC and Myeloablative Preparative Regimens

As there have been no randomized studies comparing RIC and MAC treatment approaches, relative effects on health related quality of life (QOL) are extrapolated from observational studies. Bevans and colleagues studied 41 RIC and 35 MAC recipients and concluded that the trajectory of QOL post-transplant was similar between RIC and MAC patients.[39] Andersson and colleagues studied 32 RIC and 25 MAC patients and reported greater deterioration in functioning, more symptoms, and slower recovery in the MAC group, although the groups return to baseline and are similar at one year.

Measurement of QOL in allogeneic HCT has used a variety of self-reported instruments including the Medical Outcomes Study Short Form 36 (SF-36), the Functional Assessment of Cancer Therapies-Bone Marrow Transplant module (FACT-BMT), the European Organization

for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQC30). The CTN Quality of Life and Late Effect Subcommittee has recommended at a minimum that the SF36 and the FACT-BMT be collected in CTN trials at the time of enrollment prior to protocol treatment and at the time of the primary endpoint assessment.

1.5. Summary

Several investigators have published results with a variety of RIC regimens. It is clear that these regimens do allow for engraftment of both related and unrelated donor stem cells. The primary benefits of these RIC regimens are a reduction in NRM and the potential to extend curative HCT to a broader patient population. Several retrospective studies have demonstrated a reduction in NRM with the use of RIC, but with an increased risk of relapse post-transplant. This is particularly relevant when the disease status at time of transplant is considered. For patients who do not have adequate disease control at time of transplant there appears to be an advantage using MAC; however, for patients in remission at time of HCT there was no difference in relapse risk between the MAC and RIC cohorts. The majority of data collected to date indicate that there is no significant difference in overall survival between RIC and MAC regimens. However, most of the patients enrolled into the RIC are considered higher risk in comparison to the patients enrolled into the MAC regimens. The patients who receive RIC regimens tend to be older, to have higher risk disease, and have higher co-morbidity scores. Therefore, it is plausible that RIC regimens may offer an advantage over MAC regimens in a select population of patients who are at lower risk of relapse post-transplant. Multiple studies have documented that disease status at time of transplant is an important predictor of the risk of post-transplant relapse.

Based on the data presented, we anticipate that patients with MDS or AML who have < 5% marrow myeloblasts at the time of HCT will have similar rates of relapse irrespective of conditioning intensity. We anticipate that there will be a significant reduction in NRM with RIC. Overall we anticipate that there will be a survival benefit with the use of RIC in comparison to MAC. Given the above background we propose a prospective comparison of a MAC regimen (using myeloablative doses of BU or TBI) to a RIC regimen (Flu/Mel, Flu/Bu) in patients with MDS or AML with < 5% marrow myeloblasts at time of HCT.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This prospective, multi-center, Phase III trial is designed to assess the impact of regimen intensity on outcome after allogeneic stem cell transplantation for MDS or AML. Each study arm will include either a myeloablative (MAC) or reduced intensity conditioning (RIC) regimen. Prior to randomization, the investigator will choose one RIC and one MAC regimen, and a stem cell source (peripheral blood or bone marrow stem cells). The investigator will also commit to a GVHD prophylaxis regimen that will be paired with the chosen conditioning regimen. The investigator is encouraged to choose from a list of recommended conditioning regimens and accompanying GVHD prophylaxis regimens; however alternative regimens will be permitted if they meet specified criteria. The investigator will also commit to using, or not using, anti-thymocyte globulin, irrespective of the treatment assignment.

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

Hematopoietic cell transplantation with RIC is superior to transplantation with MAC for patients with AML and MDS in remission at the time of transplantation. The premise is that reducing the intensity of the conditioning regimen will decrease treatment-related mortality without increasing relapse so that overall survival will be improved.

2.2.2. Primary Objective

The primary objective of the trial is to compare 18 month overall survival rates of the two groups of patients starting from the time of randomization to the RIC or MAC arms.

2.2.3. Secondary Objectives

Secondary objectives are to compare patients receiving an RIC conditioning regimen with those patients receiving an MAC conditioning regimen for:

1. Disease-free survival rates after transplantation;
2. Rates of transplant-related mortality;
3. Incidence of relapse;
4. Incidence of neutrophil and platelet engraftment;
5. Kinetics of donor cell engraftment;
6. Incidence of graft failure;
7. Incidence and severity of acute and chronic graft-versus-host disease (GVHD);

8. Immune reconstitution;
9. Rates of infectious complications;
10. Rates of ≥ grade 3 toxicities according to the CTCAE criteria; and,
11. Quality of life.

2.3. Patient Eligibility

The diagnosis of MDS or AML will be based on WHO criteria (Appendix A).

2.3.1. Inclusion Criteria

1. Age ≤ 65 years and ≥ 18 years.
2. Patients with the diagnosis of MDS or AML with fewer than 5% myeloblasts in the bone marrow and no leukemic myeloblasts in the peripheral blood on morphologic analysis performed within 30 days of enrollment.
3. For patients receiving treatment of their MDS or AML prior to transplantation:
   - Interval between the *start* of the most recent cycle of conventional cytotoxic chemotherapy and enrollment must be at least 30 days.
   - Interval between *completing* treatment with a hypomethylating agent or other non-cytotoxic chemotherapy and enrollment must be at least 10 days.

4. Patients must have a related or unrelated bone marrow or peripheral blood donor.

   a) 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).

   b) Related donor other than sibling must be a 7/8 or 8/8 match at HLA-A, -B, -C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing).

   c) 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.

5. HCT-Specific Comorbidity Index Score (HCT-CI) ≤ 4 (Appendix G).
6. Organ function:
   - Cardiac function: Ejection fraction ≥ 40%.
   - Hepatic function: total bilirubin ≤ 2x the upper limit of normal and ALT and AST ≤ 3x the upper limit of normal.
   - Pulmonary function: DLCO (corrected for hemoglobin) ≥ 40% and FEV1 ≥ 50%
7. Estimated creatinine clearance ≥ 50mL/min/based on the Cockcroft-Gault formula.
8. Signed informed consent.

2.3.2. Exclusion Criteria

1. Prior allograft or prior autograft.

2. Symptomatic coronary artery disease.
3. Leukemia involvement in the CNS within 4 weeks of enrollment for patients with a history of prior CNS leukemia involvement (i.e., leukemic blasts previously detected in the cerebral spinal fluid).
4. Karnofsky Performance Score < 70 (Appendix F).
5. Patients receiving supplemental oxygen.
6. Planned use of DLI therapy.
7. Patients with uncontrolled bacterial, viral or fungal infections (undergoing appropriate treatment and with progression of clinical symptoms).
8. Patients seropositive for the human immunodeficiency virus (HIV).
9. Patients with prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent > 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs.
10. Females who are pregnant or breastfeeding.
11. Fertile men and women unwilling to use contraceptive techniques during and for 12 months following treatment.

2.4. Donor Selection Criteria

Related and unrelated donors will be identified according to institutional guidelines. Peripheral blood progenitor cells will be requested, but the use of bone marrow will be allowed according to donor preferences and/or institutional guidelines for pediatric donors.

2.4.1. Donor Exclusion Criteria

1. Donors will be excluded if they are an identical twin of the recipient.
2. Females who are pregnant (positive serum β HCG) or uninterruptible breastfeeding will be excluded.
3. HIV seropositive donors will be excluded.
4. Donors receiving experimental therapy or investigational agents will be excluded unless approved by the protocol chairs and protocol officer.

2.5. Treatment Plan

Centers will declare one MAC and one RIC regimen to be used in each patient at time of enrollment prior to randomization. There are two options for RIC regimens and three for MAC regimens, these regimens are listed in Table 2.5.

TABLE 2.5: CONDITIONING REGIMENS

Reduced Intensity Conditioning (RIC)		Myeloablative Conditioning (MAC)	
A	**Fludarabine/Busulfan (Flu/Bu)** • Fludarabine (120-180 mg/m^2) • Busulfan (≤ 8 mg/kg PO or 6.4 mg/kg IV)	**C**	**Busulfan[1] /Fludarabine (Bu/Flu)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Fludarabine (120-180 mg/m^2)
B	**Fludarabine/Melphalan (Flu/Mel)** • Fludarabine (120-180 mg/m^2) • Melphalan (≤ 150 mg/m^2)	**D**	**Busulfan[1]/Cyclophosphamide (Bu/Cy)** • Busulfan (16 mg/kg PO or 12.8 mg/kg IV) • Cyclophosphamide (120 mg/kg)
		E	**Cyclophosphamide/Total Body Irradiation (Cy/TBI)** • 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.

2.5.1. Recommended Reduced Intensity Conditioning Regimens

2.5.1.1.RIC: Fludarabine and Busulfan (Flu/Bu)

The recommended Flu/Bu regimen is the following:

- Fludarabine: 30 mg/m^2/day on Day -6 to -2 (total dose of 150 mg/m^2)
- Busulfan: 4 mg/kg/day PO or 3.2 mg/kg/day IV (total dose of 8 mg/kg or 6.4 mg/kg, respectively) on Day -5 to -4.

The sequence of fludarabine and busulfan administration in RIC regimens will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above.

2.5.1.2.RIC: Fludarabine and Melphalan (Flu/Mel)

The recommended Flu/Mel is the following:

- Fludarabine: 30 mg/m^2/day on Day -5 to -2 (total dose of 120 mg/m^2)
- Melphalan: 140 mg/m^2 on Day -2

The sequence of fludarabine and melphalan administration in RIC regimens will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above. Dividing the dose of melphalan in two days is allowed.

2.5.2. Recommended Myeloablative Conditioning Regimens

2.5.2.1.MAC: Busulfan and Fludarabine (Bu/Flu)

The recommended Bu/Flu regimen is the following:

- Busulfan: 4 mg/kg/day PO, 3.2 mg/kg/day IV or 130 mg/m^2/day with Bu steady state concentration 900±100 ng/mL (total dose of 16 mg/kg, 12.8 mg/kg or 520 mg/m^2, respectively) on Day -5 to -2
- Fludarabine: 30 mg/m^2/day on Day -5 to -2 (total dose of 120 mg/m^2)

The sequence of busulfan and fludarabine administration in MAC regimens will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above.

2.5.2.2.MAC: Busulfan and Cyclophosphamide (Bu/Cy)

The recommended Bu/Cy regimen is the following:

- Busulfan: 4 mg/kg/day PO, 3.2 mg/kg/day IV or 130 mg/m^2/day with Bu steady state concentration 900 ± 100 ng/mL (total dose of 16 mg/kg or 12.8 mg/kg or 520 mg/m^2, respectively) on Day -7 to -4
- Cyclophosphamide: 60 mg/kg/day on Day -3 to -2 (total dose of 120 mg/kg)

2.5.2.3.MAC: Cyclophosphamide and Total Body Irradiation (Cy/TBI)

The recommended Cy/TBI regimen is the following:

- TBI: 1200-1420 cGy on Day -7 to -4
- Cyclophosphamide: 60 mg/kg/day on Day -3 to -2 (total dose of 120 mg/kg)

The sequence of cyclophosphamide, busulfan and TBI administration practices in MAC regimens will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above.

2.5.3. Conditioning Regimen Administration

Ideal Body Weight (IBW) Formulas:
Males IBW = 50 kg + 2.3 kg/inch over 5 feet
Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Adjusted Ideal Body Weight (AIBW) Formula:
where ABW = actual body weight
AIBW = IBW + [(0.25) x (ABW - IBW)]

2.5.3.1.Busulfan administration

RIC Regimens:
Busulfan can be administered orally in four divided doses or intravenously once daily or in four divided doses according to institutional preferences. Pharmacokinetic analysis with the intent of dose adjustment is not required for busulfan with total doses lower than 9 mg/kg. Blood collection for pharmacokinetic analysis will be performed as an ancillary study, regardless of the busulfan dose (Appendix C).

Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3.

MAC Regimens:
Participating centers will have the option of using oral or intravenous busulfan. Oral busulfan will be administered at 4 mg/kg/day for four days (1 mg/kg every 6 hours). Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3. If the center is administering busulfan orally, pharmacokinetics analysis and targeting the dose to 900±100 ng/mL must be performed. Pharmacokinetics on oral Bu will be performed according to institutional guidelines.

Intravenous busulfan is administered at a dose of 3.2 mg/kg/day or 130 mg/m^2/day for four days either in four divided doses (0.8 mg/kg) or once daily (3.2 mg/kg or 130 mg/m^2). Target dosing through pharmacokinetic assays for busulfan intravenous administration is not required under the protocol. Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3.

