A Phase 2 Study of Nonmyeloablative or Myeloablative Conditioning with Transplantation of Partially HLA-Mismatched Peripheral Blood or Bone Marrow and Post-transplant Cyclophosphamide for Patients with Hematologic Malignancies

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Principal Investigators:
Grace Ku, MD
Moores UCSD Cancer Center
3855 Health Sciences Drive
La Jolla, CA 92093

Tel: 858-822-6600
Fax: 858-822-6398
Email: gku@ucsd.edu

Carolyn Mulroney, MD
Moores UCSD Medical Center
3855 Health Sciences Drive
La Jolla, CA 92093

Tel: 858-822-6600
Fax: 858-822-6398
E-mail: camulroney@ucsd.edu

Sub Investigators:
Edward Ball, MD
Januario Castro, MD
Peter Curtin, MD
Matthew Wieduwilt, MD, PhD.
Caitlin Costello, MD

Statistician:
Karen Messer, PhD., UCSD Biostatistics Program, Shared Resource

SYNOPSIS

Study Design: This is a single center Phase 2 study of myeloablative (MA) and nonmyeloablative (NMA) conditioning, transplantation of partially HLA-mismatched bone marrow or peripheral blood stem cells and post-transplantation cyclophosphamide (Cy) in patients with hematologic malignancies including:
1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, and Burkitt's lymphoma in remission.
2) Relapsed lymphoma, including marginal zone B cell lymphoma, follicular lymphoma, and chemotherapy-sensitive large-cell or Hodgkin lymphoma.
3) Myelodysplastic Syndrome (MDS)
4) Blastic plasmacytoid dendritic cell neoplasm
5) Multiple myeloma

Primary Objective:
The primary objective is to determine overall survival 180 days after transplantation involving MA and NMA conditioning, HLA-haploidentical marrow or peripheral blood stem cell grafts, and post-transplant Cy.

Secondary Objectives:
Secondary objectives include estimating overall and progression-free survival at 100 days, 180 days, and one year after transplantation, treatment-related mortality, incidence of neutrophil and platelet recovery or engraftment, incidence of graft failure, cumulative incidence of acute and chronic GVHD, incidence of infections, and cumulative incidence of relapse/progression. We will also examine the amount of time to transplant (day of unrelated search initiation to day 0).

Eligibility Criteria:

- Age: Subjects 18-75 years old.
- Donor must be ≥ 18 years of age.
- HLA typing will be performed at high resolution (allele level) for the HLA-A, -B, Cw, DRB1, and –DQB1 loci. A minimum match of 5/10 is required.

With high resolution typing, the donor and recipient must be identical at a minimum of at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. Meeting this criterion will be considered sufficient evidence that the donor and recipient share one HLA haplotype, and typing of additional family members is not required.

- Acute Leukemias
  - Acute Lymphoblastic Leukemia in high risk CR1 as defined by at least one of the following:
    - Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), MLL rearrangements,
    - White blood cell counts of greater than 30,000 wbc/μL,
    - Patients over 30 years of age, or
    - Time to Complete Remission was greater than 4 weeks.
  - Acute Myelogeneous Leukemia in high risk CR1 as defined by at least one of the following:
    - Greater than 1 cycle of induction therapy required to achieve remission,
    - Preceding myelodysplastic syndrome (MDS),
    - Secondary leukemia (history of chemotherapy or radiation treatment as precursor to development of leukemia),
    - Presence of Flt3 internal tandem duplication (ITD),
    - FAB M6 or M7 leukemia, or
    - Adverse cytogenetics for overall survival such as
      - those associated with MDS
      - Complex karyotype (≥ 3 abnormalities)
      - Any of the following: inv(3) or t(3;3), t(6;9), t(6;11), + 8 [alone or with other abnormalities except for t(8;21), t(9;11), inv(16) or t(16;16)], t(11;19)(q23;p13.1)
  - Acute Leukemias in 2nd or subsequent CR (see remission definition in Chapter 3).
  - Biphenotypic/Undifferentiated Leukemias in 1st or subsequent CR.
- Burkitt's lymphoma: second or subsequent CR.
- Myelodysplastic Syndrome (MDS)
- Blastic plasmacytoid dendritic cell neoplasm
- Lymphoma:

  Chemotherapy-sensitive (complete or partial response; see response criteria in Chapter 3) aggressive lymphoma or Hodgkin's lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are ineligible for an autologous transplant. They may have received prior autologous transplant if greater than three months prior to enrollment.

Or

Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).

- Multiple myeloma
- Patients with adequate physical function as measured by:
  - Cardiac: Left ventricular ejection fraction at rest must be ≥ 40%,
  - Hepatic: Bilirubin, ALT, AST ≤ twice the upper limits of normal and Alkaline Phosphatase < 5 x ULN.
  - Renal: 24 hour creatinine clearance≥ 40 mL/min
  - Pulmonary: FEV_1 ,of ≥ 50% of predicted and , DLCO (diffusion capacity)≥ 40% of predicted. If unable to perform pulmonary function tests, then O_2 saturation > 92% on room air.
- Performance status: Karnofsky score 70-100%.

Treatment Description:
The preparative regimen will consist of:
NMA:
- Fludarabine 30 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide (Cy) 14.5 mg/kg IV Days –6, –5
- Total body irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of infusion of non-T-cell depleted bone marrow or peripheral blood stem cells.

MA:
- Fludarabine 25 mg/m^2 IV Days -–6, –5, –4, –3, –2
- Busulfan 110 mg/m2 days -7,-6,-5,-4
- Cyclophosphamide (Cy) 14.5 mg/kg IV Days –3, –2
- Day 0 will be the day of infusion of non-T-cell peripheral blood stem cells with CD34 dose capped at 5 million per Kg recipient weight.

The GVHD prophylaxis regimen will consist of:
- Cy 50 mg/kg IV Days +3, +4
- Tacrolimus (1 mg IV given as continuous infusion daily) beginning Day +5 with dose adjusted to maintain a level of 5-10 ng/mL. Switch to PO when tolerating POs well and levels are stable.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID beginning Day + 5, maximum dose 1 g po TID
- GCSF 5 mcg/kg/day beginning Day + 5 until ANC $\geq$ 1,000/mm^3 for 3 consecutive days

Study Duration: Patients will be followed for one year after transplantation for purposes of this study.

Accrual Objective: 15 patients

Accrual Period: 3 years

NON-MYELOABLATIVE TREATMENT SCHEMA

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

Myeloablative TREATMENT SCHEMA*

Day – 7 Busulfan 110 mg/m2/day

Days –6, –5, -4 Fludarabine 25 mg/M^2 IV daily
Busulfan 110 mg/m2/day

↓

Day -3 and -2 Fludarabine 25 mg/M^2 IV daily
Cyclophosphamide (Cy) 14.5 mg/kg IV daily
Mesna 11.6 mg/kg IV daily

↓

Day 0 Infuse non-T cell-depleted peripheral blood stem cell s with total CD34 dose capped at 5 million per kg

↓

Days 3, 4 Cy 50 mg/kg (IBW) IV daily
Mesna 40 mg/kg IV daily
(First dose of Cy must be administered 60-72 hour after infusion of marrow)

↓

Day 5 Begin tacrolimus 1mg IV qd and
MMF 15 mg/kg PO TID with maximum daily dose 3 gm/day
Begin G-CSF 5 mcg/kg/day SC or IV, continue until ANC ≥ 1000/mm^3 x 3 days

↓

Day ~28 Assess chimerism in peripheral blood

↓

Day 35 Discontinue MMF (optional if GVHD is active)
No taper

↓

Day ~56 Assess chimerism in peripheral blood

↓

Day 180 Discontinue tacrolimus (optional if GVHD is active)
Without taper
Assess chimerism in peripheral blood
Evaluate disease

↓

1 yr, Evaluate disease
Assess chimerism in peripheral blood

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1. BACKGROUND AND RATIONALE

1.1. Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a curative treatment option for patients with hematologic malignancies. An important component of this strategy involves an effect exerted by the T cells within the donor graft known as "graft-versus-malignancy" effect.[1, 2] While the best outcomes are shown in transplantation with HLA-matched sibling donors, only 25-30% of patients have this option. For the majority of patients, alternative donors are an important source of stem cells. However, several obstacles exist in finding a successful unrelated donor. First, the likelihood of finding a matched unrelated donor for Caucasians is about 70% but can be 10 -50% for ethnic minorities.[3] Second, the interval of time between the initiation of a donor search to graft procurement is approximately 4 months. Clearly this option is less than ideal for patients with high risk disease who are in urgent need of a transplant. Umbilical cord blood overcomes some of these obstacles. It is available within a few weeks. Greater than 95% of patients have at least a 4/6 potential matched cord blood unit and the majority have a potential 5/6 match (http://marrow.org). However, the use of cord blood units also has disadvantages. Most adult recipients require double cord transplantation. There are some recipients who are too large to even qualify for a double cord. Other issues include the difficulty of procuring more stem cells in case of graft failure or DLI. Additionally there is a prolonged engraftment time which leads to increased infection risk. Transplantation with HLA-haploidentical relatives offers at least two advantages compared to unrelated donors. First, there is a high likelihood of identifying an eligible donor since all biological parents and children share one HLA haplotype. Second, potential donors can be identified promptly, whereas the time from initiation of search to unrelated donor identification takes a median of 49 days[4].

While haploidentical stem cell transplantation has been studied since the late 1980s-early 1990s, early results showed high rates of graft rejection and severe graft-versus-host disease (GVHD).[5, 6] Groups at Johns Hopkins and Seattle have investigated the effect of administration of high dose, post-transplantation cyclophosphamide (Cy) on the incidence and severity of these complications in animal models[7, 8] and then in humans[9]. The rationale for administering Cy after transplantation is that recently activated, alloreactive T cells (the cells most responsible for GVHD) are selectively sensitive to the toxic effects of this drug.[10] Also, Cy is known to be stem cell sparing. Pre-clinical studies demonstrated that engraftment of major histocompatibility complex (MHC)-mismatched bone marrow could be achieved by conditioning mice with the combination of pre-transplantation fludarabine and low dose (200 cGy) total body irradiation, and post-transplantation Cy.7

Two independent clinical trials, one at Johns Hopkins (n=60) and the other at the Fred Hutchinson Cancer Research Center in Seattle (n=28), evaluated the safety and efficacy of high-dose, post-transplantation Cy in prevention of graft rejection and GVHD after outpatient NMA conditioning and T cell-replete bone marrow transplantation from partially HLA-mismatched related donors. Eighty-eight consecutive patients were accrued to these trials between 1999 and 2006.