2.5.3.2.Cyclophosphamide administration

Cyclophosphamide (Cy) will be administered on Day -3 and Day -2 at a dose of 60 mg/kg per day IV. Doses ≥ 5,000 mg must be infused IV over 2 hours. Lower doses may be administered over one hour. Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3.

2.5.3.3.Fludarabine administration

Fludarabine will be administered intravenously at a minimum total dose of 120 mg/m^2 divided into three or more daily doses according to institutional practices. Since patients with creatinine clearance < 50 mL/min are not eligible for this trial, dose adjustment for renal function will not

be performed. Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3.

2.5.3.4.Melphalan administration

Melphalan will be infused once daily intravenously to a total dose not greater than 150 mg/m^2. Dose of melphalan might be reduced to 100 mg/m^2 at the discretion of the treating physician, in the setting of renal insufficiency or other co-morbidities. Patients < 100% of ideal body weight will be dosed according to actual body weight. Patients > 100% of ideal body weight will be dosed according to their adjusted ideal body weight. If adjusted body weight is greater than the actual weight, then actual weight should be used. Formulas are available in §2.5.3.

2.5.3.5.Total body irradiation administration (TBI)

Fractionated TBI will be administered according to institutional practice. Radiation sources, dose rates, details of lung shielding, and sites receiving boost radiation will also be defined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources.

2.5.4. Additional Drugs

2.5.4.1.Allopurinol

The use of allopurinol will be allowed according to institutional guidelines. A common regimen employs allopurinol at the daily dose of 300 mg, beginning at least six hours before the start of conditioning and until the day before marrow or PBSC infusion.

2.5.4.2.Antithymocyte globulin (ATG)

The use of ATG (Thymoglobulin or ATGAM) is not part of the conditioning regimens studied in this clinical trial but is permitted. The dose and schedule of ATG will be administered according to institutional standards. Plans for the use of ATG must be disclosed prior to randomization, and must be used irrespective of the outcome of the randomization. The Physician Desk Reference's manufacturer's guidelines should be followed for administration of ATG.

2.5.5. GVHD Prophylaxis Regimen

Transplant centers are encouraged to utilize the recommended GVHD prophylaxis regimens listed in Table 2.5.5. Alternative GVHD prophylaxis regimens are permitted as per standard institutional practice with the following stipulations:

a) The regimen includes a calcineurin inhibitor that is continued for a minimum of 6 months (therapeutic blood levels for a minimum of 4 months)
b) Ex-vivo T-cell depletion is not performed
c) The GVHD prophylaxis regimen does not include post-transplantation cyclophosphamide

d) Investigational GVHD prophylaxis regimens may be allowed if co-enrollment with BMT CTN 0901 is approved by the protocol chairs.

Recommendations for the administration of the GVHD agents are listed in Sections 2.5.5.1, 2.5.5.2, and Table 2.5.5.

Table 2.5.5 RECOMMENDED GVHD PROPHYLAXIS REGIMENS

Tacrolimus ▪ Blood trough levels 5-15ng/mL ▪ Continue for minimum 6 months (taper may begin 4 months post transplantation **Methotrexate** ▪ 10-15 mg/m^2 Day 1 ▪ 5-10 mg/m^2 Day 3, 6 and 11
Tacrolimus ▪ Blood trough levels 5-15ng/mL ▪ Continue for minimum 6 months (taper may begin 4 months post transplantation **Methotrexate** ▪ 10 mg/m^2 Day 1 ▪ 5-10 mg/m^2 Day 3, 6 and 11
Other regimens may include: ▪ Cyclosporine/Methotrexate ▪ Tacrolimus/Sirolimus[1] ▪ Cyclosporine/Mycophenolate Mofetil ▪ Any other combination of agents that meet the criteria outlined in section 2.5.5.

[1]*Sirolimus given with myeloablative doses of busulfan is associated with increased risk of hepatic veno-occlusive disease.*

2.5.5.1.Tacrolimus

Tacrolimus for GVHD prophylaxis is administered beginning at least one day before transplantation for a minimum of six months. The initial dose should be based on the ideal body weight of the recipient to achieve an intravenous daily dose of 0.03 mg/kg/day. Subsequent doses are targeted to achieve whole blood levels between 5 and 15 ng/mL. When a patient is switched from intravenous to oral tacrolimus, the dose is increased by 3-4 fold to adjust for the lower bioavailability of oral compared to intravenous tacrolimus. Determinations of blood levels should be performed at least once weekly for the initial three months. Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Dose reductions for high levels without toxicity should be conservative, e.g. 25%, to avoid inadequate immunosuppression.

If there is nausea and vomiting, the drug should be given intravenously. Patients with severe intolerance of tacrolimus may be placed on cyclosporine.

Drugs that may affect tacrolimus levels are:

1. Caspofungin, phenobarbital, phenytoin, rifampin, carbamazepine, rifabutin, St. John's Wort (**lowers levels**);
2. Glucocorticoids, fluconazole, voriconazole, ketoconazole, itraconazole, grapefruit juice, amprenavir, bromocriptine, chloramphenicol, cimetidine, cisapride, clarithromycin, clotrimazole, danazol, diltiazem, erythromycin, ethinyl estradiol, metoclopramide, metronidazole, mibefradil, nefazodone, nelfinavir, nifedipine, omeprazole, quinupristin/dalfopristin, ritonavir, saquinavir, theophylline, troleandomycin, verapamil (**increases levels**).

For patients who are taking both tacrolimus and sirolimus it is recommended that serum trough levels of tacrolimus do not exceed 10 ng/mL.

Per the tacrolimus package insert, when initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary.

2.5.5.2.Methotrexate

The regimen of methotrexate for GVHD prophylaxis will employ intravenous doses of 10 or 15 mg per m^2 on Day 1 post-transplant, and 10 or 5 mg/m^2 on Day 3, 6, and 11 post-transplant according to institutional standards. Third space syndromes with large accumulation of ascites or pleural effusions are a contraindication to the use of methotrexate. Dose reductions should be made for renal, hepatic and mucosal toxicity. Determinations of blood levels are indicated 24-72 hours after administration in patients with impaired renal function. Leucovorin rescue should be considered in patients with decreased clearance, severe toxicity or fluid accumulation/effusions.

Drugs that may increase methotrexate levels are:

1. Non-steroidal anti inflammatory drugs
2. Penicillins
3. Diuretics

2.5.6. Hematopoietic Graft Collection

Bone marrow and mobilized peripheral blood progenitor cells are the graft sources in this study. The graft source collection depends on donor preference and institutional practices. Umbilical cord blood units are not a permitted graft source, per protocol.

2.5.6.1.Peripheral Blood Progenitor Cells (PBPC) Mobilization and Collection

PBPC mobilization and collection will be done according to institutional guidelines. It is recommended the following mobilization and collection:

- Donors will receive G-CSF (filgrastim) at a dose of 10 mcg/kg/day subcutaneously for 5 consecutive days. Daily dose will not exceed 1200 mcg/day, and volume per injection site will not exceed 2.0 mL. G-CSF should be administered at approximately the same time each day. The fifth dose will be given at least one hour prior to apheresis.
- Apheresis will begin on Day 5 of G-CSF administration. The recommended method for apheresis is through a continuous-flow apheresis device and ideally bilateral peripheral venous access. Donors with insufficient peripheral access will undergo placement of a central venous catheter.

Target CD34 cell dose is 5×10^6 per kg recipient body weight.

2.5.6.2.Bone marrow collection

It is recommended bone marrow donors undergo harvest on Day 0. The protocol officer and protocol chairs should be consulted regarding the use of cryopreserved bone marrow. Either general or regional (epidural, spinal) anesthesia may be used. The bone marrow cell dose recommended is approximately 4×10^8 nucleated cells per kg of recipient body weight. This dose will be unattainable for many recipients because of donor and/or recipient factors, e.g., body size mismatches. The volume of marrow shall not exceed 20 mL per kg donor weight. The estimated cell dose and a planned donor marrow volume shall be agreed upon by the donor and transplant centers for unrelated donors and between the transplant physician and cell processing laboratory for related donors before initiation of the transplant conditioning regimen.

Bone marrow processing, other than anticoagulation, filtration, packaging, and labeling in preparation for transportation, should not be performed by the collection center. Processing of bone marrow for reduction of volume, plasma, red blood cells, or fat, should be performed by the transplant center according to institutional guidelines.

The transportation of bone marrow from unrelated donors shall be done in accordance with institutional guidelines.

2.5.7. PBPC and Marrow Infusion

PBPC or BM grafts will be infused through an appropriate central catheter, according to institutional guidelines at Day 0. For recipients of related donor PBPC, whose donors require a third day of collection (Day +1), these cells will be infused separately from the Day –1 and Day 0 collections on Day +1.

2.6. Supportive Care

All supportive care will be given in keeping with BMT CTN MOP and local institutional practice.

2.6.1. Growth Factors

It is recommended that patients not receive post-transplant growth factors before Day 21, except in the case of serious infection where hastening neutrophil recovery by 1-3 days may be critical for survival. After Day 21, G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF) should be given for severe neutropenia (ANC < 500/μL), or as necessary to keep ANC > 1000/μL.

2.6.2. Blood Products

Transfusion thresholds for blood product support will be consistent with BMT CTN MOP and standard institutional guidelines. All cellular blood products will be irradiated. Patients who are CMV negative will receive CMV negative or filtered blood products from study entry.

2.6.3. Prophylaxis Against Infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peritransplant period according to the BMT CTN MOP and institutional practices.

Routine CMV antigenemia/viral load testing by hybrid capture or PCR based methods per institutional guidelines (with preemptive ganciclovir or valganciclovir therapy in patients who develop a positive assay, as per institutional guidelines). CMV testing is recommended weekly through at least Day +100 post transplant.

2.6.4. Intravenous Immune Globulin (IVIG)

IVIG administration will be left to local institutional standard practice.

2.6.5. Failure to Engraft

If the ANC has not reached 500/μL by Day 21, G-CSF, GM-CSF or other cytokines may be utilized. If the ANC is < 100/μL on Day 28 post-transplant, the patient should be considered for a second infusion of stem cells from the original donor or retransplantation from a different donor using appropriate institutional guidelines.

2.6.6. ABO Incompatibility

All patients with ABO incompatibility should be evaluated and treated per standard practice at the individual centers. Recommended approach is detailed in the BMT CTN MOP.

2.6.7. Anti-seizure Prophylaxis

Phenytoin or levetiracetam (Keppra) should be used with busulfan in accordance with standard practice at individual centers.

2.6.8. Antiemetics

Anti-emetics should be administered in accordance with institutional guidelines.

2.6.9. Post-transplant Donor Leukocyte Infusions (DLI)

DLI may be given to patients for a recurrent or a second malignancy according to institutional practice, if the donor is available and provides consent. The protocol officer and protocol chairs should be consulted regarding the use of DLI for recurrent disease, loss of chimerism and secondary malignancy. The use of planned DLI therapy is NOT permitted per protocol.

2.7. Risks and Toxicities

2.7.1. Busulfan

Since its FDA approval in 1999, IV busulfan has been used increasingly in combination with cyclophosphamide or fludarabine.[17, 18, 19, 20] IV busulfan was initially administered every 6-hours, similar to oral busulfan. However, several studies have used the drug with once or twice daily administration. In terms of safety, IV busulfan and oral busulfan appear to have similar toxicity profiles. It has been proposed that sinusoidal obstruction syndrome and mucositis may be reduced in incidence and severity with IV busulfan.[21] The IV formulation at a dose of 0.8 mg/kg IV every 6-hrs is considered equivalent to the oral formulation at a dose of 1 mg/kg PO every 6 hrs in conditioning regimens. On this basis a regimen using 4x0.8 = 3.2 mg/kg as a single daily dose has been developed.[19, 22]

Pharmacokinetic parameters have been determined for different schedules of IV Bu, including a standard four times daily for a total of 16 doses, as with oral busulfan, and two dosing schedules of once or twice daily for four days. The inter-patient variability in the clearance of IV busulfan is similar to that of oral busulfan. After oral busulfan (given every 6 hours), pharmacokinetic sampling at 7 time points over 6-hours after dose 1, and 5 blood samples after doses 5 and 9 allows a target Css to be achieved reliably. In a limited number of patients (N=10), a low intra-patient variability was present in the clearance of IV busulfan dosed every 24 hours with fludarabine (106.8 ± 16.7 mL/min/m^2 after dose 1 vs. 106.9 ± 21.6 mL/min/m^2 after dose 4).[1519] Thus, less frequent blood sampling may be possible with IV busulfan in that: (i) more predictable pharmacokinetics after IV administration should permit for fewer samples per Css determination, and (ii) less intra-patient variability may lead to fewer Css determinations per patient. In this protocol, we will obtain pharmacokinetic samples after a single busulfan dose in patients at participating centers and compare overall exposure to treatment outcomes, such as toxicity, treatment-related mortality, and disease relapse (see Appendix C).