Patients on the two protocols were treated in three separate groups (Hopkins A, Hopkins B, and Seattle) which differed in postgrafting immunosuppression (Figure 1.1). Conditioning consisted of Cy 14.5 mg/kg/day IV on Days –6 and –5, fludarabine 30 mg/m^2/day IV on Days –6 to –2, and 200 cGy of TBI on Day –1. On Day 0, patients received donor marrow. The marrow was obtained in a targeted collection of 4 x 10^8 nucleated cells/kg recipient weight and depleted of red blood cells. On Day +3, 50 mg/kg Cy was administered over 90 min together with Mesna (80% dose of Cy in 4 divided doses over 8 hr) by IV infusion (Hopkins A and Seattle). The Hopkins B group received an additional dose of Cy on Day +4. Pharmacologic prophylaxis of GVHD was initiated on the day following completion of post-transplantation Cy. All patients received tacrolimus, initiated at a dose of 1 mg IV daily and adjusted to a therapeutic level of 5-15 ng/ml. Tacrolimus was converted to oral form until discontinuation. If there was no active GVHD, tacrolimus was tapered after Day 90 (Seattle) or discontinued on Day 50 or 180 (Hopkins A and B, respectively). All patients received mycophenolate mofetil (MMF) until Day+ 35 at a dose of 15 mg/kg PO twice daily (Hopkins A) or thrice daily (Hopkins B and Seattle), with a maximum daily dose of 3 g in the Hopkins B group. Patients received filgrastim, 5 μg/kg/day by subcutaneous injection starting on Day 1 (Hopkins) or Day 4 (Seattle) and continuing until recovery of neutrophils to >1000/μL for three days.

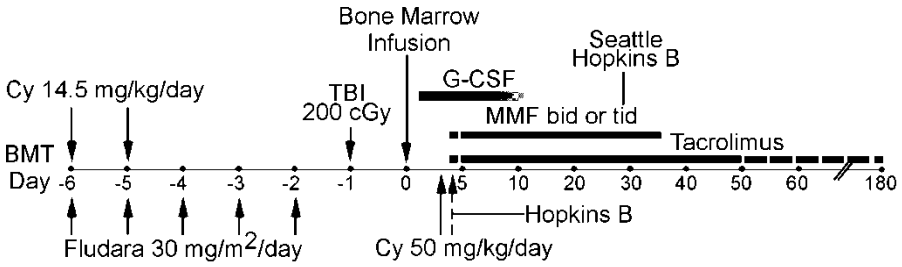

Figure 1.1 Treatment Schema

Engraftment and chimerism. By high resolution typing, donors differed from their recipients by a median of 3 of 8 (HLA-A, -B, -Cw, and DRB1) HLA alleles in both the host-versus-graft (HVG) and graft-versus-host (GVH) directions. About one-third of donor-recipient pairs were mismatched for all four of these HLA antigens. There were no differences in the three groups with respect to the donor age, donor-patient relationship, or total number of HLA allele mismatches in either the HVG or GVH directions.

Median times to neutrophil and platelet recovery were 15 and 24 days, respectively. Multivariate analysis showed that the factors associated with significantly delayed recoveries of neutrophils and platelets were lower graft CD34$^+$ cell content and administration of a second dose of post-transplantation Cy.

Graft failure occurred in 15 of 84 evaluable patients (18%): 6 of 19 (32%) in the Hopkins A group, 3 of 26 (12%) in the Seattle group, and 6 of 39 (15%) in the Hopkins B group. Engrafting patients

achieved full donor chimerism rapidly. With few exceptions, donor chimerism in patients with sustained engraftment was virtually complete (>95%) by 2 months post-transplantation.

As a result of these encouraging single center studies the BMT CTN opened a phase 2 multicenter clinical trial, BMT CTN 0603.[11] This involved nonmyeloablative (NMA) conditioning (fludarabine, cyclophosphamide, TBI) with HLA haploidentical bone marrow (haplo-marrow) transplantation followed by post-transplant Cy. This trial was run in parallel to BMT CTN 0604 using NMA conditioning and double umbilical cord blood (dUCB) transplantation. These data were published in Blood in 2011 and the results are summarized below.

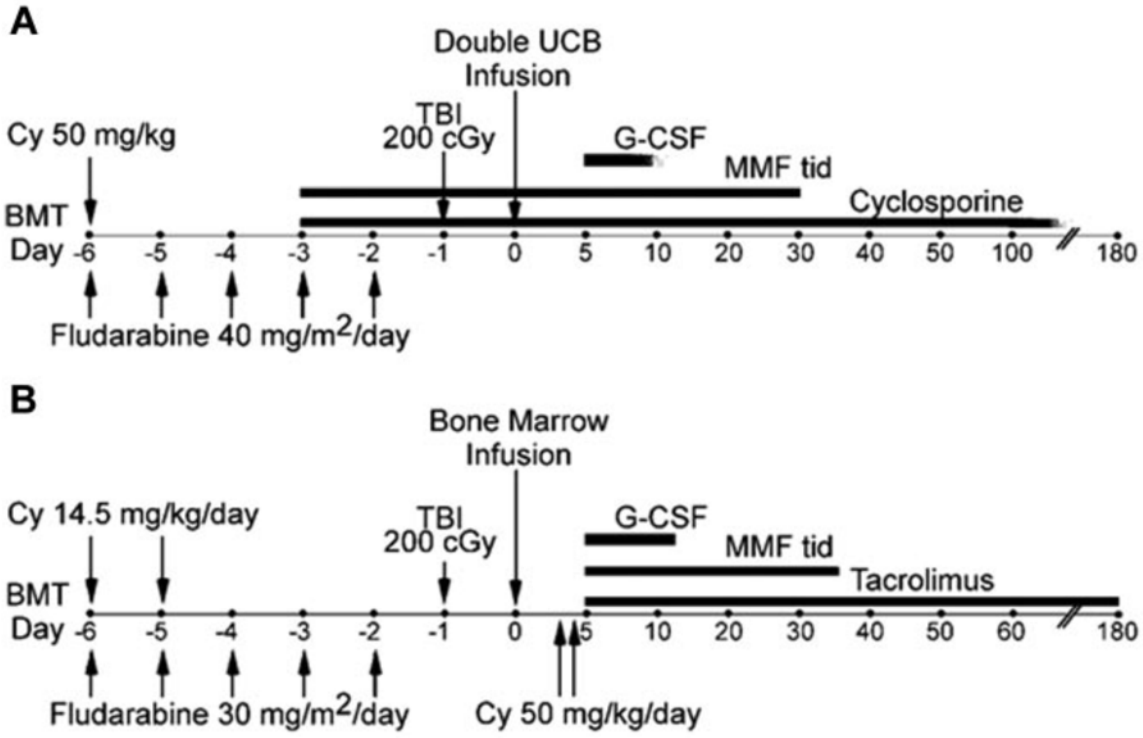

Figure 1.2 BMT CTN 0604 and 0603 Treatment Schema

In BMT CTN 0603, 50 patients were treated according to protocol and accrued between December 2008 and May 2010. Median age of recipients was 48 years (range 7-70 years). More than 75% of the HLA haploidentical donors were mismatched for at least 4 HLA alleles.
The median time of neutrophil recovery to >500 μL was 16 days and platelet recovery ≥ 20,000/μL was 24 days. There was one case of primary graft failure. All engrafted patients had 100% donor chimerism at day +56 after transplant.

Targeted grade 3-5 toxicities were reported in 30% of the haplo-marrow recipients and these are noted below in Table 1.1. There were no grade 5 toxicities reported in either study.

Table 3. Protocol targeted grade 3-4 toxicity day 0-180*

	CTN 0604 dUCB no. of events (no. of patients)		CTN 0603 Haplo-marrow no. of events (no. of patients)	
Organ/system	Grade 3	Grade 4	Grade 3	Grade 4
Hypertension	8 (8)	0 (0)	7 (5)	0 (0)
Hypotension	7 (6)	0 (0)	1 (1)	0 (0)
Cardiac arrhythmia	4 (3)	1 (1)	1 (1)	0 (0)
Left ventricular systolic dysfunction	3 (3)	2 (2)	0 (0)	0 (0)
Hepatic†	9 (6)	1 (1)	3 (3)	1 (1)
Pulmonary†	9 (6)	9 (6)	4 (4)	5 (2)
Hemorrhagic cystitis	5 (3)	0 (0)	3 (2)	0 (0)
Hemorrhage	0 (0)	1 (1)	0 (0)	0 (0)
Mucositis stomatitis	2 (2)	0 (0)	2 (2)	0 (0)
Somnolence	7 (5)	0 (0)	0 (0)	0 (0)
Seizure	0 (0)	0 (0)	1 (1)	0 (0)

dUCB indicates double umbilical cord blood; and haplo-marrow, HLA-haploidentical related donor bone marrow.

*Excludes dUCB infusional toxicity.

†Hepatic indicates alanine aminotransferase and/or alkaline phosphatase; pulmonary indicates hypoxia and/or dyspnea.

Table 1.1 Targeted Toxicities in BMT CTN 0604 and 0603

Cumulative incidence of grade 2-4 aGVHD at day +100 was 32% in the haplo-marrow group. There were no cases of grade 3-4 aGVHD. One year cumulative incidence of cGVHD was 13%. These results were comparable and perhaps superior to the earlier single center haploidentical transplant trials at Johns Hopkins and Seattle. In the concurrently run dUCB trial, BMT CTN 0604, the cumulative incidence of grade 2-4 and 3-4 aGVHD at day +100 were 40% and 21% respectively. One year cumulative incidence of cGVHD was 25%. GVHD incidence for the two trials is shown in Figure 1.3.

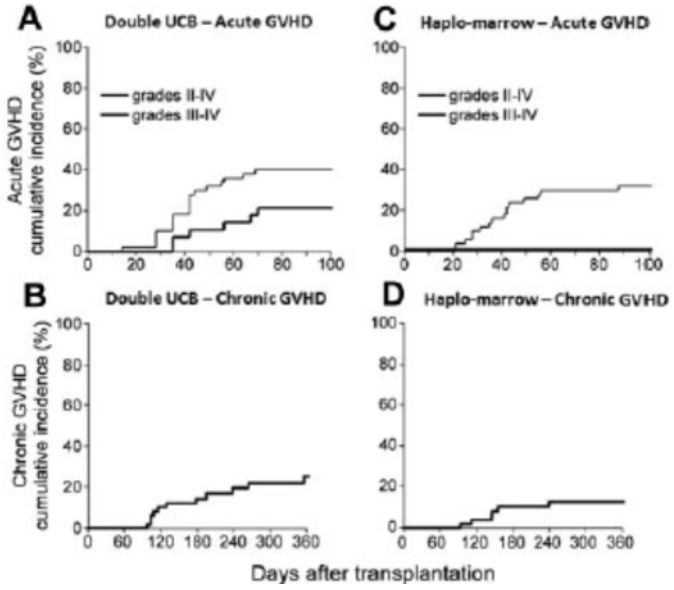

Figure 1.3 GVHD in BMT CTN 0603 and 0604

With median follow up 357 days for surviving haplo-marrow recipients the one year cumulative incidence of NRM was 7% and relapse/progression was 45%. One year PFS and OS were 48% and 62% respectively. In dUCB group the median follow up was 365 days with a 1 year cumulative incidence of NRM of 24% and relapse/progression of 31%. The one year PFS and OS in the dUCB trial were 46% and 54% respectively. In both groups, relapse was the most frequent cause of death. Long term outcomes are shown in Figure 1.4.

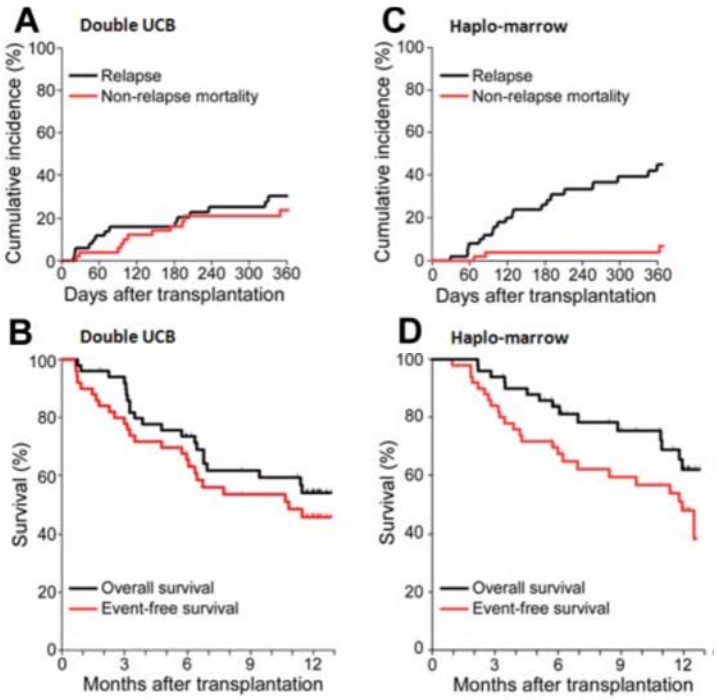

Figure 1.4 Long term outcomes in BMT CTN 0603 and 0604

Data have also been reported for Myeloablative strategies in patients who are considered to be candidates for an ablative transplant based on very high risk disease and comorbidity analysis. Solomon et al [Biol Blood Marrow Transplant 18: 1859-1866 (2012)](16) reported on a series of patients treated with an ablative regimen utilizing Busulfan, cyclophosphamide, and fludarabine. Post transplant immunosuppression included the same strategies as noted in the CTN trials. Donor egraftment occurred in all patients with full donor chimerism in all patients at day+30. The cumulative incidence of GVHD grade 2-4 was 30% with the incidence of grade 3-4 acute GVHD only 10%. The cumulative incidence of chronic GVHD was 35%. The nonrelapse mortality at 100 days and 1 year was 10%. The estimated 1 year survival overall was 69% and disease free survival was 50%. These outcome data with respect to NRM and aGVHD compare favorably to the outcome for nonmyelablative double umbilical cord blood transplants but the incidence of chronic GVHD are increased as compared to double umbilical cord blood transplants. While the overall outcome as compared to the nonmyelablative regimens is similar there is a risk of more severe grade 3-4 acute GVHD and an increased risk of chronic GVHD. The overall similarity in survival at 1 year may be related to the potential benefit for chronic GVHD in decreasing relapse.

In summary, HLA-haploidentical BMT after both ablative and non-myeloablative conditioning and using 2 doses of post-transplantation Cy followed by TID MMF is a well-tolerated procedure.

The toxicity of the procedure compares favorably to the toxicity of ablative and non-myeloablative transplantation using unrelated donors.

To place these results in context, the table below (Table 1.2) compares major outcomes of patients in BMT CTN 0603 and 0604 to those in a report containing the largest number of patients receiving unrelated donor grafts after NMA conditioning (n= 89)[12]. The table demonstrates that the two procedures appear roughly equivalent in terms of time to neutrophil engraftment. It appears that haplo-marrow transplant recipients may have had superior outcomes in the incidences of sustained donor chimerism, acute GVHD, and NRM. The recipients of unrelated grafts fared somewhat better in terms of overall and disease-free survival at 1 year, but it is not possible in a retrospective comparison to know whether these differences are attributable to the relative efficacies of the treatment or to differences in the patient populations.

	BMT CTN 0603 HLA-haploidentical (n=50)	**BMT CTN 0604 dUCB (n=50)**	**Solomon et al N=20**	**Unrelated (n=89)***
Median age (years)	48	58	44	53
Time to ANC > 500/mL (days)	16	15	16	15
Time to platelets > 20K/mL (days)	24	38	27	4
Sustained donor engraftment (total)	98%	88%		79%
Among recipient of PBSCs	-	-	100%	85%
Among recipients of marrow	98%	-		55%
aGVHD II-IV	32%	40%	30%	52%
aGVHD III-IV	0%	21%	10%	10%
1 year non-relapse mortality (NRM)	7 %	24%	20%	17%
1 year survival	62 %	54%	69%	52%
1 year disease-free survival (DFS)	48 %	46%	50%	38%

*Maris MB et al, Blood 102: 2021-2030, 2003

Table 1.2 Comparison of Donor Sources. Matched unrelated donor peripheral blood stem cell and bone marrow transplants as compared to dUCB and haplo-marrow transplant. All NMA conditioning.

Based upon the encouraging safety and efficacy data from CTN 0603 and Solomon et al we wish to offer haplo-marrow and peripheral blood stem cell transplants using the same conditioning regimens with post-transplant Cy to our patients who do not otherwise have a suitable donor. In doing so, we would like to assess safety and anti-tumor efficacy of this treatment protocol when done at our center. Although we participated in CTN 0603 we accrued only one patient prior to study completion. In addition we have completed 3 other haploidental transplants at UCSD prior to the opening of this trial. This includes one NMA bone marrow graft which failed to engraft and was subsequently salvaged by a NMA peripheral blood stem cell graft from the same donor. In addition we have recently completed one MA haplidentical transplant in a 60 year old man with very high risk leukemia. Patient accrual in CTN 0603 occurred rapidly. We believe that there could potentially be center based differences that could impact the outcome measures. Center based differences can result from both patient and system characteristics. Local transplant centers may attract higher risk patients due to their inability to travel to larger centers. In addition there may be logistical factors which interfere with donor collections that might result in delays in treatment. While direct comparisons between BMT 0603 and 0604 cannot be made, the haplo-marrow results look promising. BMT CTN 1101, a phase 3 randomized multicenter trial comparing dUCB to HLA-haploidentical related bone marrow is in development. Based on the results of this trial, HLA- haploidentical related bone marrow may become the preferred alternative donor source and may become a widely offered transplant option.

2. STUDY DESIGN

2.1. Study Overview

This is a single center Phase 2 study to assess our institution's outcomes in terms of safety and efficacy of haploidentical bone marrow transplantation (haplo-marrow) using a nonmyeloablative (NMA) or a myeloablative (MA)preparative regimen and post-transplant cyclophosphamide (Cy). The purpose is to determine if these transplants performed at UCSD would show similar outcomes to those published by the recent trials. If the results of this therapy are acceptable, we plan to offer this therapy as a routine option to patients who do not have a related sibling, matched unrelated donor, or cord option. We plan on following clinical parameters that are routinely gathered for all our transplant patients here as part of the CIBMTR/NMDP/NMDP data registry, which all patients undergoing transplantation here provide consent for separately and routinely. The only additional information that is not specifically gathered for CIBMTR/NMDP is time from unrelated donor search to Day 0.

2.2 Hypotheses and Specific Objectives

Hypotheses

Primary Hypothesis: This is a Phase 2 study assessing 180 day survival after MA and NMA haplo- marrow or peripheral blood stem cell transplantation. We hypothesize that we will have a 180 day survival of about 60% which is the benchmark for reduced intensity transplant outcome.[13]

Based on the data published by Solomon et al (16) we would expect the MA haploidentical peripheral blood stem cell grafts would fall within this benchmark as well.

Study objectives

The primary objective is to determine overall survival 180 days after transplantation involving MA or NMA conditioning, HLA-haploidentical marrow or peripheral blood graft, and post-transplant Cy. Secondary objectives include estimating overall and progression-free survival at 100 days, 180 days, and one year after transplantation, treatment-related mortality, incidence of neutrophil and platelet recovery or engraftment, incidence of graft failure, cumulative incidence of acute and chronic GVHD, incidence of infections, and cumulative incidence of relapse/progression. We will also examine the amount of time to transplant (day of unrelated search initiation to day 0).