Toxicities associated with busulfan administration include:

a.) Gastrointestinal: nausea, vomiting, constipation, diarrhea, abdominal discomfort, anorexia, dyspepsia and mucositis.

b.) Hepatobiliary: busulfan is associated with the development of hepatic veno-occlusive disease. Pharmacokinetic dose targeting and intravenous formulation decrease the risk of this complication. Co-administration of sirolimus as GVHD prophylaxis has been shown to accentuate the risk for this complication.

c.) Neurologic: Busulfan decreases the seizure and concomitant use of prophylactic use of anti-seizure medication successfully reduces the risk of this complication. Other neurologic side effects related to Bu include headache and insomnia.

d.) Cardiovascular: Bu is associated with hypertension, hypotension and tachycardia.

e.) Other toxicities:

- Rhinorrhea
- Hypermagnesemia, hyperglycemia and hyperphosphatemia
- Amenorrhea
- Infertility
- Skin rashes
- Cataracts
- Dyspnea
- Lung fibrosis

2.7.2. Cyclophosphamide

Cyclophosphamide is frequently used as a cytotoxic agent. Cyclophosphamide is converted to its active form in vivo by hepatic enzymes. After a single dose, tissue enzymes degrade most of the active metabolites. After high doses (> 40 mg/kg), the alkylating activity in the plasma is minimal by 24 hours. Several of the metabolites appear to have toxic actions. One of the metabolic products, acrolein (CH_2=CH-CHO), is known to be toxic to the bladder urothelium and can cause hemorrhagic cystitis when Cy is administered at high doses.

- Fluid Retention: Cyclophosphamide can cause an antidiuretic effect with development of inappropriate ADH secretion.
- Cardiomyopathy: within 0-10 days after high-dose cyclophosphamide a clinical syndrome of severe CHF has been observed (usually in patients given doses of 200 mg/kg), Characterized by cardiomegaly, pericardial effusions, diffuse voltage decrease on ECG and decreased LVEF. Mortality is >50%. There are nine retrospective studies of post-HCT cardiomyopathy published in 1976-2001. In the four studies with >100 patients, incidence was 0.4 – 4%.
- Hemorrhagic Cystitis: Cyclophosphamide can cause hemorrhagic cystitis. To prevent the development of hemorrhagic cystitis, patients are kept well hydrated, and mesna therapy

or bladder irrigation is used per institutional guidelines. ***The recommended prophylaxis is mesna therapy*** unless contraindicated clinically, e.g., bladder outlet obstruction as in prostatic hypertrophy.

- Nausea/Vomiting/Anorexia.
- Other Toxicities:
  - Myelosuppression
  - Gonadal function impairment
  - Alopecia
  - Rare pulmonary toxicity

2.7.3. Fludarabine

Fludarabine can lower the white blood cell count, in particular the CD4+ T-cells. The immunosuppression observed with the use of fludarabine increases the risk of infection, which can be life threatening. Hematopoietic suppression and immunosuppression are expected to occur as a direct effect of the antimetabolite. The most serious toxicity of fludarabine is neurological, and may consist of both peripheral neuropathy and encephalopathy. Toxicity can be manifested by fatigue, weakness, paresthesias, visual disturbances, somnolence and coma, that usually develop between 30 and 60 days from therapy. The incidence of serious neurological toxicity has been 36% in patients treated with $\geq$ 96 mg/m^2 per day for 5-7 days,[40] a dose > 3 times higher than used in this protocol. Other adverse effects include fever, nausea, vomiting, diarrhea, stomatitis, skin rash, cough and idiopathic pneumonitis.

2.7.4. Melphalan

High-dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC/marrow transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC infusion and colony stimulating factors. Gastrointestinal toxicity, which includes severe stomatitis, esophagitis and diarrhea, can be severe or life-threatening. Most patients receiving high-dose melphalan will require parental narcotics for mucositis-related pain, IV hydration; may require IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

See the FDA-approved package insert for a comprehensive list of adverse events.

2.7.5. Total Body Irradiation

TBI given in myeloablative doses can be given with or without lung shielding according to institutional guidelines. The toxicities associated with irradiation include marrow suppression, gastrointestinal mucosal toxicity, fever, nausea, vomiting, diarrhea, parotiditis, reversible skin pigmentation, alopecia among others. Dosimetry calculations are performed by the radiation

physicist. Late effects may include cataract formation, growth retardation, pulmonary damage, carcinogenesis, and sterilization.

2.8. Quality of Life Assessments

2.8.1. Instruments

FACT-BMT: The Functional Assessment of Cancer Therapy – Bone Marrow Transplant subscale[41] version 4.0 instrument is a 37 item scale comprised of a general core questionnaire, the FACT-G, that evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Trial Outcome Index, comprised of the physical well being scale, the functional well being scale and the BMT specific items, will be used as the outcome measure in summarizing the FACT-BMT data. The FACT-BMT takes 6 minutes to complete, and is being collected in BMT CTN 0201 and 0801.

MOS SF-36: The Medical Outcomes Study Short Form 36 is a 36 item general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data. These summary scores are derived by multiplying the z-score for each scale by its respective physical or mental factor score coefficient and summing the products. Resulting scores are then transformed into T-scores (mean=50; standard deviation=10). The SF-36 takes 6 minutes to complete, and is being collected in BMT CTN 0801.[42, 43]

MDASI: The MD Anderson Symptom Inventory is a 19 item instrument that captures 13 symptoms (0="not present" to 10="as bad as you can imagine") and 6 items measuring interference with life from 0 ("did not interfere") to 10 ("interfered completely"). It provides two summary scales: symptoms and interference.[44] The MDASI takes less than 5 minutes to complete, and is current being collected in BMT CTN 0802 trial of acute GVHD treatment.

Global QOL: Four standard questions will assess patient self-assessed Karnofsky performance status, overall health and overall quality of life, (excellent, very good, good, fair, poor) and a rating scale for overall quality of life (where 0 equals death and 100 equals perfect quality of life). In addition, the presence and severity of chronic GVHD will be assessed (mild, moderate, severe). These questions take 1 minute to complete and are being collected in BMT CTN 0201 and 0801.

Occupational functioning: Occupational functioning will be measured using 6 items that assess current job status, type of work (will be captured using Hollingshead categories), number of hours of paid and unpaid work, school, importance of work and change in work goals. The same scale has been used in NHLBI-sponsored HCT studies and BMT CTN protocol 0201 (randomized peripheral blood vs. marrow for unrelated transplantation).

EQ-5D: The EQ-5D will collect data that may be used to calculate patient-reported utilities for cost-utility analyses. The EQ-5D contains a five item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D takes approximately 1 minute to complete (Agency for Healthcare Research and Quality, 2005).

2.8.2 Administration

The self report questionnaires will be completed prior to transplantation and subsequently at 100 days, 12 months, and 18 months from randomization or until death. Only English speaking patients are eligible to participate in the HQL component of this trial. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. The method of survey completion, the date, and the language will be recorded in the database. Surveys may not be completed by surrogates.

Table 2.8. – Required Patient-Reported Outcomes Data Collection

Instrument	N items	Pre	100 days	12 and 18 mos
Socio-demographics	8	X		
Global quality of life	4	X	X	X
FACT-BMT	37	X	X	X
MOS SF-36	36	X	X	X
MDASI	19	X	X	X
Occupational functioning	6	X	X	X
Chronic GVHD	2			X
EQ-5D	5	X	X	X
Alternative contacts	2	X		X
TOTAL N ITEMS		117	107	111
ANTICIPATED TIME		30 min	25 min	30 min

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITION

3.1. High Risk Disease

Patients enrolled in this trial will be identified as high or standard risk disease. High-risk AML is defined according to cytogenetic and certain molecular abnormalities identified prior to transplantation. Poor-risk cytogenetics according to the ECOG/SWOG cytogenetic classification will be considered high-risk AML (Appendix E). Additionally, patients with FLT-3 internal tandem duplication mutation, regardless of cytogenetic abnormalities and patients in CR $\geq$ 3 will be considered high risk for disease. High-risk MDS is defined as patients with intermediate-II or high International Prognostic Scoring System (IPSS) (Appendix D).

3.2. Disease Status and Disease Response Assessment

Assessment after transplantation response will be assessment as follows:

Complete Remission:

- Bone Marrow Myeloblasts < 5% by morphologic assessment;
- No circulating leukemic myeloblasts;
- Neutrophil count $\geq$ 1,000/μL;
- Absence of previous cytogenetic or molecular abnormality identified prior to transplantation in the bone marrow aspirate.

Disease Relapse for Patients with AML:

- Increase in bone marrow blast to $\geq$ 5% by morphologic assessment not attributed to other causes (e.g., bone marrow regeneration); or if < 5%, reappearance of blasts with the same leukemia phenotype as present at diagnosis.
- Reappearance of blasts with aberrant phenotype by Flow Cytometry.
- Reappearance of leukemic blasts in the peripheral blood.
- Reappearance of previous cytogenetic or molecular marker of disease present prior to transplantation.
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.
- Institution of any therapy to treat relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse regardless of whether the criteria described above are met.

Disease Relapse for patients with MDS:

- Satisfying above criteria for evolution into acute leukemia; or,
- Reappearance of pre-transplant morphologic abnormalities, detected in two consecutive bone marrow specimens taken at least one month apart; or,
- Reappearance of pre-transplant cytogenetic abnormality in at least one metaphase on each of two separate consecutive examinations at least one month apart, regardless of the number of metaphases analyzed.
- Institution of any therapy to treat relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse regardless of whether the criteria described above are met.

3.3. Primary Endpoint

3.3.1. Overall Survival

The primary endpoint is to compare the 18 month overall survival probabilities between treatment arms. Patients are considered a failure of the primary endpoint if they die from any cause. The time to this event is the time from randomization to death, loss to follow up or end of study whichever comes first.

3.4. Secondary Endpoints

3.4.1. Overall Survival (OS)

OS probabilities will be compared between treatment arms, adjusting for disease risk (defined in Section 3.1), donor type, and significantly imbalanced covariates. Patients are considered a failure of this endpoint if they die from any cause. The time to this event is the time from randomization to death, loss to follow up or end of study whichever comes first.

3.4.2. Disease-Free Survival (DFS)

DFS at different time points will be included as a secondary endpoint. Patients are considered a failure of this endpoint if they die or suffer from disease relapse. The time to this event is the time from randomization to relapse, death, initiation of non-protocol AML or MDS therapy, loss to follow up or end of study whichever comes first.

3.4.3. Treatment-related Mortality (TRM)

TRM is defined as death occurring in a patient from causes other than disease relapse. Individuals who relapse are censored for the event of TRM.

3.4.4. Neutrophil and Platelet Engraftment

The kinetics of post-transplant recovery of both neutrophil and platelet engraftment post transplantation and compared between treatment arms. Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) > 500 μL for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil engraftment.

ANC = Total WBC x (%Neutrophils + %Bands)

Platelet engraftment is defined as a platelet count > 20,000/μL for three consecutive measurements over three or more days without requiring platelet transfusions. The first of the three days will be designated the day of platelet engraftment. Subjects must not have had platelet transfusions during the preceding 7 days. The time to a platelet count > 50,000/μL will be collected as well. This endpoint will be evaluated through 100 days.

3.4.5. Donor Cell Engraftment

The kinetics and extent of donor cell engraftment will be assessed by donor/recipient chimerism studies. Bone marrow is the preferred source for chimerism analysis, which will be performed, at minimum, on Day 28, 100 and 18 months post transplantation (Table4.3).

Additionally donor cell engraftment will be assessed by donor recipient chimerism studies. For the purposes of this protocol, ***mixed chimerism*** will be defined as the presence of donor cells, as a proportion of the total population of < 95% in the peripheral blood or bone marrow. ***Full donor chimerism*** is defined as > 95% donor cells. Mixed or full donor chimerism will be evidence of ***donor engraftment***. For the purposes of this protocol, ***graft rejection*** is defined as the inability to detect or loss of detection of greater than 5% donor cells as a proportion of the total population.

3.4.6. Acute GVHD of Grades II-IV and III-IV

Acute GVHD is graded according to the BMT CTN MOP. The first day of acute GVHD onset at a certain grade will be used to calculate cumulative incidence curves for that GVHD grade (e.g., if the onset of grade I acute GVHD is on Day 19 post-transplant and onset of grade III is on Day 70 post-transplant, time to grade III is Day 70). This endpoint will be evaluated through 100 days and compared between treatment arms.