2.3 Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible to enroll on this study:

1. Age: Subjects 18-75 years old.
2. Donor must be ≥ 18 years of age.
3. HLA typing will be performed at high resolution (allele level) for the HLA-A, -B, Cw, DRB1, and –DQB1 loci. A minimum match of 5/10 is required.

   With high resolution typing, the donor and recipient must be identical at a minimum of at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. Meeting this criterion will be considered sufficient evidence that the donor and recipient share one HLA haplotype, and typing of additional family members is not required.
4. Acute Leukemias.
   - Acute Lymphoblastic Leukemia in high risk CR1 as defined by at least one of the following:
     - Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), MLL rearrangements,
     - White blood cell counts of greater than 30,000 wbc/μL,
     - Patients over 30 years of age, or
     - Time to Complete Remission was greater than 4 weeks.
   - Acute Myelogeneous Leukemia in high risk CR1 as defined by at least one of the following:
     - Greater than 1 cycle of induction therapy required to achieve remission,
     - Preceding myelodysplastic syndrome (MDS),
     - Secondary leukemia (history of chemotherapy or radiation treatment as precursor to development of leukemia),
     - Presence of Flt3 internal tandem duplication (ITD),
     - FAB M6 or M7 leukemia, or
     - Adverse cytogenetics for overall survival such as
       - those associated with MDS
       - Complex karyotype (≥ 3 abnormalities)
       - Any of the following: inv(3) or t(3;3), t(6;9), t(6;11), + 8 [alone or with other abnormalities except for t(8;21), t(9;11), inv(16) or t(16;16)], t(11;19)(q23;p13.1)
   - Acute Leukemias in 2nd or subsequent CR (see remission definition in Chapter 3).
   - Biphenotypic/Undifferentiated Leukemias in 1st or subsequent CR.

5. Myelosdysplastic Syndrome

6. Burkitt's lymphoma: second or subsequent CR.

7. Blastic plasmacytoid dendritic cell neoplasm

8. Lymphoma that is: chemotherapy-sensitive (complete or partial response; see response criteria in Chapter 3) aggressive lymphoma or Hodgkin's lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are ineligible for an autologous transplant. They may have received prior autologous transplant if greater than three months prior to enrollment.

or

Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).

9. Multiple myeloma

10. Patients with adequate organ function as measured by:

- Cardiac: Left ventricular ejection fraction at rest must be ≥ 40%,
- Hepatic: Bilirubin, ALT, AST ≤ twice the upper limits of normal and Alkaline Phosphatase < 5 x ULN.
- Renal: 24 hour creatinine clearance ≥40 mL/min
- Pulmonary: FEV_1 ,of ≥ 50% of predicted and , DLCO (diffusion capacity)≥ 40% of predicted. If unable to perform pulmonary function tests, then O_2 saturation > 92% on room air.

11. Performance status: Karnofsky score 70-100%.

2.4 Patient Exclusion Criteria

Patients fulfilling the following criteria are ineligible for this study:

1. Autologous hematopoietic stem cell transplant < 3 months prior to enrollment.
2. Pregnancy or breast-feeding.
3. Evidence of HIV infection or known HIV positive serology.
4. Current uncontrolled bacterial, viral or fungal infection (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).
5. Prior allogeneic hematopoietic stem cell transplant.
6. Patients with a history of primary idiopathic myelofibrosis.

2.5 Donor Inclusion Criteria

1. Donors must be HLA-haploidentical first-degree relatives of the patient. Eligible donors include biological parents, siblings, children, or half-siblings.
2. Age ≥ 18 years.
3. Donors must meet the selection criteria as defined by the Foundation for the Accreditation of Cell Therapy (FACT) and will be screened per the American Association of Blood Banks (AABB) guidelines.
4. Donors must be willing and able to donate bone marrow product or peripheral blood stem cells.

2.6 Donor Exclusion Criteria

1. A donor is excluded if the recipient has anti-donor HLA antibody. This is because of a concern for engraftment failure.

2.7 Donor Prioritization Schema

Also see Appendix C, Guidelines for Donor Typing and Selection.

In the event that two or more eligible donors are identified, the following order of priority:

1. For CMV seronegative recipients, a CMV seronegative donor
2. Red blood cell compatibility
   a. RBC cross-match compatible
   b. Minor ABO incompatibility
   c. Major ABO incompatibility

2.8 Treatment Plan

Non-Myeloablative Treatment Plan:

Day –6, -5	Fludarabine 30 mg/M^2 IV over 30-60 minutes Cyclophosphamide 14.5 mg/kg IV over 1-2 hours*
Day –4→-2	Fludarabine 30 mg/M^2 IV over 30-60 minutes
Day –1	TBI 200 cGy
Day 0	T cell replete BMT or T cell replete peripheral blood stem cell infusion
Days +3,+4	Cyclophosphamide 50 mg/kg IV Mesna 40 mg/kg IV
Day +5	Begin tacrolimus, mycophenolate mofetil, and G-CSF

*Uroprophylaxis per institutional standard-see Section 2.5.3

Myeloablative Treatment Plan:

Day -7	Busulfan 110 mg/m2/d
Day –6, -5, -4	Fludarabine 25 mg/M^2 IV over 30-60 minutes Busulfan 110 mg/m2/d
Day -3 and -2	Fludarabine 25 mg/M^2 IV over 30-60 minutes Cyclophosphamide 14.5 mg/kg IV over 1-2 hours*
Day 0	T cell replete PBSC
Days 3,4	Cyclophopshamide 50 mg/kg IV Mesna 40 mg/kg IV
Day 5	Begin tacrolimus, mycophenolate mofetil, and G-CSF

*Uroprophylaxis per institutional preference (see 2.5.3 below)

2.8.1 Indwelling Central Venous Catheter

Placement of a double lumen central venous catheter will be required for administration of IV medications and transfusion of blood products.

2.8.2 Fludarabine

A. NMA Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2.

For decreased creatinine clearance (< 61 mL/min) determined by the Cockcroft Formula:

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (IBW) (kg)}}{P_{Cr} \times 72} \times 0.85 \text{ (for women)}$$

C_{Cr} 46-60 mL/min, fludarabine = 24 mg/m^2
C_{Cr} 40-45 mL/min, fludarabine = 22.5 mg/m^2

B.MA Fludarabine 25 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2.

For decreased creatinine clearance (< 61 mL/min) determined by the Cockcroft Formula:

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (IBW) (kg)}}{P_{Cr} \times 72} \times 0.85 \text{ (for women)}$$

Fludarabine dosage should be reduced as follows:

C_{Cr} 46-60 mL/min, fludarabine = 20 mg/m^2
C_{Cr} 40-45 mL/min, fludarabine = 18.75 mg/m^2

2.8.3 Pre-transplantation Cyclophosphamide

A. NMA: Cy 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion with a high volume fluid flush on Days –6 and –5. Cy will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see below for formulas).

Mesna will be given as uroprophylaxis according to our institutional practice:

Mesna 11.6 mg/kg/day (80% of Cy dose) given as a continuous infusion beginning 30 minutes prior to Cy administration. Total volume of 500 mL volume to be run at 22 mL/hour x 24 hours daily with each dose of Cy.

B. MA: Cy 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion with a high volume fluid flush on Days –3 and –2. Cy will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see below for formulas). Mesna will be given in the following manner:_____

Mesna will be given as uroprophylaxis according to our institutional practice:

Mesna 11.6 mg/kg/day (80% of Cy dose) given as a continuous infusion beginning 30 minutes prior to Cy administration. Total volume of 500 mL volume to be run at 22 mL/hour x 24 hours daily with each dose of Cy.

2.8.4 Busulfan

MA: Busulfan

Give on days -7,-6,-5,-4

-Avoid acetaminophen 72 hours prior to and 72 hours after the administration of Busulfan.

Use Ideal or Actual body weight, whichever is lower. For obese or severely obese patients (25% above Ideal body weight), an Adjusted "Ideal" Body

Dose is 110 mg/m2 administered in saline with final concentration approximately 0.5 mg/ml. Infuse over 2 hours

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 Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.8.5 Total Body Irradiation

NMA: Total body irradiation in the NMA conditioning : 200 cGy will be administered in a single fraction on Day −1.

Patients undergoing MA conditioning will not receive TBI

2.8.6 Bone marrow and peripheral blood stem cell transplantation

On Day 0, patients will receive unprocessed marrow or peripheral blood stem cells unless there is a major ABO incompatibility, in which case red blood cell depletion will be performed. Minor ABO incompatibilities will be processed per our institutional standards in conjunction with the blood bank consultation. Donor bone marrow will be harvested with a target yield of 4 x 10^8 total nucleated cells (TNC)/kg recipient IBW. A sample of the product to be infused will be sent for flow cytometry to determine the content of $CD34^+$ $CD3^+$, $CD4^+$, and $CD8^+$ cells. This is done routinely. Donor peripheral blood stem cells shall be collected and the total infused CD34 count will be capped at 5x10^6 CD34/kg.

Marrow collection will be performed per UCSD policy/standard of operation (SOP) [BMTP-22.5]. At UCSD and other transplant programs, the standard marrow cell dose target is 4 x 10^8 TNC/kg of recipient body weight. This target is standard for all our bone marrow transplants. There has not been an established absolute minimum number of cells needed for engraftment of marrow. As per UCSD standard practice, the bone marrow donor is usually harvested the day of planned infusion. However, there may be rare instances due to donor factors (such as availability) that the treating physician may elect to harvest the donor on a different day. In this case the marrow may be cryopreserved and handled according to UCSD stem cell processing laboratory (SCPL) SOPs.

For the bone marrow grafts there is not a maximum amount of TNC/kg to be infused. Per UCSD standards, there is a maximum amount of marrow product that can be collected from the donor for safety reasons (maximum 20 mL/kg donor weight). The stem cell processing laboratory (SCPL) will calculate a mid-run TNC (done approximately once half of the maximum marrow volume has been collected). The mid-run will then be used to calculate how much more volume needs to be collected to meet the target (again not exceeding a maximum volume of 20mL/kg donor weight).