3.4.7. Chronic GVHD (cGVHD)

Chronic GVHD is scored according to the BMT CTN MOP. The first day of cGVHD onset will be used to calculate cumulative incidence curves. Rates and severity of cGVHD will be compared between treatment arms.

3.4.8. Incidence of Primary Graft Failure

This is defined by lack of neutrophil engraftment by 28 days. Rates of primary graft failure will be compared between treatment arms.

3.4.9. Incidence of Secondary Graft Failure

This is defined by initial neutrophil engraftment followed by subsequent decline in neutrophil counts < 500/μL unresponsive to growth factor therapy. Rates of secondary graft failure will be compared between treatment arms.

3.4.10. Incidence of Toxicities Grade ≥ 3

All Grade ≥ 3 toxicities will be tabulated by grade for each treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as well as cumulative over time.

3.4.11. Incidence of Infections

The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after transplant. The cumulative incidence of severe, life-threatening, or fatal infections will be compared between the two treatment arms at 6, 12, and 18 months from transplant or until death.

3.4.12. Immune Reconstitution

Quantitative assessments of peripheral blood CD3, CD4, CD8, CD19 and CD56 positive lymphocytes will be done through flow cytometric analysis at baseline, 100 days, 12 months and 18 months post transplantation. Results will be tabulated according to time from transplant.

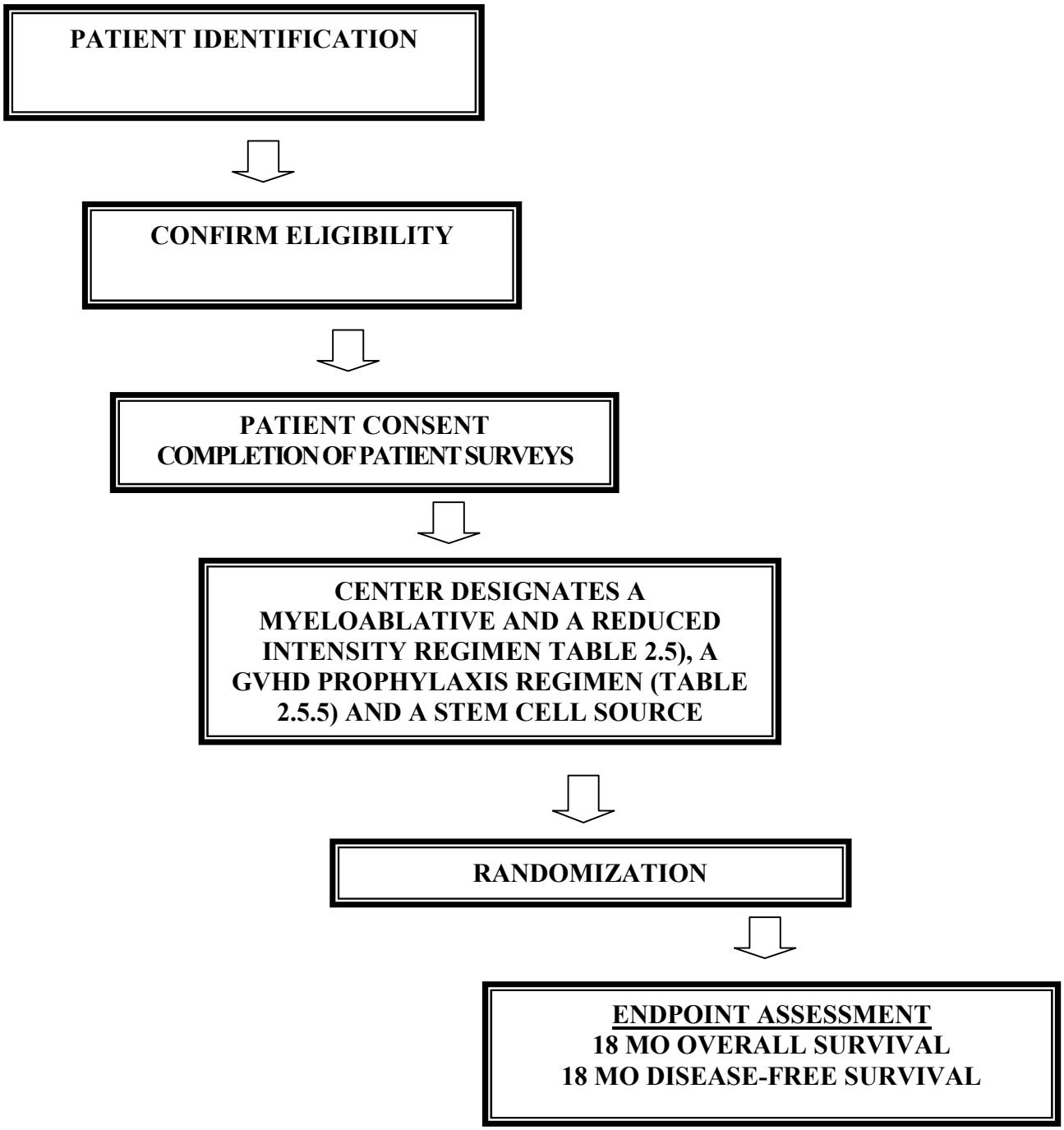
3.4.13. Quality of Life

The instruments will be scored according to the recommendations of the developers. See Section 2.8.1 for detailed descriptions of the instruments. The FACT-BMT instrument will be summarized by the Trial Outcome Index, comprised of the physical, functional and BMT-specific items. The MOS SF-36 will be summarized by the Physical Component Summary (PCS) and Mental Component Summary (MCS). The MDASI will be summarized by the interference and symptoms scores. The EQ-5D utility score will be calculated.

HQL will be described and compared between the two treatment arms over time. The self report questionnaires will be completed prior to transplantation and subsequently at 100 days, 12, and 18 months from randomization or until death. Only English speaking patients are eligible to participate in the HQL component of this trial.

CHAPTER 4

4. TREATMENT SCHEMA



4.1. Patient Enrollment and Evaluation

4.2. Enrollment Procedures

4.2.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). The following procedures should be followed:

1. Within the 14 days prior to initiation of the conditioning regimen, an authorized user at the transplant center enters the patient demographics and completes the Segment 0 Enrollment Form in AdvantageEDC. The Segment 0 form includes a question confirming that the patient (or legally authorized representative) signed the informed consent. The patient will be assigned a study number at this time. Additionally, Segment 0 requires completion of the Regimen Intensity HLA-typing form (patient and donor) to confirm that the HLA-typing meets protocol criteria. Upon successful completion of the two Segment 0 forms, the authorized user will proceed to Segment A and complete the Segment A enrollment form in which the chosen RIC and MAC regimens, the GVHD prophylaxis regimen and graft source will be indicated. In addition, the transplant center must commit to using or not using anti-thymocyte globulin irrespective of the treatment assignment.
2. If the patient is eligible, a treatment assignment is displayed upon completion of the Segment A Enrollment Form. The user should make a copy of this form to keep in the patient record.
3. A visit schedule based on treatment start date is displayed for printing and is referred to as 'Segment A Follow-up.'

4.3. Study Monitoring

4.3.1. Follow-up Schedule

The follow-up schedule for scheduled study visits is outlined in Table 4.3.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide.

TABLE 4.3.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day Post-Transplant
1 week	7 ± 2 days
2 week	14 ± 2 days
3 week	21 ± 2 days
4 week	28 ± 2 days
5 week	35 ± 2 days
6 week	42 ± 2 days

Study Visit	Target Day Post-Transplant
7 week	49 ± 2 days
8 week	56 ± 2 days
9 week	63 ± 2 days
10 week	70 ± 2 days
11 week	77 ± 2 days
12 week	84 ± 2 days
100 day	100± 14 days
6 month	180 ± 28 days
12 month	365 ± 28 days
18 month	540 ± 28 days

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Recipient death information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #0901 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post- transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

Weekly GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day 100 post-transplant for GVHD. Patients will also be assessed at each follow-up visit (6, 12 and 18 months) for the presence of GVHD.

4.3.2. Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of

knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals as defined on the Form Submission Schedule.

4.3.3. Patient Assessments

Table 4.3 summarizes patient clinical assessments over the course of the study.

4.3.3.1. Pre-transplant evaluations

The following observations are considered standard evaluations for transplant eligibility and should be performed ≤ 4 weeks of enrollment.

1. History, physical examination, height and weight.
2. HCT-specific comorbidity index (Appendix G).
3. Karnofsky performance score (Appendix F).
4. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST.
5. CMV antibody test, hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab, HepC Ab), herpes simplex, syphilis, HIV and HTLV1 I/II antibody, and varicella zoster virus.
6. Cerebral spinal fluid assessment (for patients with prior leukemia CNS involvement).
7. For sibling donors, HLA typing at HLA–A and –B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing). For related donors other than a sibling, HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing).. For unrelated donors, HLA typing at HLA-A, -B, -C, and –DRB1 at high resolution using DNA-based typing if not already performed.
8. Left ventricular ejection fraction or shortening fraction (preferably ≤ 4 weeks from enrollment and must not be more than 8 weeks prior to enrollment).
9. DLCO and FEV1 (preferably ≤ 4 weeks from enrollment and must not be more than 8 weeks prior to enrollment).
10. Bone marrow biopsy and/or aspirate for pathology, flow cytometry (if available) and cytogenetics and analysis of peripheral blood. These assessments must also occur ≤ 30 days from initiation of conditioning for patients with AML or high grade MDS (≥ 5% myeloblasts at any time) and ≤ 50 days from initiation of conditioning for patients with low grade MDS (bone marrow myeloblasts never ≥ 5%); otherwise, must be repeated.
11. β-HCG serum pregnancy test for females of childbearing potential.
12. Chest x-ray.
13. Blood for pre-transplant chimerism assay.

14. Blood samples for evaluation of immune reconstitution by flow cytometry (CD3, CD4, CD8, CD19, and CD56+).
15. Optional blood sample for future research to be shipped to the Repository.
16. Health Quality of Life Instruments to be completed by English speaking patients.

4.3.3.2.Post-transplant evaluations

The following evaluations are considered standard evaluations for transplant recipients:

1. History and physical exam to assess GVHD and other morbidity weekly until Day 100 post-transplant, then at six months, one year and 18 months post-transplant. GVHD evaluation and grading to be in keeping with BMT CTN MOP.
2. CBC at least three times a week from Day 0 until ANC > 500 μL for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until 12 weeks, then six months, one year and 18 months post-transplant.
3. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, and then at six months, one year and 18 months post-transplant.
4. Blood quantitative assessment of CD3, CD4, CD8, CD19 and CD56 positive cells at Day 100, 12 months and 18 months.
5. Blood or bone marrow aspirate sample for post-transplant T-cell and myeloid chimerism assay collected at Day 28, 100, and 18 months. Whole bone marrow chimerism is an acceptable alternative if lineage-specific chimerism analysis is not available. Peripheral blood chimerism can be substituted for bone marrow chimerism if bone marrow sample is not available.
6. Bone marrow biopsy and/or aspirate at Day 100 ± 30 days, and 18 months ± 30 days. All follow-up studies should include relevant cytogenetic or molecular testing to assess for residual disease.
7. Toxicity assessments at Day 28, 56, 100, 6 months and 12 months.
8. Busulfan pharmacokinetics at 6-7 time points after the first dose of Bu for patients receiving busulfan only at centers participating in this ancillary study (see Appendix C).
9. Health Quality of Life Instruments to be completed by English speaking patients at 100 days, 12 months, and 18 months post-transplant.

TABLE 4.3.: SUMMARY OF PATIENT CLINICAL ASSESSMENTS

			DAYS POST-TRANSPLANT															
Study Assessments/Testing*	**Baseline**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 42**	**Day 49**	**Day 56**	**Day 63**	**Day 70**	**Day 77**	**Day 84**	**Day 91**	**Day 100**	**6 mo**	**12 mo**	**18 mo**
History, physical exam, height, weight[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCT-specific comorbidity index	X																	X
Karnofsky performance score	X																	
CBC[2], differential, platelet count, and blood chemistries[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CSF[4]	X																	
LVEF or shortening fraction	X																	
DLCO and FEV1	X																	
Bone marrow biopsy and/or aspirate for pathology, flow cytometry and relevant cytogenetics and molecular studies [5,6]	X														X			X
Chest X-ray	X																	
ß-HCG serum pregnancy test (females only)	X																	
Immune reconstitution assays[7]	X														X		X	X
GVHD and other morbidity assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessments					X				X						X	X	X	
Blood or Bone Marrow for Myeloid and T-cell Chimerism[8]					X										X			X
Health Quality of Life[9]	X														X		X	X
Optional blood sample for research[10]	X																	
Blood sample for busulfan pharmacokinetics[11]	X																	

All evaluations are standard of care for treatment or transplantation of patients with AML and MDS. Quality of life assessments are not considered standard of care.

Table 4.3 Notes:

[1] Height is only required at baseline.

[2] CBC performed at least three times a week from Day 0 until ANC >500 μL for three days after nadir. CBC performed twice weekly until Day 28. CBC performed weekly after Day 28 until 12 weeks post-transplant.

[3] A standard chemistry panel to include: CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST twice a week until Day 28 (or four weeks) and then weekly until 12 weeks post transplant, and then at six months, one year and 18 months post-transplant.

[4] CSF assessment for patients with prior leukemia CNS involvement only.

[5] Flow cytometry is optional if not available at the treatment center.

[6] Baseline bone marrow biopsy and/or aspirate to be performed ≤ 30 days of initiation of conditioning for patients with AML or high grade MDS (as defined in Section 4.3.3.1) and ≤ 50 days of initiation of conditioning for patients with low grade MDS (as defined in Section 4.3.3.1); otherwise, it must be repeated.

[7] Quantitative assessment of peripheral blood CD3, CD4, CD8, CD19 and CD56 to be performed by local institutional or reference laboratory.

[8] Chimerism will be measured by RFLP or microsatellite on bone marrow aspirate sample. Lineage-specific chimerism is highly preferred, but whole blood chimerism can be substituted if not available at treatment center. Peripheral blood chimerism can be substituted for bone marrow chimerism if bone marrow sample not available.

[9] Only English speaking patients will complete the Health QOL assessments.

[10] Single blood sample to be shipped to the repository.

[11] Only in patients who receive Bu at centers participating in this ancillary study.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The study is designed as a Phase III, randomized, multicenter prospective comparative study of myeloablative (MAC) versus reduced intensity (RIC) conditioning regimens in allogeneic hematopoietic stem cell transplantation (HCT) for AML or MDS. The premise is that reducing the intensity of the conditioning regimen will decrease treatment-related mortality without increasing relapse so that overall survival will be improved. The target enrollment is 356 patients, 178 for each arm.

5.1.1. Accrual

It is estimated that four years of accrual will be necessary to enroll the targeted sample size.

5.1.2. Randomization

Patients will be randomized at a ratio of 1:1 between the treatment arms using permuted blocks of random sizes. Randomization will be stratified by center.

5.1.3. Primary Endpoint

The primary endpoint of this study is overall survival (OS) at 18 months post-randomization. The 18-month time point was chosen based on a retrospective analysis of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) where more than 80% of events had occurred by this time. The primary analysis will be performed using the intention-to-treat principle so that all randomized patients will be included in the analysis. Death from any cause will be considered events for this endpoint.

5.2. Sample Size and Power Calculations

The primary analysis will be done using a group sequential comparison of the 18 month survival probabilities using the difference in Kaplan-Meier estimates (see Gu et al. [45]); sequential monitoring is described further in section 5.3. Since with no censoring prior to 18 months, the 18 month survival probabilities reduce to simple binomial proportions, we approximated the sample size calculations based on a group sequential analysis using a two-sample Z test of binomial proportions. The final patient enrolled will be followed up for a minimum of 18 months. We anticipate minimal (<3%) censoring for survival prior to 18 months, because the primary endpoint involves survival rather than a disease assessment and because transplant centers are required to report survival data on all allogeneic transplant recipients to the CIBMTR as part of the Stem Cell Therapeutic Outcomes Database (SCTOD). A pointwise comparison of survival at 18 months is proposed for the primary analysis rather than a log-rank test because of

the potential for crossing hazards; the logrank test would have poor power to detect a difference between these two groups if the hazards cross.

The sample size is 356, 178 per treatment arm. Assuming 3% loss to follow-up 18 months post randomization, complete survival information would be available for 346 patients. Even with 3% loss to follow-up, the targeted sample size of 356 is sufficient to maintain Type I error of 5% across all planned interim analyses while providing 80% power for a two-sided test to detect an increase in OS at 18 months from 45% in the MAC arm to 60% in the RIC arm. This sample size provides sufficient power to detect a 15% increase in OS at 18 months between treatment arms for various true survival probabilities in the MAC arm as shown in Table 5.2.1, even with 3% loss to follow-up.

TABLE 5.2.1 POWER TO DETECT 15% INCREASE IN OS PROBABILITY IN THE RIC ARM FOR VARIOUS SURVIVAL PROBABILITIES IN THE MAC ARM, AS A FUNCTION OF THE PROPORTION OF PATIENTS LOST TO FOLLOW-UP BY 18 MONTHS

	Power	
True 18-month OS probability in the MAC arm	0% loss to fu	3% loss to fu
.25	86	85
.35	81	80
.45	81	80
.55	83	82
.65	89	88

5.3. Interim Analysis and Stopping Guidelines

We recommend no interim analyses for futility because the investigators are also interested in using the lower bound of the confidence interval for the survival difference at 18 months to learn about the magnitude of the survival difference. Stopping early for futility would result in substantially wider confidence intervals, leading to greater uncertainty about the magnitude of the survival difference when it is not likely to be as large as targeted.

Interim analysis for efficacy will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately one year intervals. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review and are not formal "stopping rules" that would mandate automatic closure of study enrollment. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis.

5.3.1. Interim Analysis for Efficacy

Analyses will be performed as described below for the primary endpoint. At the time of each interim analysis, a two-sided test to detect either an increase or decrease in the proportion of patients surviving will be performed. The test statistics will be based on the Kaplan-Meier proportions, which have independent increments as described in Gu et al[45]. All patients randomized prior to the time of the interim analyses will be used to compute the Kaplan-Meier estimate of overall survival at 18 months. If the test statistic exceeds the critical value, the DSMB will discuss the continuation of the trial.

In order the preserve the overall Type I error rate at 5%, the critical value for the test statistic will be inflated above 1.96, the value that would be used if no repeated testing were used. Equivalently, the nominal p-value at which an observed difference is declared significant will be reduced below 0.05. The actual critical values and nominal p-values will be computed using statistical methods for group sequential testing with O'Brien Fleming boundaries. Information is defined as the reciprocal of the variance of the difference in Kaplan-Meier estimates between the two treatments. The final information at the end of the study reduces to the reciprocal of the variance of the difference in two binomial proportions, assuming no censoring prior to 18 months, computed as 365.13. Then the information fraction is the ratio of the information at an interim analysis to the final information at the end of the study.

As an example, Table 5.3.1 shows the critical values and nominal p-values for tests conducted after four equally spaced information increments, starting when 25% of the information is accrued. Table 5.3.1 shows the critical values and cumulative Type I error at each analysis along with the power to reject the null hypothesis by each look. The power at each look is the probability of stopping to reject the null hypothesis at that look if the true increase in OS at 18 months is 15% in the RIC arm compared to the MAC arm. In particular, there is 55% power to detect a 15% improvement in 18-month survival by the third look and there is 80% power to detect the same improvement by the final look.

TABLE 5.3.1 CRITICAL VALUES AND OPERATING CHARACTERISTICS

Information Fraction	Critical Value	Nominal Type I Error	Cumulative Type I Error	Cumulative Probability of Stopping under H_a
0.25	4.049	0.0000	0.0000	0.0043
0.50	2.863	0.0042	0.0042	0.1956
0.75	2.337	0.0167	0.0209	0.5521
1.00	2.024	0.0291	0.0500	0.8000

To permit necessary flexibility in scheduling interim analyses, the critical values will be recomputed to correspond to the actual available statistical information using the "use-function" approach of Lan and DeMets.

5.3.2. Guidelines for Safety Monitoring

There will be no pre-specified stopping guidelines for safety monitoring for two reasons. First, the toxicity and mortality profiles are expected to be somewhat different, with lower early transplant-related mortality (TRM) in the RIC arm accompanied by possibly higher late relapse risk. We feel that long-term follow-up using the primary endpoint of 18 month overall survival is the best way to assess and compare these treatments. If the trial were stopped early due to excessive early treatment-related mortality, this would limit our ability to assess the crucial tradeoff between relapse and TRM for these conditioning regimens. Second, myeloablative and reduced intensity conditioning regimens are common procedures in HCT, and the specific regimens included in each of these groups are the ones used most frequently in practice. The toxicities associated with each type of conditioning regimen are well established and not likely to be different in this study. However, even though we are not including pre-specified stopping guidelines, toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis.

5.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, Karnofsky/Lansky performance status, HCT-comorbidity index, disease, disease status at transplant, time from diagnosis to transplantation, cytogenetic at diagnosis, AML risk stratification (Section 3.1), IPSS (Appendix D), HLA matching, conditioning regimen, use of ATG, GVHD prophylaxis, graft source, donor type, donor age, donor/recipient gender match, donor recipient CMV status. Between groups comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test. Demographic and baseline characteristics which are statistically different between treatment arms will be adjusted for in secondary analysis for all outcome comparisons.

5.5. Analysis Plan

5.5.1. Analysis of the Primary Endpoint

The primary outcome of the trial is overall survival at 18 months after randomization. The primary null hypothesis of the study is that there is no difference in overall survival between the treatment arms at 18 months post transplantation. In the primary analysis, the intention-to-treat principle will be used. The primary analysis will be performed using the difference in Kaplan-Meier estimates for overall survival at 18 months. A 95% confidence interval for the difference in OS at 18 months will also be constructed. In addition to a point-wise comparison at 18 months, Kaplan-Meier curves will also be constructed and confidence bands for the difference between treatments will be generated to compare the survival probabilities.

5.5.2. Analysis of Secondary Endpoints

5.5.2.1.Overall Survival (OS) at 18 months (adjusted comparison)

In this analysis, the 18-month OS probabilities will be compared using the adjusted OS probabilities proposed by Zhang et al.[46] The adjusted survival probabilities are estimated using the Cox proportional hazards model stratified by treatment. Disease risk, donor type and all demographic and baseline characteristic shown to be significantly different between treatment arms will be included in the Cox model to adjust for potential imbalances.

5.5.2.2.Disease-free survival

The event is relapse or death. The time to this event is the time from randomization to relapse, death, initiation of non-protocol AML or MDS therapy, loss to follow up or end of study whichever comes first. Disease-free survival curves will be estimated using Kaplan-Meier estimator. Kaplan Meier estimates of DFS at 18 months will be compared between treatment arms. In addition to a pointwise comparison at 18 months, confidence bands for the difference between treatments will be generated to compare the entire DFS curves. A secondary analysis of DFS will be performed by comparing the adjusted DFS probabilities at 18 months using the same method described in 5.5.2.1.

5.5.2.3.Treatment-related mortality (TRM)

The event is death occurring from causes other than relapse. Incidence of TRM will be estimated using cumulative incidence function, treating relapse as a competing risk. Incidence of TRM will be compared between the treatment arms using Gray's test[48]. In a secondary analysis, TRM will be compared between arms using a Cox proportional hazards model with treatment as the main effect. Disease risk, donor type and baseline characteristics which are significantly different between arms will be included as covariates in the Cox model to adjust for potential imbalances. The proportional hazards assumption will be checked for all covariates. If there are indications of differential effects over time, the final model will be stratified by factors with non-proportionality.

5.5.2.4.Relapse

Incidence of relapse will be estimated using cumulative incidence function, treating death in remission as a competing risk. Incidence of relapse will be compared between the treatment arms using Gray's test[48]. In a secondary analysis, relapse rates will be compared using a Cox proportional hazards model with treatment as the main effect. Disease risk, donor type and significantly imbalanced characteristics will be adjusted for as described in 5.5.2.4.

5.5.2.5.Neutrophil and Platelet Engraftment

Incidence of neutrophil and platelet engraftment will be estimated using the cumulative incidence function with death prior to engraftment as the competing risk. Incidence of neutrophil engraftment at 28 days and incidence of platelet engraftment at 60 days will be

compared between the treatment arms using a pointwise comparison of the cumulative incidence probabilities.

5.5.2.6.Donor cell engraftment

Donor chimerism at 100 days and 18 months will be described in each treatment arm, according to proportions with full (>95%), mixed (5-95% donor cells), graft rejection (<5%), or death prior to assessment of donor chimerism. These proportions will be compared between the two groups at each time point using the chi-square test.