UCSD marrow processing and storage will be performed per UCSD policy/SOP set forth by the SCLP (SCPL-0515, SCPL-0523, SCPL-0528, SCPL-0529). Marrow product is intended to be infused “fresh,” i.e. non-cyropreserved. It may be red cell depleted or plasma depleted depending upon ABO compatibility and with blood bank consultation. As mentioned, in rare cases, it may be cryopreserved if the harvest is done prior to day of planned infusion.

Peripheral blood stem cell collection will be performed per UCSD policy/standard operation . The peripheral blood stem cell target is 5 million per kg recipient weight

2.8.7 Post-transplantation Cyclophosphamide with Mesna

Hydration prior to Cy will be given in the following manner: A minimum of one liter normal saline will be given to patients the night prior to cyclophosphamide administration. The rate is at the inpatient team's discretion. Two hours prior to the start of cyclophosphamide, hydration with normal saline at 3 ml/kg/hr IV will begin. One hour prior to cyclophosphamide, the rate will be reduced to 2 ml/kg/hr and continued for 8 hours post-cyclophosphamide. Maximum rate will not exceed 200 mL/hr.

Mesna uroprophylaxis will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide. Mesna dose will be based on the Cy dose being given. The total daily dose of mesna is equal to 80% of the total daily dose of Cy.

Cy [50mg/kg IBW] will be given on Day 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cy will be given as an IV infusion over 1-2 hours (depending on volume).

It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids as anti-emetics.

2.8.8 Tacrolimus

Tacrolimus will be given at a dose of 1 mg IV continuous infusion daily. Tacrolimus begins on Day + 5. Dosing will be changed to oral dosing schedule once a therapeutic level is achieved and oral medications are well tolerated. Serum levels of tacrolimus will be measured around Day 7 and then checked weekly. The dose will be adjusted to maintain a level of 5-10 ng/mL. Tacrolimus will be discontinued around Day 180 but may be continued if active GVHD is present. Cyclosporine (target concentration 200-400 ng/ml) may be substituted for tacrolimus if the patient is intolerant of tacrolimus.

2.8.9 Mycophenolate Mofetil (MMF)

MMF will be given at a dose of 15 mg/kg PO TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 gram PO TID). MMF prophylaxis begins Day+ 5 and will be discontinued after the last dose on Day +35 but may be continued if active GVHD is present.

2.8.10 Supportive Care

Patients will receive transfusions, infection prophylaxis and nutritional support according to our institutional standards. Infection prophylaxis includes, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to prevent herpes simplex, cytomegalovirus (CMV), Pneumocystis carinii, and fungal infections.

2.8.11 Transfusion Support

Platelet and packed red cell transfusions will be given per current institutional standards.

2.8.12 Anti-Ovulatory Treatment

Menstruating females should be started on an anti-ovulatory agent prior to the initiation of the preparative regimen.

2.8.13 Post-transplant Evaluation

Patients will be followed by their transplant physician as per our institutional standards. Immediately post-transplant, they are followed out through a minimum of day 100 (if patient referred from outside institution) or longer if transplant related issues arise. Additional follow-up at 6 months and 1 year after transplantation is performed here if patient is from an outside institution.

2.9 Risks and Toxicities

Cyclophosphamide:

- Cyclophosphamide side effects include: nausea/vomiting, cardiomyopathy, skin rash, mucositis, stomatitis, sterility, diarrhea, hemorrhagic cystitis, fluid weight gain/edema, alopecia and cytopenias.

Fludarabine:

- Neurotoxicity: Agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy or weakness has been reported. Severe neurologic effects, including blindness, coma, and death are seen in 36% of patients treated with doses approximately four times greater than recommended; severe CNS toxicity is rarely seen with doses in the recommended range for nontransplant therapy of hematologic malignancies. Effect of chronic use on the CNS is unknown, although patients have received recommended doses for up to 15 courses. The dose used in this study is approximately 1.5 times the usual one-course dose given in non-transplant settings. Doses and schedules such as those used in this study have been used in adult and pediatric patients and increased neurotoxicity has not been observed.

- Anemia: Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported after one or more cycles of therapy in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission; no mechanisms for development of this complication have been identified. Corticosteroids may or may not be effective in controlling these episodes. The majority of patients re-challenged developed a recurrence of the hemolytic process.

- Cardiovascular: Deep venous thrombosis, phlebitis, transient ischemic attack, and aneurysm (1%) are reported.

- Fever: 60% of patients develop fever.

- Skin Rash: 15% of patients develop a skin rash, which may be pruritic.

- Digestive: Gastrointestinal side effects include: nausea/vomiting (36%), diarrhea (15%), stomatitis (9%), anorexia (7%), GI bleeding and esophagitis (3%), mucositis (2%), liver failure, abnormal liver function test, constipation, dysphagia (1%) and mouth sores.

- Some other effects are: Chills (11%), peripheral edema (8%), myalgia (4%), osteoporosis (2%), pancytopenia, arthralgia (1%), dysuria (4%), urinary tract infection and hematuria (2%); renal failure, abnormal renal function test, and proteinuria (1%); and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

- Late effects may include secondary malignancy.

Total Body Irradiation:

- TBI can cause: nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema, hyperpigmentation, fever, mucositis, and alopecia.

- Late effects include: possible growth retardation, vertebral deformities, cataracts, probable increased risk of secondary malignant neoplasms, sterility, nephropathy, interstitial pneumonitis and veno-occlusive disease.

Busulfan:

- Hematologic: Pancytopenia
- Hepatic and Gastrointestinal: moderately emetogenic and require antiemetic therapy; mild to moderate nausea and vomiting occurred in 92% and 95% of patients, respectively, during high-dose clinical trials; nausea was severe in 7% of patients. Severe stomatitis (26%), esophagitis (2%), diarrhea (75%, severe 5%), constipation (38%),

dyspepsia (44%), hematemesis (2%), pancreatitis (2%), rectal discomfort (24%), and anorexia (mild/moderate 64%, severe 21%) Hepatic veno-occlusive disease (VOD) has been reported in patients receiving busulfan, usually in combination with cyclophosphamide or other agents prior to bone marrow transplantation. Busulfan-induced hepatic VOD has been associated with high AUC values (> 1500 micro-mol•min/L) of busulfan. VOD 8-12% incidence with iv Busulfan . A reduced incidence of hepatic VOD and other regimen-related toxicities have been observed in patients treated with high-dose oral busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for > 24 hours after the last dose of busulfan.

- Hyperbilirubinemia occurred in 49% with grade 3/4 hyperbilirubinemia occurred in 30% of patients within 28 days of transplantation and was considered life-threatening in 5% of these patients. Hyperbilirubinemia was associated with graft-versus-host disease in 6 patients and the hepatic veno-occlusive disease in 5 patients. Elevated hepatic enzymes including grade 3/4 SGPT elevations (7%), mild to moderate alkaline phosphatase increases (15%), and mild to moderate jaundice (12%) were also reported in patients following high-dose therapy.

- Pulmonary: Interstitial pulmonary fibrosis is rare but potentially fatal complication. Symptoms have been reported to occur within 8 months to 10 years after the initiation of therapy; the average onset is within 4 years of busulfan therapy. Most patients die within 6 months of diagnosis. Mild or moderate dyspnea in 25% (severe 2%) of patients and hyperventilation in 5% of patients. Alveolar hemorrhage (5%), rhinitis (44%), cough (28%), epistaxis (25%), pharyngitis (18%), hiccups (18%), asthma (8%), atelectasis (2%), pleural effusion (3%), hypoxia (2%), hemoptysis (3%), and sinusitis (3%).
- Skin hyperpigmentation (5—10%), nail discoloration, urticaria, erythema multiforme, alopecia, porphyria cutanea tarda, excessive dry skin (xerosis) and skin fragility with anhidrosis, rash (unspecified) (57%), pruritus (28%), alopecia (17%), vesicular rash (10%), maculopapular rash (8%), vesicular-bullous rash (10%), exfoliative dermatitis (5%), erythema nodosum (2%), acne/acneiform rash (7%),
- Cataracts, corneal thinning and lens changes
- Cardiac: mild to moderate sinus tachycardia (44%), arrhythmias (unspecified) (5%), atrial fibrillation (2%), ventricular extrasystoles (2%), third degree heart block (2%), hypertension (36%, grade 3/4 7%), hypotension (11%, grade 3/4 3%), flushing/hot flashes (25%), cardiomegaly (5%), mild ECG abnormalities (2%), and grade 3/4 left-sided heart failure in one patient (2%).
- Gonadal suppression, atrophy of the testis, azoospermia, and gynecomastia has been reported in male patients receiving busulfan. Amenorrhea, anovulation, ovarian suppression, and ovarian failure including failure to reach puberty may occur in premenopausal women treated with busulfan. Fertility and normal menses may return; however, infertility may be permanent following busulfan therapy. Teratogenesis and fetal death may occur, which may occur even after busulfan therapy is completed. Busulfan-induced fetal malformations and anomalies include significant alterations in the musculoskeletal system, body weight gain, and size. In animals, busulfan produced

sterility in both male and female offspring due to the absence of germinal cells in the testes and ovaries; germinal cell aplasia or sterility in offspring of mothers receiving busulfan during pregnancy has not been reported in humans.

- Secondary malignancy, including acute myeloid leukemia and malignant tumors, within 5—8 years of chronic oral busulfan therapy. Busulfan may cause cellular dysplasia in many organs including lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs and bone marrow. This cytologic dysplasia may be severe enough to interfere with interpretation of exfoliative cytologic examinations of the lungs, bladder, breast, and uterine cervix. In addition, chromosomal aberrations have been reported in cells from patients receiving busulfan.
- Generalized complaints: headache (64%, severe 5%), abdominal pain (69%, severe 3%), asthenia/weakness (49%, severe 2%), unspecified pain (43%, severe 2%), injection site reaction (inflammation 25%, pain 15%), allergic reactions including anaphylactoid reactions (26%), chest pain (unspecified) (26%), arthralgia (13%), and ear disorder (3%).
- Seizures may occur during high-dose busulfan therapy. Prophylactic anticonvulsant therapy, usually with phenytoin, is recommended. Patients with a history of seizures, head trauma or who are taking medication which may decrease the seizure threshold may be at increased risk. Insomnia (84%), anxiety (75%), dizziness (30%), depression (23%), confusion (11%), hallucinations (5%), lethargy (7%), delirium (2%), agitation (2%), and encephalopathy (2%).
- The solvent used in the busulfan intravenous formulation, dimethylacetamide (DMA), has been associated with neurologic effects, including hallucinations, and hepatic toxicity.

Mycophenolate Mofetil:

- Side effects include: pancytopenia, nausea, vomiting, diarrhea, hypertension, headache, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, and leg cramps/bone pain.

Tacrolimus:

- Side effects include: reversible renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, and neurologic toxicity.

Graft Failure:

- Based on historical data, there is a 5-15% chance of graft failure with the NMA regimens. Recovery of autologous hematopoiesis occurred in 14 out of 16 patients experiencing graft failure in the original Johns Hopkins/Seattle trial. In the more recent BMT CTN 0603 trial, primary graft failure occurred in 1/50 patients. In that patient, no second transplant was done and the patient died at day +67. No cases of secondary graft failure were reported. There were no cases of graft failure reported with the MA preparative regimen and peripheral blood stem cell transplant. The risk of graft failure is known to be higher after bone marrow grafts as opposed to stem cells grafts. In the experience so far at UCSD, of the 3 patients transplanted one patient had primary engraftment failure following a NMA bone marrow graft. This was felt to be related by the low total nucleated cells infused due to a collection that was limited by the donor size. This patient was subsequently able to undergo salvage with the same donor using peripheral blood stem cells.

2.10 Growth Factor Support

G-CSF will be given beginning on Day 5 at a dose of 5 mcg/kg/day (rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is $\geq 1{,}000/mm^3$ for three consecutive days. G-CSF may be given by IV or subcutaneously.

2.11 Management of Slow Engraftment and Graft Failure

Slow engraftment or graft failure shall be managed according per physician preference, and may include the administration of colony stimulating factors and prophylactic antibiotics.
If the recipient is eligible for both an ablative and a nonmyeloablative transplant the treating physician will ultimately make a decision regarding using the ablative versus nonmyeloablative preparative regimens as described above. This decision is generally based upon the underlying diagnosis , the age of the patient, and the comorbidities. If the stem cell donor is able to donate either stem cells or bone marrow the decision to use peripheral blood stem cells versus bone marrow collection will be based upon the logistics of coordinating the bone marrow collection (avoiding extended delays in treatment) , the preference of the treating physician, and the donor preference. At UCSD there are frequently logistical constraints that result in delay of adequate operating room time which can result in delay of transplant.

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is overall survival at 180 days from the time of transplantation.

3.2 Secondary Endpoints

- Neutrophil Recovery

Neutrophil recovery is defined as achieving an ANC $\geq 500/mm^3$ for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil recovery. The only competing event for neutrophil recovery is death without neutrophil recovery.

- Primary graft failure

Primary graft failure is defined as < 5% donor chimerism on all measurements.

- Secondary graft failure

Secondary graft failure is defined as initial recovery followed by neutropenia with < 5% donor chimerism. If no chimerism assays were performed and ANC is $< 500/mm^3$, then it will be counted as a secondary graft failure.

- Platelet recovery

Platelet recovery is defined by two different metrics. It will be counted as the first day of a sustained platelet count $>20,000/mm^3$ or $>50,000/mm^3$ with no platelet transfusions in the preceding seven days. The first day of the sustained platelet count will be designated the day of platelet engraftment.

- Donor Cell Engraftment

Donor cell engraftment is defined as donor chimerism ≥ 5% on Day ≥ 56 after transplantation. Chimerism should be evaluated on Days ~28, ~56, ~180, and ~365 after transplantation. Chimerism may be evaluated in whole blood or mononuclear fraction.

- Acute Graft-versus-Host Disease

The cumulative incidences of grade II – IV and III – IV acute GVHD will be determined. Acute GVHD will be graded as shown below. This is already standard practice for patients at UCSD.

The time to onset of acute grades II-IV GVHD and grades III-IV GVHD will be recorded, as well as the maximum grade achieved.

Stages of Acute GVHD: Individual Organ

Stage	Skin % BSA (rules of 9s)	Liver (bilirubin)	Gut (stool volume, mL)
0	0	<2	≤500
1	<25	2-3	>500*
2	25-50	3.1-6	>1000
3	>50	6.1-15	>1500
4	Bullae	≥15	>2000(**)

*or persistent anorexia, nausea, vomiting
**or severe abdominal pain with or without ileus
Glucksberg et al. Transplantation 1974; 18:295.

Consensus Grading (modified Glucksberg)

Grade	Skin Stage	Liver Stage	Gut Stage
I	1-2	none	none
II	3	1	1
III	--	2-3	2-4
IV	4	4	4

- Chronic Graft-versus-Host Disease

Chronic GVHD will be scored in the historical manner. This is already standard for all UCSD transplant patients. The time to onset of limited and extensive chronic GVHD will be recorded. Given the short duration of this study, cGVHD data is being documented for purposes of our participation in CIBMTR/NMDP.

Chronic GVHD Grading

Limited: localized skin involvement and/or evidence of hepatic dysfunction

Extensive:
-generalized skin involvement or
-localized skin involvement or hepatic dysfunction plus at least one of the following:

- liver histology showing chronic progressive hepatitis, bridging necrosis, cirrhosis
- eye involvement (Schirmer's test with <5 mm wetting)
- minor salivary gland or oral mucosa involvement (on labial or mucosal biopsy specimen)
- involvement of any other target system

- Progression-free Survival

Progression-free survival is defined as the minimum time interval of the time to relapse, recurrence, death, or last follow-up.

- Treatment-Related Mortality (TRM)

The cumulative incidence of TRM will be estimated at Day 100, 180, and at 1 year. An event for this endpoint is death without evidence of disease progression. Documented disease progression is a competing risk.

- Infections

Infections will be reported by anatomic site, date of onset, organism and resolution, if any. Patients will be followed for infection for 1 year post-transplant.

- Time from initiation of unrelated donor search to Day 0.

- Relapse and Residual Disease

Relapse of Malignancy – Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is

defined by either morphological or cytogenetic evidence of acute leukemia consistent with pre-transplant features, or radiologic evidence (including the recurrence of fluoro-deoxyglucose [FDG]-avid lesions on PET scan) of progressive lymphoma. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Minimal Residual Disease – Minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot, or Western blot, or polymerase chain reaction (PCR), or other techniques, in absence of morphological or cytogenetic evidence of disease in blood or marrow. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease will not be sufficient to meet the definition of relapse in the context of this study. Data on tapering immunosuppression, administering chemotherapy or biological agents to in response to detection of minimal residual disease will be captured in the case report forms.

Acute Leukemia – Relapse will be diagnosed when there is:

1. The reappearance of leukemia blast cells in the peripheral blood; or,
2. > 5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration); or
3. The appearance of new dysplastic changes within the bone marrow; or,
4. The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

Lymphoma – Relapse will be diagnosed when there is:

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the sum of the product diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<.1.5 cm in its long axis by CT).

TABLE 3.2 RESPONSE CRITERIA FOR LYMPHOMA

Table 2. Response Definitions for Clinical Trials

sponse	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
ed disease PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

lations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, the product of the diameters; SD, stable disease; PD, progressive disease.

From Cheson, B.D. et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 5:579-586, 2007.

Acute Leukemia - Remission is defined as < 5% blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in a bone marrow with > 20% cellularity, peripheral blood counts showing ANC >1000/µl, including patients in CRp.

4. PATIENT ENROLLMENT AND EVALUATION

Enrollment Procedures

Screening and Eligibility Procedures

Patients who have an indication for an allogeneic transplant but no suitable unrelated donor, matched related donor or cord blood option will be screened for this study. Review for eligibility will be done by treating physician (all transplant physicians at UCSD will be sub-investigators). If treating physician unavailable, then review will be performed by the PI.

Patients will be registered using the standard procedures currently used for all patients transplanted at UCSD. This includes pre-registration with CIBMTR/NMDP/NMDP, documentation of disease status and classification, comorbidities, prior treatment, and donor characteristics.

Study Monitoring

Follow-up Schedule:
Currently at UCSD Medical Center patients are hospitalized from the beginning of the preparative regimen through neutrophil engraftment. After discharge patients will be seen weekly by a medical provider until day 60 post transplant then as dictated by physician preference and institutional practices. Data will be collected from clinical assessments around day 30, day 100, day 180, and 1 year post transplant. This is standard institutional practice.

Reporting Patient Deaths**:**
Patient deaths will be reported to CIBMTR/NMDP per our standard reporting procedures for allogeneic and autologous transplant. This is not for the purpose of the study. Otherwise, deaths are already automatically reported to our group.

CIBMTR/NMDP Data Reporting**:**
As a Center for International Blood and Marrow Transplant Research/National Marrow Donor Program (CIBMTR/NMDP) participating transplant center, we are required to pre-register all transplant recipients with the CIBMTR/NMDP. This is done with patient consent through a different consent form. In addition, we will complete the CIBMTR/NMDP Day 100 Report Form (including the Core Form and Graft Inserts) and Core Follow-up Forms at 6 months then at one year CIBMTR/NMDP forms will be submitted directly to the CIBMTR/NMDP at the times specified on the Form Submission Schedule; The endpoints of this study are already being collected for CIBMTR/NMDP and automatically entered into our own CIBMTR/NMDP database registry. We will be creating a separate file within the standing secured database to group these patients together. The only additional piece of data is time to transplant. This will be added to the UCSD portion of the registry for these patients.

Weekly GVHD Monitoring:
GVHD will be monitored in accordance with CIBMTR/NMDP guidelines. . Patients should be assessed weekly until Day 100 post-transplant for GVHD. After Day 100 patients will be assessed at each follow-up visit (Day 180, 365) for the presence of GVHD.