5.5.2.7.Acute GVHD of Grades II-IV and III-IV

Cumulative incidence of acute GVHD will be estimated using the cumulative incidence function, treating death prior to aGVHD as the competing risk. Cumulative incidence of aGVHD will be compared between treatment arms using Gray's test.[4]

5.5.2.8.Chronic GVHD (cGVHD)

Cumulative incidence of cGVHD will be estimated using the cumulative incidence function, treating death prior to aGVHD as the competing risk. Cumulative incidence of cGVHD will be compared between treatment arms using Gray's test.[48]

5.5.2.9.Incidence of Primary Graft Failure

The proportions of patients alive at Day 28 but with primary graft failure will be described and compared between the treatment arms using the chi-square test or Fisher's exact test as appropriate.

5.5.2.10. Incidence of Secondary Graft Failure

The cumulative incidence of secondary graft failure out of those who had initial engraftment will be described using the cumulative incidence estimator, treating death prior to secondary graft failure as a competing event.

5.5.2.11. Incidence of Toxicities Grade ≥ 3

All Grade ≥ 3 toxicities will be tabulated by grade for each treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as well as cumulative over time.

The cumulative incidence of Grade ≥ 3 toxicity will be compared between treatment arms at 1, 3, 6, 12, and 18 months.

5.5.2.12. Incidence of Infections

The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after transplant. The cumulative incidence of severe, life-threatening, or fatal infections, treating death as a competing event, will be compared between the two treatment arms at 6, 12, and 18 months.

5.5.2.13. Immune Reconstitution

Quantitative assessment of peripheral blood CD3, CD4, CD8, CD19 and CD56 by flow cytometric analysis will be tabulated by time period after transplant. The concentration of lymphocyte subsets will be compared between treatment arms at 100 days, 12 and 18 months from transplant using a nonparametric Mann-Whitney test. To account for potential imbalances caused by differences in survival probabilities, the concentration of lymphocyte subsets for patients who died prior to the assessment period will be assigned as zero.

5.5.2.14. Quality of Life

QOL will be described and compared between all treatment arms utilizing the FACT-BMT Trial Outcome Index, the MOS-SF36 Physical Component Score (PCS) and Mental Component Score (MCS), the MDASI interference and symptom subscales, the EQ-5D utility score, and the categorical components of the occupational functioning, global quality of life, and chronic GVHD self reported scales. The questionnaires will be scored according to standard procedures. The self report questionnaires will be completed prior to transplantation and subsequently at 100 days, 12 months, and 18 months from randomization or until death. Only English speaking patients are eligible to participate in the HQL component of this trial.

Differences in quality of life will be assessed in several ways. For the descriptive analysis, only QOL scores for survivors at specific time points will be compared between treatment arms using simple T-tests. In the primary analysis, linear mixed models will be used to assess differences in QOL scores over time and to explore covariates associated with QOL in survivors. Additional secondary analysis to account for differences in survival rates between treatment groups will be performed using the Integrated Quality Adjusted Survival[49]. The Integrated Quality Adjusted Survival approach aggregates QOL over the entire period of observation. Finally, if missing data occur for survivors, mechanism and patterns of missing data will be analyzed. In addition, the joint mixed-effects model for informatively censored longitudinal data developed by Schluchter[50] will be explored to identify clinical events associated with changes in QOL overtime.

APPENDIX A

WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATIONS

APPENDIX A

WORLD HEALTH ORGANIZATION CLASSIFICATIONS

WHO CLASSIFICATION OF ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia with recurrent genetic abnormalities

- Acute myeloid leukemia with t(8;21)(q22;q22), (AML1/ETO)
- Acute myeloid leukemia with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), (CBF /MYH11)
- Acute promyelocytic leukemia with t(15;17)(q22;q12), (PML/RAR) and variants
- Acute myeloid leukemia with 11q23 (MLL) abnormalities

Acute myeloid leukemia with multilineage dysplasia

- Following MDS or MDS/MPD
- Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50% of cells in 2 or more myeloid lineages

Acute myeloid leukemia and myelodysplastic syndromes, therapy related

- Alkylating agent/radiation-related type
- Topoisomerase II inhibitor-related type (some may be lymphoid)
- Others

Acute myeloid leukemia, not otherwise categorized

- Acute myeloid leukemia, minimally differentiated
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/acute monocytic leukemia
- Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma

WHO CLASSIFICATION AND CRITERIA FOR THE MYELODYSPLASTIC SYNDROMES

Disease	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia *only* < 5% blasts < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia *only* ≥ 15% ringed sideroblasts < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 X 10^9/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines < 5% blasts in marrow No Auer rods < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 X 10^9/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines ≥ 15% ringed sideroblasts < 5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias < 5% blasts No Auer rods < 1 X 10^9/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ± < 1 X 10^9/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes < 5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia < 5% blasts Platelets normal or increased	Normal or increased megakaryocytes with hypolobated nuclei < 5% blasts No Auer rods Isolated del(5q)

APPENDIX B

PATIENT INFORMED CONSENTS

Informed Consent to Participate in Research

Your Name: _____

Study: BMT CTN 0901: 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-Investigator: Bart Scott, MD
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, D1-100
Seattle, WA 98109-1023
Phone: (206) 667-1990

Co-Investigator: Mitchell Horwitz, MD
Duke University
2400 Pratt Street, DUMC 3961
Durham, NC 27710
Phone: (919) 668-1045

Transplant Center Investigator: _____

Sponsor: The National Institutes of Health (NIH) gave financial support for this research study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Introduction

We are inviting you to join a research study. The main goals of the study are to:

- Compare two kinds of treatments used to destroy diseased cells and prepare your body for transplant. This process is also called a conditioning regimen.
- Measure how well your disease (acute myeloid leukemia or myelodysplastic syndrome) responds to the treatment.

Combinations of chemotherapy and sometimes radiation are used as a treatment to destroy cancer cells and help donor cells start to grow in your bone marrow. Depending on the combination used, each treatment (or conditioning regimen) can have a different intensity or strength.

- High intensity treatment uses high doses of chemotherapy or radiation.
- Reduced intensity treatment uses lower doses of chemotherapy or radiation.

Both kinds of treatments are used by stem cell transplant doctors around the world and are not experimental. Our goal is to see if one kind of treatment is better than the other for people who have a stem cell transplant to treat either their acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS).

If you volunteer to join this study, we will randomly assign you to receive either a high intensity or a reduced intensity treatment before you receive the stem cells from your donor.

We believe this study will last about 18 months for most patients who decide to join. About 356 patients will take part in the study at transplant centers around the United States. We will explain the two different treatments in this consent form. Every participating clinic will report their results, so we can compare and share the results at the end of the study.

This consent form tells you about the study, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take your time to make your decision.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [*insert name of facility or institution*].

- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to take part, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

Background

This research study is sponsored by The National Institutes of Health (NIH) through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Conditioning Regimen

The conditioning regimen is a combination of chemotherapy and/or radiation given to patients before the donor cells are infused. This treatment allows donor cells to engraft and start growing in your bone marrow. The treatment also helps to kill cancer cells that might not be detectable.

Different chemotherapy drugs can be used as part of the conditioning regimen. Some common combinations of chemotherapy drugs used for transplant are:

- Busulfan + cyclophosphamide or fludarabine
- Fludarabine + melphalan
- Radiation + cyclophosphamide

Each combination of chemotherapy drugs or radiation has a different strength. This strength can also be described as the treatment "intensity."

Stem cell transplant destroys cancer in two ways.

- The treatment (or conditioning regimen) destroys cancer cells.
- The immune cells from the donor can recognize cancer cells and kill them.

High intensity treatments are also known as myeloablative conditioning (MAC) regimens. These treatments work well to destroy cancer cells because they use very high amounts of chemotherapy or radiation. High intensity treatments can also have more side effects during and after transplant.

Using a lower or "reduced" intensity treatment before transplant can have fewer serious problems from the chemotherapy drugs. While the cancer killing effects may also be lower,

studies show that immune cells given during the transplant can help destroy remaining cancer cells. Transplants with reduced intensity conditioning (RIC) regimens are often used for people who cannot have high doses of chemotherapy drugs or radiation because of their age or other medical problems.

This study will compare high intensity and reduced intensity treatments used to destroy cancer cells and prepare bone marrow for transplant. Our goal is to see if one kind of treatment is better than the other for people who have a stem cell transplant to treat either their AML or MDS.

Purpose

You are invited to join this research study because you have AML or MDS and are currently being evaluated for an allogeneic transplant. The main goal of this study is to see if patients with AML or MDS have better results with transplants using reduced intensity treatment compared to high intensity treatment.

Right to ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact [*insert contact info*].

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time.

If you choose to not take part or to leave this study, your regular medical care will not be affected in any way. The conditioning regimen of your transplant will be the standard of care. If you decide to leave this study after taking the study treatment, or are asked to leave by your doctor for medical reasons, you will be asked to come back to the doctor's office for tests for your safety and as part of your routine medical care.

- Even if you withdraw from the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

- Your study doctor and study staff will be available to answer any questions that you may have about your participation in, or your withdrawal from this study.

Procedures

Before you join the study, we will evaluate your general health, medical history, and your current medications.

Study Participation

You will need to go to clinic at least once before the study begins. Your participation in the study starts after your sign this consent form. After your transplant you will have weekly evaluations for the first 3 months of this study. After 3 months, you will have an evaluation at 6, 12 and 18 months after your transplant.

These evaluations will be done if you are in the hospital ward or clinic, or if your disease becomes active again after the transplant.

Before You Start Your Treatment

You will have at least one clinic visit before you begin the study. This visit will collect information about your:

- Physical health (including history, height, weight and temperature);
- Heart, lung and kidney function;
- Chest x-ray;
- Bone marrow biopsy and aspirate;
- Routine blood tests, including cell counts, liver and kidney function;
- Routine markers of infectious diseases, including hepatitis, herpes, HIV, syphilis, varicella zoster (shingles) among others;
- Pregnancy test (if it applies to you);
- HLA typing for you and your donor; and,
- Health quality of life for English speaking patients (see below).

Randomization

We selected five different treatment options based on the ones that are most often used by transplant centers. The treatment options are listed in Table 1.

Your doctor will choose one reduced intensity treatment (A or B in the table below) and one high intensity treatment (C, D or E in the table below) to use for this study. These are often the most commonly used at [*insert Institution name*]. A computer program will then assign you by chance to either the reduced intensity or the high intensity treatment option.

You will have an equal chance of being placed in either group. This means that half of the people in the study will be in the reduced intensity group and half will be in the high intensity group.

TABLE 1: TREATMENT OPTIONS (CONDITIONING REGIMENS)

Reduced Intensity Treatments	
A	Fludarabine + Busulfan (Flu/Bu)
B	Fludarabine + Melphalan (Flu/Mel)

High Intensity Treatments	
C	Busulfan + Fludarabine (Bu/Flu)
D	Busulfan + Cyclophosphamide (Bu/Cy)
E	Cyclophosphamide + Total Body Irradiation (Cy/TBI)

Study Evaluations

We will measure your health at specific times during your study participation. These tests and how often they are scheduled are standard for what we do for all patients receiving an allogeneic transplant. We would do them even if you were not part of this study.

- History, physical exam and weight: weekly for 3 months, 6, 12 and 18 months.
- Routine blood tests, including cell counts, liver and kidney function: weekly for 3 months, 6, 12 and 18 months.
- Bone marrow biopsy and/or aspirate: at Day 100 and 18 months.
- Graft-versus-host disease (GVHD) and infections monitoring: weekly for 3 months, 6, 12 and 18 months.
- Side effects or toxicity: monthly for the first 3 months, then at 6, 12 and 18 months.
- Blood or bone marrow tests to find out the proportion of donor cells present in the recipient (chimerism) at 1, 3 and 18 months.
- Blood samples to determine the level of busulfan in your blood after the first dose (if you received busulfan as part of your treatment) only if your transplant center is participating in the ancillary study.
- Health quality of life for English speaking patients (see below) at 3, 12 and 18 months.

♦ ♦

<u>Blood Samples for Busulfan Pharmacokinetics</u>

Some transplant centers may be participating in this ancillary study.

Researchers are trying to learn more about how your body breaks down one of the drugs (busulfan) given as part of the conditioning regimen in this study. Samples for this test will be collected from you only if you receive this drug and your transplant center is participating in this ancillary study. These tests measure how much busulfan is concentrated in the blood. Busulfan

levels are already done routinely in some settings in order to avoid too high levels. Every patient can have different levels of this drug after receiving the same dose of busulfan.

The goal of this study is to see if these levels can be tied to the success of the transplant. This study will explore the levels of busulfan in these two treatment intensities and compare with what happens after transplant.

This study will collect up to seven blood samples within 6 to 8 hours after a dose of busulfan was given to you. Each blood sample volume is 3 mL (1/2 teaspoon). Once all seven blood samples are collected from you, they will be sent to a laboratory for testing. None of your personal information will be shared with the laboratory.