Adverse Event Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP

home page (http://ctep.cancer.gov). The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

Definitions
An **adverse event** (AE) is any symptom, sign, illness or experience, regardless of causality, that develops or worsens in severity during the course of the study.

Attribution:

- Not related - The adverse event is most likely related to other factors such as the patient's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the patient.

- Related – There is a reasonable possibility that the study drug caused or exacerbated the adverse event, ie, there is evidence to suggest a causal relationship between the study treatment and the adverse event.

An unexpected adverse event is defined as any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review (typically the protocol, investigator's brochure and prescribing information) nor mentioned in the consent form.

Adverse Event Documentation
Adverse events as specified above occurring after the initiation of the study treatment (day -5) through day 30 must be documented and reported on patient CRFs. Given the high volume of transplant-related adverse events and laboratory abnormalities expected in this population, hematologic and other non-clinically significant laboratory abnormalities and expected grade 1-3 adverse events assessed by the investigator as related to the transplant procedure will not be captured. Organ toxicity reporting required by the NMDP/CIBMTR will be reported on the NMDP/CIBMTR report forms.

It is expected that all patients who undergo the transplant procedure experience depression of their blood counts. Therefore, hematological lab results of this nature will not be reported as adverse events. Further to this, abnormal laboratory results deemed not to be clinically significant but for which the patient is receiving treatment will not be reported as adverse events, per investigator judgment.

Thus, given the high number of transplant-related adverse events in the patient population being studied, adverse events will be reported on patient CRFs using the following guidelines:

All grades 4-5 AEs through day 30, excluding hematologic lab abnormalities and other laboratory results deemed by the investigator not to be clinically significant, will be reported on the case report forms.
All documented infections through day 100 will be reported
All GVHD through day 100 will be reported

All UPRs through day 100 will be reported

UPR Reporting and Follow-up

Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that researchers promptly report "any unanticipated problems involving risk to subjects or others" (UPIRTSOs). http://irb.ucsd.edu/Factsheet_UPR_120208.pdf

As soon as an investigator or study personnel becomes aware of an adverse event which meets the definition of a UPR this should be reported by phone, fax or email to the extent that information is available to the BMT Clinical Trials Office at 858-822-6387/6397/6396/6382. And reported per UCSD IRB SOPs.

PI Responsibilities

The PI is required to review all unanticipated problems, serious adverse events, and all deaths associated with the protocol and provide an unbiased written report of the event.
At the minimum the PI should comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship
to participation in the study. UPRs should be promptly reported to the UCSD IRB.

Patient Assessments

Table 4.2.3 summarizes patient clinical assessments over the course of the study.

Pre-transplant evaluations

The following observations are considered standard evaluations for transplant eligibility and should be determined < 4 weeks before initiation of conditioning therapy, unless otherwise noted. This evaluation is standard practice for potential transplant patients.

1. History, physical examination, height and weight.
2. Karnofsky performance status.
3. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST. Urine for 24 hour creatinine clearance. Serum beta HCG test for females of child bearing potential.
4. CMV antibody test, hepatitis panel (HepA Ab, HepB sAb, HepB SAg, HepB Core Ab, HepC Ab), syphilis, herpes simplex virus, varicella zoster virus, HIV and HTLV1 I/II antibody.
5. HLA typing, if not already performed.
6. EKG, < 6 weeks before initiation of conditioning therapy.

7. Transthoracic echocardiogram to evaluate left ventricular ejection fraction or shortening fraction, < 6 weeks before initiation of conditioning therapy.
8. Pulmonary function testing to evaluate DLCO, FEV1, and FVC or O_2 saturation. < 6 weeks before initiation of conditioning therapy.
9. Bone marrow aspirates for pathology and cytogenetics and/or biopsy.
10. β-HCG serum pregnancy test for females of childbearing potential.
11. Chest imaging (Chest X-Ray or Chest CT) as clinically indicated.
12. Lymphomas (large/aggressive cell, B- cell, and Hodgkin): Whole Body PET/CT as clinically indicated.

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. GVHD evaluation and grading to be in keeping with CIBMTR/NMDP reporting.
2. CBC at least three times a week from Day 0 until ANC > 500 mm^3 for 3 days after nadir reached. Thereafter CBC at a minimum of twice per week until Day 28, then weekly until 12 weeks, then at six months, one year post-transplant.
3. Creatinine, bilirubin, alkaline phosphatase, ALT, AST, at least twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, and then at six months, one year years post-transplant.
4. Heparinized blood on Day ~28, ~56, ~180, and ~365 for post-transplant chimerism assay.
5. Immunizations will be given per institutional guidelines.
6. Toxicity assessments at Days ~ 28, ~56, ~180 s, and ~365.
7. Disease status evaluation required within 100 days of transplant (may be done from day 80-120) and at ~1 year. Testing to determine disease status should follow pre-transplant evaluation process.

TABLE 4.2.3: SUMMARY OF PATIENT CLINICAL ASSESSMENTS

Study Assessments/ Testing	Baseline	Days after Transplantation										
		7	14	21	28	35	42	49	56	100	180	365
History, physical exam, weight, height, and Karnofsky/Lansky performance status	X	X	X	X	X	X	X	X		X	X	X
CBC[1], differential, platelet count, and blood chemistries[2]	X	X	X	X	X	X	X	X		X	X	X
Infectious disease titers[3]	X											
EKG, LVEF, or shortening fraction	X											
DLCO, FEV1 and FEV or O_2 saturation	X											
Bone marrow aspirate for pathology and cytogenetics and/or biopsy[4]	X[4]									X[4]	X[4]	X[4]
Chest X-ray	X											
ß-HCG serum pregnancy test (females only)	X											
GVHD and other morbidity assessments[5]		X	X	X	X	X	X	X		X	X	X
Toxicity assessments	X				X					X	X	X
Chimerism[6]	X				X				X		X	X

Notes:

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

[2] Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly until Day 28. Blood chemistries performed weekly after Day 28 until 12 weeks post-transplant.

[3] Infectious disease titers include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, varicella zoster virus, syphilis, HIV and HTLV I/II antibody.

[4] LEUKEMIA PATIENTS ONLY. Bone marrow biopsy and aspirates to pathology and aspirate for cytogenetics. Flow cytometry required on aspirate. Day 21 bone marrow aspirate only if WBC < 500.

[5] GVHD and other morbidity assessments performed weekly until Day 100 post-transplant, and then at Day 180 and 365.

6 Chimerism will be measured by RFLP or microsatellite analysis of a peripheral whole blood sample..

5. STATISTICAL CONSIDERATIONS

5.1 Study Design

The study is a Phase 2 single center study designed to assess our outcomes in the context of previously published outcomes in haplo-identical transplant. It is designed to assess overall survival 180 days after peripheral blood stem cell or bone marrow transplantation using a myeloablative or nonmyeloablative preparative regimen and post-transplantation Cy using a partially HLA-mismatched first-degree relative (parent, sibling, or child) as a donor. Patients with acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, marginal zone B-cell lymphoma, follicular lymphoma, and chemotherapy-sensitive Burkitt, large-cell/aggressive lymphoma, and Hodgkin lymphoma are eligible.

5.2 Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age.

5.3 Study Duration

Patients will be followed by UCSD as per CIBMTR/NMDP guidelines for transplant patients. Patient data and monitoring for the purposes of this study will continue for 1 year.

5.4 Randomization

There is no randomization in this trial.

5.5 Primary Objective

The primary endpoint is the proportion of patients who survive for 180 days after transplantation, the same primary endpoint as in the BMT CTN 0603 trial as well as in a larger published study for reduced intensity transplant (RIC) of unrelated donors.[13] The primary analysis will include all transplanted patients.

5.6 Sample Size and Power Considerations

15 patients will be enrolled in total. We determined the sample size based on a Simon's two-stage design[14.] In the BMT CTN 0603 trial overall survival at 180 days was 84% with 95% CI 70% - 92%[11]. We hypothesize that the proportion of OS at day +180 in this study would be similar to that. We will test the null hypothesis H_0: $p \leq 60\%$ against the alternative hypothesis H_1: $p > 60\%$, where p is the overall survival proportion at day +180. Of note, 60% was the survival rate at 180-day reported after RIC adult unrelated donor transplantation[13]. The proposed two stage design will have 80% power to reject the null and conclude that the true rate is above 60%, if the true rate is ≥85%, at 10% significance level. (The calculation was carried out using PASS 2008.)

The study design can be described in detail as follows:

Stage 1: Seven patients will be accrued; accrual will be held up until the overall survival at day +180 for all 7 patients are known. The trial will be terminated at Stage 1 if ≤4 of the 7 patients have survived at day +180; otherwise it continues to Stage 2.

Stage 2: Eight more patients will be accrued. We will reject the therapy if the number of total 15 (=7+8) patients who have survived at day +180 is ≤11.

Interim analysis and early stopping: The interim analysis will be conducted as soon as the first 7 patients have been accrued and are evaluable for the primary endpoint. If ≤4 subjects have survived at day +180, the trial will be stopped early for lack of efficacy. Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 58%.

Final analysis: If the study continues, after all 15 subjects are evaluable the study data set will be locked. Out of the total of 15 subjects, if the number of subjects who have survived at day +180 is 12 or more, the conclusion will be that the trial has demonstrated a statistically significant improvement in survival against 60% at 6 months. The point estimation and 95% confidence interval for the OS proportion at 6 months will be estimated based on the method described in Koyama T., Chen H. Proper inference from Simon's two-stage designs. Statistics in Medicine 2008; 27: 3145-54.[15]

5.7 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, HLA match, disease type and stage, remission status and number, number of prior treatments, prior autologous transplantation (yes or no), serum bilirubin level, serum creatinine level, donor age, donor gender, and donor ethnicity.

5.8 Analysis of Primary Endpoint

The primary analysis will consist of estimating the 180 day overall survival probability based on the Kaplan-Meier product limit estimator. The 180 day overall survival probability and confidence interval will be calculated. All registered patients will be considered for this analysis.

5.9 Analysis of Secondary Endpoints

1. **Overall survival**: The overall survival distribution at one year after transplantation will be estimated by the Kaplan-Meier curve. All patients will be followed for one year post-transplant for mortality.
2. **Neutrophil recovery**: To assess the incidence of neutrophil recovery from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to neutrophil recovery will be considered a competing risk.
3. **Platelet recovery:** To assess the incidence of platelet recovery from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to platelet recovery will be considered a competing risk.
4. **Chimerism**: The degree of donor chimerism will be assessed on Days 28, 56, 180, and 365 after transplantation.

5. **Graft failure**: To assess the incidence of primary and secondary graft failure a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to graft failure will be considered as a competing risk.
6. **Acute GVHD:** To assess the incidence of grades II-IV and grade III-IV acute GVHD from day of transplant. The first day of acute GVHD onset at a certain grade will be used to calculate a cumulative incidence curve for that acute GVHD grade. An overall cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant with graft failure, disease progression, and death considered a competing risk.
7. **Chronic GVHD:** To assess the incidence and severity of extensive chronic GVHD from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at one and two years post-transplant. The first day of clinical onset of extensive chronic GVHD will be used. Death, disease progression, or graft failure prior to occurrence of chronic GVHD will be considered competing risks.
8. **Treatment-related mortality**: Treatment-related mortality at 100 days, six months, and one year will be estimated. Disease progression is considered a competing risk.
9. **Relapse/progression**: To assess the incidence of relapse/progression from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to relapse or progression will be considered a competing risk.
10. **Progression-free survival**: To assess current progression-free survival, the one and two year progression-free survival probability after transplantation and 95% confidence interval will be calculated based on the Kaplan-Meier product limit estimator.

APPPENDIX A

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient, donor, and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principal investigator or other designated physician in a private setting.

2. Confidentiality

Confidentiality of a subject's protected health information will be maintained by the following methods: study-specific records containing protected health information and copies of study-related medical records will be kept in locked filing cabinets and on computers with password-access. Access to such information will be limited to those study personnel who need to use it to accomplish the purpose of the research. When protected health information is sent outside of the University of California, it will be disclosed only to those parties listed in the subject's authorization, and an audit trail log will be maintained of what information was sent and to whom it was sent.

Study patients are assigned a study number which is entered on all case report forms. No direct identifiers will be recorded on the study records. Study staff members will keep a confidential log of all patients enrolled on the study.

The medical record number is included in the consent form in order for it to be filed in the patient medical record. No study related documents other than the consent form will be filed in the medical records.

Only data directly related to the study will be shared amongst the study team members.

3. Participation of Women and Minorities

Women and ethnic minorities and other populations will be included in this study.

APPENDIX B

LABORATORY PROCEDURES

1. HLA TYPING

HLA typing will be performed for all patients and donors in an American Society of Histocompatibility and Immunogenetics (ASHI)-approved laboratories. HLA typing must be performed by DNA methods for HLA-A, -B, -Cw, DRB1, and DQB1 at high resolution (allele level).

2. CHIMERISM

Prior to transplantation, a sample of peripheral blood from the patient and from the donor is collected for chimerism studies according to institutional standards. Patient samples are also collected on Day ~28, ~56, ~180 and ~365 after transplantation. Chimerism will be measured by RFLP or microsatellite. Donor chimerism after transplantation shall be measured on samples of whole blood or mononuclear fraction.

APPENDIX C

GUIDELINES FOR DONOR TYPING AND SELECTION

An HLA-haploidentical donor is defined as a family member who shares one complete HLA haplotype with the recipient, and is variably HLA mismatched on the non-shared haplotype. A transplant recipient is HLA-haploidentical to each parent, to each child, and each sibling has a 50% chance of being HLA-haploidentical to the recipient. Typing all siblings, parents, and children is neither practical nor economically feasible. Siblings are always typed first in the attempt to find an HLA-matched donor.

If an HLA-matched donor is unavailable (Section 2.4), the following sequence is recommended:

1. Review HLA-typing of siblings and perform extended family typing, as appropriate, to ascertain parental haplotypes. If an HLA-haploidentical donor is identified, then proceed with criteria for "preferred donor" below. If no HLA-haploidentical donor is identified and there are additional siblings or half-siblings willing to be typed for potential donation, then perform HLA and ABO typing and determine CMV serologic status of the remaining siblings or half-siblings.
2. If a *preferred donor* (defined below) is not identified from the siblings or half-siblings, then consider performing HLA and ABO typing and determining CMV serologic status of parents that are ≤ 60 years of age and children ≥ 18 years of age. If typing of parents and children is not performed, and no HLA-haploidentical sibling meets the criteria for a *preferred* donor, then choose a *suitable donor*, defined as the HLA-haploidentical sibling who meets most of the criteria for preferred donor, in the order listed. If typing of parents and children is performed but no preferred donor is identified, then choose the most suitable donor.
3. If a preferred or suitable donor is still not identified, perform HLA and ABO typing and determine CMV serologic status of parents ≥60 years old.

A *preferred donor* is defined as one who meets all the following criteria:

1. Medically and psychologically fit and willing to donate.
2. If the patient is CMV seronegative, then the donor should be CMV seronegative.
3. No major ABO incompatibility:
    a. If the patient is blood type "O", then the donor should be type "O".
    b. If the patient is blood type "A", then the donor should be type "A" or "O"
    c. If the patient is blood type "B", then the donor should be type "B" or "O"

If more than one preferred donor or more than one suitable donor is identified and there is no medical reason to prefer one of them, then the following guidelines are recommended:

1. If the patient and family express a strong preference for a particular donor, use that one
2. If the donor is a sibling, choose the youngest sibling
3. If the donor is not a sibling, choose a parent over a child (for psychological reasons)

If the recipient is eligible for both an ablative and a nonmyeloablative transplant the treating physician will ultimately make a decision regarding using the ablative versus nonmyeloablative preparative regimens as described above. This decision is generally based upon the underlying diagnosis , the age of the patient, and the comorbidities. If the stem cell donor is able to donate either stem cells or bone marrow the decision to use peripheral blood stem cells versus bone marrow collection will be based upon the logistics of coorrdinating the bone marrow collection (avoiding extended delays in treatment) , the preference of the treating physician, and the donor preference. At UCSD there are frequently logistical constraints that result in delay of adequate operating room time which can result in delay of transplant.

APPENDIX D

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APPENDIX E.

Data Safety Monitoring and Verification:

Overview: The Moores UCSD Cancer Center has established DSMB Policies and Procedures for cancer clinical trials in order to insure the safety of participants; the validity of data; and the appropriate, early termination for findings of unjustifiable risk, of likely futility due to inadequate accrual or data acquisition, or if interim analysis shows the emergence of a significant benefit among intervention alternatives. DSMB Policies and Procedures specifically address the integration of ongoing protocol review and clinical trials monitoring functions into a comprehensive DSM program; the DSMB requirements for clinical trials; procedures for DSMB review and confidential reporting of decisions to investigators, the IRB, FDA, and supporting NIH Institutes and Centers; and procedures for assuring compliance by investigators with DSM requirements for study conduct, monitoring, and adverse event reporting. The complete UCSD Cancer Center DSM policies and procedures are available on the UCSD website in a publication entitled "**UCSD Cancer Center: Policies And Procedures**" at the following website:

https://ccweb2.ucsd.edu/ONcLINE/documents/DSM_PP_2012_Final_062912.pdf

Specific elements of DSM for this trial will include:

1. Review and approval by the Cancer Center PRMC: The purpose of the PRMC is to promote the conduct of scientifically meritorious clinical cancer research under the authority of the Cancer Center. This goal is accomplished through systematic research protocol review, interim monitoring of progress, and oversight of protocol prioritization, as required by NCI.
2. Data collection by Study Staff: Data is collected by the trained study coordinator (SC) who is assigned to the trial. SC will enter the data into the study specific case report forms and also the CIBMTR/NMDP data collection forms used for transplant patients. Audits of the data will be performed by the Cancer Center DSMB and its auditing coordinator.

   Data review and analysis by the PI: Patient eligibility and outcome data is reviewed by the PI, including severity of signs, symptoms, and adverse reactions associated with the transplant procedures and during follow-up and also relevant outcome events during the 1 year follow-up for progression-free survival .
   Data audit by the UCSD Cancer Center CTO: The CTO is a Shared Resource of the UCSD Cancer Center, and its purpose is to provide a supportive environment for the successful conduct of clinical trials within the center in order to enhance the excellence of clinical cancer research at UCSD. To fulfill this mission, the CTO provides centralized administrative and management support for all UCSD cancer clinical trials at every stage of development. The CTO has the responsibility of providing monitoring support as part of the Cancer Center DSM Policies and Procedures. The CTO Administrative Coordinator conducts regularly scheduled monitoring of UCSD Clinical Trials data. Data

that is monitored for this study will be extracted from the completed case report forms.

3. DSMB reports will be provided by the PI to the DSMB every 3 months. In-Depth Audits are conducted annually and at least 25% of the subject records (minimum of 5) are reviewed. The audit includes informed consent, eligibility criteria, protocol compliance, dose modifications, toxicity and adverse event reporting, drug accountability, record keeping, drug inventory, quality of data and timeliness of data submission. Individual aspects of study conduct are assessed for compliance with protocol-specified procedures and with Good Clinical Practice guidelines. Audit findings are detailed in a Level 3 Audit Report, prepared by the Auditing Coordinator for presentation at a quarterly meeting of the Cancer Center DSMB.

4. Review of data by the Data Safety Monitoring Board (DSMB): The DSMB exists to assure that all cancer clinical trials conducted with the support of the Moores UCSD Cancer Center receive monitoring for issues of protocol compliance, adverse events, and data quality. The purpose of the Center DSMB activity is to insure the safety of participants, the validity of data, and the appropriate closure of studies when interim data analysis indicates futility, unanticipated risks, or early accomplishment of study objectives. The DSMB provides review of the conduct and outcomes of clinical trials through scrutiny of data collection and adverse event summary reports, and interim data analysis. This study will be monitored and audited by the Moores UCSD Cancer Center Data Safety and Monitoring Board (DSMB). The UCSD Cancer Center DSMB will also review serious adverse effects (SAEs). The DSMB will also review the conclusions of this Phase2 trial, including the 1 year survival data.