The busulfan blood tests are part of this clinical trial at select centers, but your center may repeat these tests as part of the routine transplant procedure. If this happens, your doctor will either collect 6 mL (1 teaspoon) each time as described above, or collect 3 mL for the research tests on another day that busulfan is given.

♦ ♦

Health Quality of Life

We will ask you about your general health and how well you feel while you participate in this study. Even though different treatments may treat a disease equally well, there might be a difference in how patients feel or the side effects they have after their treatment. This is important information for when we evaluate the treatments in this study.

We will collect information by using surveys. The surveys will ask about:

- How you feel
- What symptoms you might have and how they affect you
- How well can you do regular daily activities

You will need to fill out the surveys and each survey should take about 30 minutes to finish. Your answers will help us understand how your transplant treatment affects how you feel, what you can do, and your general quality of life.

Other Treatment Choices

It is your choice to join this study. If you decide you do not want to participate, you may still receive a transplant for treatment of your disease. It is possible that you may have a treatment and evaluations that are very similar to what would be if you joined this study.

Your study doctor will discuss these choices with you. If you decide you do not want to join this research study, your medical care will not be affected in any way.

Risks and Discomforts

The risks and discomforts of stem cell transplant are the same if you join this study, or if you do not join this study. The differences in side effects from medications are because of the different levels of treatment strength.

High intensity treatments usually have more side effects early after transplant compared to reduced intensity treatments. Other problems with transplant, such as graft-versus-host disease (GVHD) and infections happen equally in patients who have high intensity or reduced intensity treatments.

Risks Related to Medications or Radiation Used in Conditioning Regimens

All chemotherapy and radiation treatments used as conditioning in this study are commonly used in allogeneic stem cell transplantation. The side effects can change based on the amount of drug given. This is true for busulfan, which is used for reduced intensity and high intensity treatments but in different amounts.

TABLE 2 – ADVERSE EVENTS

Cyclophosphamide	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	Damage to male (testes) and female (ovaries) sex glands Diarrhea Fluid retention Hair loss Infertility Irregular or no menstrual cycles Loss of appetite Nausea, Vomiting Suppression of the immune system	Bleeding in the bladder Inflammation of the heart muscle (heart failure) Shortness of breath	Allergic reaction Lung fibrosis Serious skin rashes

Fludarabine	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	Diarrhea Mouth sores Nausea and vomiting Suppression of the immune system	Fever Numbness in the extremities Sleepiness Visual changes Weakness	Coma Cough Inflammation of the lung Interstitial Pneumonia Skin rash

TABLE 2 – ADVERSE EVENTS, continued

Busulfan	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	Abdominal discomfort Constipation Diarrhea Dizziness Fluid retention Headache Heartburn Insomnia Lack of appetite Mouth sores Nausea and vomiting Running nose Skin rashes Irregular or no menstrual cycles Tachycardia	Cough Hepatic Veno-occlusive disease High blood pressure High magnesium and phosphorus levels in the blood High sugar levels in the blood Infertility Low blood pressure Seizures	Cataracts Lung fibrosis

Melphalan	**Likely Side Effects** (May happen in more than 20% of patients)	**Less Likely** (May happen in less than 20% of patients)	**Rare** (May happen in less than 2% of patients)
	Constipation Diarrhea Hair loss Mucositis Nausea and vomiting	Heart rhythm abnormalities Hepatitis Kidney failure	Allergic reaction Interstitial Pneumonia Seizure Lung fibrosis

Total Body Irradiation (TBI):

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Diarrhea Nausea Stomach cramps Vomiting (throwing up) Painful swelling of the salivary glands under the ears for a few days Short-term hair loss Anemia Infection Bleeding Cataracts Sterility (inability to have children) Slow growth Hormone problems (such as thyroid disease or diabetes) Mouth sores	Lung inflammation Pneumonia Redness of the skin Serious liver problems	Risk of developing other cancers in the future Difficulty swallowing Back problems Kidney problems Learning problems

Risks Related to the Medication Used to Help Prevent Graft-versus-Host Disease

Graft-versus-Host Disease (GVHD) is a medical condition that can become serious enough to cause death. GVHD is a common development after allogeneic stem cell transplant. It happens when the donor cells attack and damage your organ tissues after transplant. GVHD can cause:

- Skin rashes
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Abdominal pain
- Diarrhea
- Liver damage or jaundice (yellowing of the skin or eyes)

Your doctor will prescribe medication to prevent GVHD. You will start GVHD prevention around the time you get your donor cells, and it can last many months after the transplant. These medications do not completely prevent GVHD and more drugs might be needed to manage this complication.

Your doctor will decide which GVHD prevention treatment is the best choice for you. This decision is not part of the research study. Your doctor will also decide your medications based on what is regularly used for transplant in this hospital or clinic. Below is a list of commonly used drugs used to prevent GVHD. Your doctor may choose to use other medications than what is listed here.

- **Tacrolimus**: This drug is used to try to prevent GVHD. Early side effects you may have include: feeling sick to your stomach (nausea) or throwing up (vomiting) after you swallow. Other side effects include high blood pressure (hypertension), shaking hands (tremor), increased hair growth and possibly how clearly you can think or make decisions (mental function).

  If you have these effects, they generally go away if your doctor lowers the amount of medication you take. A few patients have had a seizure while on this medication.

  Your liver or kidneys might not work as well as they did before. If this happens, your doctor may lower the amount of drug you take or stop giving the drug completely. You might be more likely to have kidney problems if you need to take other medications at the same time. This is especially true for drugs that we know might cause kidney problems, such as antibiotics. Sometimes, the kidney damage caused is serious enough for you to need an artificial kidney machine (hemodialysis).

  Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

  It is very important that you do not eat grapefruit or drink grapefruit juice. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs, including tacrolimus, used in this study. Common soft drinks that have bergamottin are Fresca, Squirt and Sunny Delight.

- **Methotrexate:** This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells and can affect many different parts of your body. It may cause mouth sores or mouth inflammation. Or if you already have these problems from your treatments and other medications, they can get worse.

  Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can also cause kidney damage. If your kidneys are already damaged for

other reasons, it can make your kidneys worse. If kidney damage does happen, your doctor might give you a lower dose of methotrexate, or stop giving it completely.

- **Tacrolimus and Methotrexate:** These medications can affect your body's immune system and make it easier for you to get infections. Even simple infections can become very serious and even life-threatening. As a result, you might have more infections for several months after transplant, especially viral infections and pneumonia.

- **Risks Related to the Transplant Procedure:** The following risks are part of the transplant process and not connected to any one medication or the transplanted donor cells.

  - **Bleeding:** Platelets help your blood to clot. When you have low amounts of platelets, you may have bleeding problems. Once your new bone marrow starts to grow, your platelets will increase and your blood will start to clot normally again.

    Bleeding problems can range from minor bleeding, such as nosebleeds or bruising, to more serious bleeding in your brain and lungs. Serious bleeding can be very dangerous and can happen if your platelet levels stay low. Usually, we can prevent major bleeding problems with transfusions of platelets. However, if your body does not respond well to transfused platelets, you may be at serious risk for bleeding.

  - **Veno-occlusive Disease (VOD):** High dose chemotherapy, radiation therapy and medications used to prevent GVHD can cause veno-occlusive disease (VOD). VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the belly (abdominal cavity) and other parts of the body. We can usually manage veno-occlusive disease very well, to the point where it goes away. However, complications can happen with VOD that may put your life in danger.

  - **Mouth Sores and Diarrhea:** The large doses of chemotherapy and radiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores, we will give you medicine to help control the pain. If your mouth sores are very bad, you may not be able to eat normally until the sores are healed. Mouth sores get better when your white blood count starts to rise, and your donor cells start to grow (also called engraftment).

  - **Capillary Leak Syndrome:** This can happen from your chemotherapy and radiation treatments. The blood vessels may become 'leaky' and fluid enters your abdomen, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult

to manage if extra fluid enters your lungs and makes it hard to breathe. You may die if fluid continues to build up in your lungs.

- **Unexpected Organ Damage and Other Side Effects:** You might have unexpected, life-threatening heart, lung, kidney, or liver damage as a result of your transplant. High doses of chemotherapy and radiation can cause very bad lung damage that may not get better with time or medications. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multiple organ failure (such as lung and kidney failure) can happen, which can lead to death.

- **Fluid Build-up:** We will give you intravenous (IV) fluids during the transplant process and it can be hard for your body to eliminate this fluid. We will also give you Furosemide, which is a medication that can help your body get rid of the extra fluid. One risk of Furosamide is hearing loss. Some side effects may be loss of body chemicals such as potassium and sodium.

- **Late Effects:** You may have side effects happen a few months to many years after your transplant.
    - You may have problems with your thyroid gland that require you to take thyroid medication.
    - You may get cataracts earlier in life compared to a person who has not had a transplant. If you develop cataracts (cloudiness in the eyes) they may need treatment.
    - Your kidneys could be affected and cause anemia (low red blood cell count) or high blood pressure.
    - You may develop a second cancer as a result of the chemotherapy, radiation and/or underlying disease. If secondary cancers happen they generally do not develop until 10 to15 years after your transplant.
    - We do not know the long-term effects of transplant on your heart, lungs and brain.

- **Unforeseen Risks:** New risks might appear at any time during the study that are different from the risks listed in this Consent Form. We will promptly tell you of any new information that may affect your decision to participate.

- **Risk to the unborn:** The treatments in this study have NOT been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who have the potential of becoming pregnant must use some form of effective birth control while receiving chemotherapy, TBI, and GVHD prophylaxis. Effective birth control is defined as the following:
    - Refraining from all acts of vaginal intercourse (ABSTINENCE)
    - Consistent use of birth control pills
    - Injectable birth control methods (Depro-Provera, Norplant)
    - Tubal sterilization or male partner who has undergone a vasectomy
    - Placement of an IUD (intrauterine device)
    - Use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.
    - Sterility and future childbearing potential for men and women. Chemotherapy and/or irradiation may affect your ability to have children. Male patients may become sterile (unable to produce sperm) and should discuss with their doctor regarding sperm banking prior to transplantation. Female patients who have attained puberty may find that their menstrual cycle becomes irregular or stops permanently. However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control during transplant and afterwards until you are off GVHD prophylaxis. Damage to reproductive tissue may result in infertility (inability to have children). It is not known if the damage could result in birth defects. You should discuss these risks and options in detail with your doctor before entering this study.

Possible Benefits

Taking part in this study may or may not make your health better compared to receiving the transplant through your routine medical care. We do know that the information from this study will help doctors learn more about selection of conditioning regimen intensities. This information could help patients in the future who are in need of an allogeneic transplant.

What if I change my mind?

You can change your mind at any time about allowing us to use your samples and health information for research. We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form.

If you withdraw yourself from this protocol, even if you allowed your samples to be used for research, your samples will not be used from that point and they will be discarded. However,

samples and information that have already been shared with other researchers cannot be taken back or destroyed.

New Information Available During the Study

During this research study, new information about the study drug or the risks and benefits of the study may become known to the study doctors. If this happens, they will tell you about the new information.

The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study. If this happens, the study doctor will stop your participation in the study and you will be offered all available care to suit your needs and medical conditions.

Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical and research records remains confidential. We will not discuss or publish information about your health with any unauthorized person or persons. However, we cannot guarantee total privacy.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your study number is not related to your name, social security number or medical record number at [*insert facility name*].

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), and
- Other authorized study organizations

We will not identify you by name in any publications or reports that come from these organizations or groups.

Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and you may be asked to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment.

The study sponsor may decide to end the study at any time. If you are asked to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

Physical Injury as a Result of Participation

It is important that you tell your study doctor or study staff if you feel that you have been hurt or injured because of taking part in this study. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for this treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Compensation or Payment

You will not be paid for your participation in the research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

Costs & Reimbursements

Most of the visits for this research study are standard medical care for patients undergoing allogeneic transplants and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for the busulfan blood samples required for the study or the optional blood sample for research on this study.

Ethical Review

The ethical aspects of this research study have been reviewed and approved by [*name of IRB*].

Further Information

If you need any information about this study, or if you have any problems while you are participating in this study you can contact the study doctor or his/her staff. They may be contacted at the telephone numbers listed below.

[*Insert name and contact details*].

Independent Contact

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

[*Insert appropriate contact details*].

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. **Purpose**:
As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

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

B. **Individual Health Information to be Used or Disclosed**:
My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams

1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. **Parties Who May Disclose My Individual Health Information**:
The researcher and the researcher's staff may collect my individual health information from:
[*List hospitals, clinics or providers from which health care information can be requested*]

D. **Parties Who May Receive or Use My Individual Health Information**:
The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff:
  Dr. Bart Scott, Co-Principal Investigator
  Dr. Mitchell Horwitz, Co-Principal Investigator
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Study sponsors: Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data and Coordinating Center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

E. **Right to Refuse to Sign this Authorization**:
I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:
I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:
My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

Blood Samples for Future Research (*optional*)

Researchers also want to learn how to better predict possible health problems and how to make transplants more successful. Much of this research is done using human tissue or blood.

We would like to store a sample of your blood for use in future research studies. Your blood would be collected at your transplant center before your transplant. We would keep the sample at a central place called the BMT CTN Research Sample Repository (this will be called the "Repository" in the rest of the consent form). A Repository is a place that protects, stores and sends out samples for approved research studies.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission. You should feel free to talk over your decision with your family, friends, doctor, and health care team. If you decide to not let us store research samples now or in the future, it will not affect your medical care.
- Research is meant to gain knowledge that may help people in the future. You will not get any direct benefit from taking part.
- All testing done on your blood is for research purposes. You or your doctor will not be given results and they will not be added to your medical record.
- You will not get paid for any samples or for any products that may be developed from current or future research.

If you agree to provide a blood sample, here is what will happen:

1. A single 6 mL sample of your blood (approximately 1 teaspoon) will be collected before your transplant and stored solely for research purposes. The collection will be done at the same time as the routine blood collection done for the study.

2. The research sample will be given unique bar code designation that cannot be linked to you by the researcher testing your samples.

3. Researchers can apply to study the materials stored in the Repository.

4. Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the remaining research samples and clinical data will be made available outside of this network. Researchers from other universities, the

government, and drug or health-related companies can apply to use the samples and information. Only skilled researchers will be allowed to use the samples and information.

5. The BMT CTN Steering Committee or the BMT CTN Biomarkers Committee must approve each study application before they will share samples or information with researchers. This kind of review is to make sure that the investigators requesting the samples are qualified, and that the research they propose has a high potential of success and for contribution of scientific knowledge.

6. DNA from your stored blood sample might be used in genome-wide association (GWA) or pharmacogenomics studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease. Pharmacogenomics studies are similar genetic tests but look specifically at genes related to how the body breaks down medications.

   If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

7. A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Statement of Consent

The purpose of storing blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for future research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I agree to allow my blood samples to be stored for research.
- ❑ I do not agree to allow my blood samples to be stored for research.

_____ _____

Signature Date

TITLE: **BMT CTN 0901:** 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-INVESTIGATOR:
Bart Scott, MD
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, D1-100
Seattle, WA 98109-1023
Phone: (206) 667-1990

CO-INVESTIGATOR:
Mitchell Horwitz, MD
Duke University
2400 Pratt St. DUMC 3961
Durham, NC 27710
Phone: (919) 668-1045

- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.
- I understand that the transplant intensity will be randomly assigned to me.
- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

Participant Signature Print Name Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Signature of Counseling Physician Date

Signature of Interpreter Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. BUSULFAN PHARMACOKINETICS (PK) STUDIES

Patients receiving busulfan (Bu) as part of the conditioning regimen regardless of the intensity will participate in this ancillary study if their transplant center agrees to participate in this study. Even though Bu PK is routinely done in some instances to optimize Bu exposure and minimize toxicity with myeloablative Bu doses, this practice is not done in patients who receive reduced intensity Bu doses. This study will analyze Bu PK in all eligible patients at a central laboratory with the objective of correlating PK results with post-transplant outcomes, including rates of relapse, treatment-related mortality, disease-free and overall survival. Patients who receive Bu will be asked to provide up to 7 peripheral blood samples, using a pre-set sampling strategy after the first dose of Bu. Samples will be collected up to 8 hours post administration of Bu. Patients who already have Bu PK performed as part of their routine clinical care will need additional samples to be analyzed at a central laboratory for this study. They can be collected on the same day or another day busulfan is given.

Samples Required
One 3 mL peripheral blood sample will be collected in a 6 mL-fill, sodium heparin-containing Vacutainer® tubes at up to seven scheduled post-Bu dose sample collection time points for a total of 6 or 7 samples (21 mL maximum). Peripheral blood samples will be placed on ice immediately after collection, centrifuged at 1000 g at 4ºC for 5 minutes for plasma separation. The plasma will be removed from each vacutainer and placed in a single polypropylene cryovial corresponding for each time point. The cryovials will be labeled and frozen at -70ºC. The plasma samples must be well frozen prior to shipping to the project laboratory.

Samples Shipment
Samples will collected at 6-7 different time points depending on the route of Bu administration and Bu dosing schedule. The table below outlines the proposed sampling strategy after the first dose of Bu. The final schedule will be provided in the BMT CTN 0901 Laboratory Sample Guide.

Dosing Schedule	Bu Sample Collection Time Points						
	#1	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**
IV Q6 hours	End of Infusion (EOI)[1]	EOI+ 15 min	EOI+ 30 min	240 min (4hrs)[2]	300 min (5 hrs)[2]	360 min (6 hrs)[2]	---
IV Q24 Hours	End of Infusion (EOI) [1]	EOI+ 15 min	240 min (4 hrs)[2]	300 min (5 hrs) [2]	360 min (6 hrs)[2]	480 min (8hrs)[2]	---
Oral Busulfan (suspension)	15 min	30 min	60 min (1 hrs)	120 min (2 hrs)	240 min (4 hrs)	300 min (5 hrs)	360 min (6 hrs)
Oral Busulfan (tablet)	30 min	60 min (1 hr)	90 min (1.5 hrs)	120 min (2 hrs)	240 min (4 hrs)	300 min (5 hrs)	360 min (6 hrs)

[1] **For the initial EOI sample, be sure all of the drug has been delivered and the lines have been thoroughly flushed by Saline before drawing the end of infusion (EOI) sample.**

[2] From the start of the infusion.

Samples Shipment and Test Result Reporting
Clinical centers will ship the set of six or seven frozen plasma cryovials in 5 kg of dry ice by priority overnight FedEx either on (1) the day of collection (Monday through Thursday) or (2) on the day following collection if sample collection is performed Monday through Wednesday. If the sample collection occurs Friday through Sunday, the samples will need to be stored for Monday shipment. Testing results will be provided by the Project Laboratory to the submitting clinical center, for subsequent entry into the Advantage EDC study data system.

2. OPTIONAL SAMPLE FOR UNDEFINED FUTURE RESEARCH

Patients consenting to provide optional research samples to be submitted to the BMT CTN Research Sample Repository for future testing will have an additional baseline peripheral blood sample collected.

Samples Required
A 6 mL peripheral blood sample will be collected at within 30 days of the initiation of preparative regimen in a 6 mL-fill, EDTA containing Vacutainer® tube (lavender). The peripheral blood sample will be stored upright in a rack at room temperature while preparing to ship the sample on the same day to the BMT CTN Research Sample Repository. Centers should arrange to have these patient samples collected on Monday-Thursday for receipt at the repository on Tuesday-Friday.

Sample Shipment
Clinical centers will ship the peripheral blood tube at ambient temperature by priority overnight FedEx on the day of collection directly to the BMT CTN Research Sample Repository for processing and long-term storage of whole blood aliquots.

SCHEDULE OF LABORATORY EVALUATIONS

RESEARCH TOPIC	RESEARCH SAMPLE PURPOSE	TYPE OF SAMPLE	SAMPLE COLLECTION, PROCESSING AND STORAGE REQUIREMENTS	SAMPLE COLLECTION TIME POINTS	SHIPPING SPECIFICATIONS
Busulfan Pharmacokinetics Studies[1]	**Serial Busulfan Levels**	Up to seven 3 mL peripheral blood samples collected in 6 mL sodium heparin containing, green-top vacutainer tube.	Gently mix blood with heparin by inverting the tube 8-10 times. Centrifuge at 1000 g at 4ºC to separate plasma. Freeze the plasma in polypropylene cryovials. Ship the complete set of PK samples to Project Laboratory.	Up to 7 time points from completion of the first dose of Bu until 6-8 hours later.	Cryovials set will be shipped frozen in 5 kg on dry ice directly to the Project Laboratory by priority overnight Fed Ex delivery for processing and busulfan testing. Guidelines for the final specimen collection schedule, handling and shipment to the Project Laboratory is detailed in the BMT CTN 0901 Laboratory Research Sample Guide.
(Optional) Investigational Future Research Sample[2]	**Undefined Future Studies**	One 6 mL peripheral blood sample collected in an EDTA containing, lavender-top vacutainer tube.	Gently mix blood with EDTA by inverting the tube 8-10 times. Store upright in a rack at room temperature while preparing to ship to the BMT CTN Research Sample Repository.	**Pre-transplant** Within 30 days of the initiation of preparative regimen.	Peripheral blood tube will be shipped at ambient temperature on the day of collection, directly to the BMT CTN Research Sample Repository by priority overnight Fed Ex delivery for processing and long-term storage of whole blood aliquots. Guidelines for specimen handling and shipment to the Repository are detailed in the BMT CTN 0901 Laboratory Research Sample Guide.

[1] To be collected only from patients receiving busulfan at participating transplant centers.
[2] To be collected only from patients consenting to future research sample.

APPENDIX D

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) FOR PATIENTS WITH MDS

APPENDIX D

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) FOR PATIENTS WITH MDS

IPSS* for MDS: Survival and AML Evolution

Prognostic Value	Score Value				
	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-20
Karyotype†	Good	Intermediate	Poor		
Cytopenias	0 or 1	2 or 3			

Scores for risk groups are as follows: Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5-2.0; and High =≥ 2.5.

* International Prognostic Scoring System [21]

† Good, normal, -Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

APPENDIX E

SWOG CYTOGENETIC CLASSIFICATION FOR AML

APPENDIX E

SWOG CYTOGENETIC CLASSIFICATION FOR AML

Risk status	SWOG coding
Favorable	inv(16)/t(16;16)/del(16q), t(15;17) with/without secondary aberrations; t(8;21) lacking del(9q) or complex karyotypes
Intermediate	Normal, +8, +6, -Y, del(12p)
Unfavorable	del(5q)/-5, -7/del(7q), abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9), t(9;22) and complex karyotypes (≥ 3 unrelated abn)
Unknown	All other abnormalities

APPENDIX F

KARNOFSKY PERFORMANCE SCORE

APPENDIX F

KARNOFSKY PERFORMANCE STATUS SCALE

Index	**Specific Criteria**	**General**
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

APPENDIX G

HCT-SPECIFIC COMORBIDITY INDEX SCORE

APPENDIX G

HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		**0**
Osteoporosis		**0**
Osteoarthritis		**0**
Hypertension		**0**
Gastrointestinal	Including inflammatory bowel disease	**0**
Mild pulmonary	DLCo and/or FEV_1 >80% or Dyspnea on moderate activity	**0**
Mild renal	Serum creatinine 1.2-2 mg/dl	**0**
Endocrine		**0**
Bleeding		**0**
Coagulopathy	Deep venous thrombosis or pulmonary embolism	**0**
Asthma		**0**
Arrhythmia		**1**
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EF≤50%	**1**
Mild hepatic	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	**1**
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	**1**
Morbid obesity		**1**
Diabetes	Requiring treatment	**1**
Depression/anxiety		**1**
Infection	Requiring continuation of treatment after Day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	**2**
Moderate pulmonary	DLCo and/or FEV_1 66-80% or Dyspnea on slight activity	**2**
Peptic ulcer	Patients who have required treatment	**2**
Moderate-severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	**2**
Valvular heart disease	Except mitral valve prolapse	**3**
Prior solid tumor	Requiring treatment with chemotherapy	**3**
Moderate-severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN	**3**
Severe pulmonary	DLCo and/or FEV_1 ≤65% or Dyspnea at rest or requiring oxygen	**3**

Total score is the sum of all comorbidities present at time of transplantation.

APPENDIX H

HUMAN SUBJECTS

APPENDIX H

HUMAN SUBJECTS

Subject consent: Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates and enroll them onto the study. The study coordinator at each center will provide the patient with information about the purpose of the study and obtain consent. The Network will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms. Each center must provide evidence of IRB approval.

Confidentiality: Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

Participation of women, children, minorities and other populations: Women and ethnic minorities will be included in this study. Children will not be included.

Accrual will be monitored within each center with the expectation that the enrolled patient population is representative of the transplanted patient population at each center. Representation will be examined by comparing gender, race, ethnicity, and age distributions. Accrual of minority patients will be expected to be in proportion to the number of minority patients transplanted at each center. The DCC and NHLBI will discuss enrollment anomalies with the centers.

APPENDIX I

REFERENCES

APPENDIX I

REFERENCES

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