



Protocol Abstract Page

Three-arm Clinical Trial for Patients with Hematologic Malignancies and Mismatched Donors - Haploidentical, 1 Antigen Mismatch Related or Unrelated, and Matched unrelated donor (MUD)- Using a T-cell Replete Allograft and High-dose Post-transplant Cyclophosphamide 2009-0266

Core Protocol Information

Study Chairman:	Stefan Ciurea
Department:	Stem Cell Transplantation and Cellular Therapy
Phone:	713-794-5780
Unit:	423
Full Title:	Three-arm Clinical Trial for Patients with Hematologic Malignancies and Mismatched Donors - Haploidentical, 1 Antigen Mismatch Related or Unrelated, and Matched unrelated donor (MUD)- Using a T-cell Replete Allograft and High-dose Post-transplant Cyclophosphamide
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Abstract

Objectives:

To determine the safety and 100-day non-relapse mortality (NRM) of T-cell replete allogeneic stem cell transplantation using melphalan, thiotepa, and fludarabine conditioning followed by high-dose post-transplant cyclophosphamide for patients with hematologic malignancies without a matched donor, treated on 5 arms: 1) Haploidentical related, 2) One antigen mismatched related or unrelated, 3) Matched unrelated donor (MUD), 4) Second transplant, and 5) Myelofibrosis.

Secondary objectives

1. To determine the NRM at 6 months.
2. To estimate the proportion of patients with engraftment/graft failure.
3. To estimate the cumulative incidence of grade III-IV Acute Graft vs. Host Disease (aGVHD).
4. To assess immune reconstitution and the incidence of infectious episodes
5. To assess the rate of chronic GVHD within the first year post transplantation
6. To assess disease response, disease-free survival (DFS) and overall survival (OS) after transplantation.

Rationale: (Be as concise as possible)

Haploidentical stem cell transplantation has been associated traditionally with a high rate of graft-versus-host disease. Recently, a novel immunosuppression regimen using high-dose post transplant cyclophosphamide has been reported for patients receiving a haploidentical graft. Using this approach the rates of GVHD are similar with those seen in the matched sibling donor setting. We are proposing to use this approach for patients with hematologic malignancies who lack a matched sibling or unrelated donor.

Eligibility: (List All Criteria)

Inclusion:

- 1) Patients < 55 years (Myeloablative regimen #1) or > 55 and <= 75 years or significant comorbidities (Reduced intensity regimen #2) old lacking a matched related volunteer donor identified in time for transplant for which a related haploidentical donor (<= 7/8 allele match at the A, B, C, DR loci), a 7/8 allele matched related or unrelated donor is identified, or a matched unrelated donor (MUD). The patients must be diagnosed with a high-risk disease defined as following:
- 2) Acute lymphocytic leukemia (ALL) in CR1 with high-risk features including adverse cytogenetics such as t(9;22), t(1;19), t(4;11), or MLL gene rearrangements; ALL in second or greater remission or ALL with relapsed disease, peripheral blood blasts < 1000/microliter, ALL patients must show response to most recent received chemotherapy;
- 3) Acute myeloid leukemia (AML) in CR1 with intermediate-risk disease or high-risk features defined as: Greater than 1 cycle of induction therapy required to achieve remission; Preceding myelodysplastic syndrome (MDS) or myeloproliferative disease; Presence of FLT3 mutations or internal tandem duplications; FAB M6 or M7 classification; Adverse cytogenetics, -5, del 5q, -7, del7q, abnormalities involving 3q, 9q, 11q, 20q, 21q, 17, +8 [> 3 abnormalities], peripheral blood blasts <1000/microliter, AML patients must show response to most recent received chemotherapy;
- 4) AML in second or greater remission, primary induction failure and patients with relapsed disease, peripheral blood blasts <1000/microliter; patients > 55 years and <= 75 years need to be in morphologic remission at transplant (< 5% blasts).
- 5) Myelodysplastic syndrome (MDS) with International Prognostic Scoring System (IPSS) intermediate-2 or higher; or therapy-related MDS
- 6) Aplastic anemia with Absolute neutrophil count (ANC)<1000 and transfusion dependent after they failed immunosuppression therapy
- 7) Chronic myeloid leukemia (CML) >=1st chronic phase, after failed >=2 lines of tyrosine kinase inhibitors; in accelerated or blast phase with > 30% bone marrow blasts;
- 8) Prior allogeneic stem cell transplant more than 6 months from the first transplant, in remission.
- 9) Chemotherapy-sensitive relapsed lymphoma (Complete or partial response), Hodgkin's or non-Hodgkin's lymphoma, no evidence of "bulky" disease (> 10 cm in diameter);
- 10) Patients with chemo-sensitive CLL with persistent or recurrent disease after fludarabine-based regimens, no evidence of "bulky" disease (> 10 cm in diameter)
- 11) Patients with poor prognosis multiple myeloma by cytogenetics (del13, del 17p, t(1;14) or t(14;16) or hypodiploidy, with advanced disease (stage>=2) and /or relapsed after autologous stem cell

transplant.

- 12) Patients with myelofibrosis (Lille >0 , transfusion dependency, progression to blast phase; however, in remission from AML) or CMML. These patients will be treated with the reduced-intensity conditioning regimen #2 and will be subject to the same stopping rule as the group ≥ 55 years or with comorbidities.
- 13) Zubrod performance status 0-1 or Lansky PS greater or equal to 70%.
- 14) Patients above ≥ 65 years old should have an age-adjusted co-morbidity index of ≤ 3 .
- 15) Available donor able to undergo a bone marrow harvest. For matched unrelated donor transplants only: Peripheral blood stem cells may be collected if donor is unavailable for bone marrow harvest or if adequate bone marrow cannot be collected.
- 16) Bilirubin ≤ 1.5 mg/dl (unless Gilbert's syndrome), ALT or AST ≤ 200 IU/ml.
- 17) Serum creatinine clearance ≥ 50 ml/min (calculated with Cockcroft-Gault formula); Creatinine for children ≤ 1.5 mg/dl or ≤ 2 times upper limit of normal for age (whichever is less);
- 18) Diffusing capacity for carbon monoxide (DLCO) $\geq 45\%$ predicted corrected for hemoglobin. For pediatric patients, if unable to perform pulmonary function, $\geq 92\%$ oxygen saturation with pulse oximetry.
- 19) LVEF $\geq 40\%$.
- 20) Patient or patient's legal representative, parent(s) or guardian should provide written informed consent. Assent of a minor if participant's age is at least seven and less than eighteen years.

Exclusion:

- 1) HIV positive; active hepatitis B or C
- 2) Patients with active infections. The PI is the final arbiter of the eligibility.
- 3) Liver cirrhosis with greater than grade 1 stage 1 inflammation/fibrosis
- 4) Uncontrolled CNS involvement by tumor cells
- 5) Patients with AML must have less than 30% bone marrow blasts and no peripheral blood blasts.
- 6) History of another primary malignancy that has not been in remission for at least 3 years. (The following are exempt from the 3-year limit: non-invasive nonmelanoma skin cancer, fully excised melanoma in situ [Stage 0], curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.)
- 7) Positive Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization.
- 8) Inability to comply with medical therapy or follow-up

Is there an age limit? Yes

Why? Provide scientific justification:

Above age 75 the expected outcomes are significantly worse.

Disease Group:

Blood And Marrow Transplantation

Treatment Agents/Devices/Interventions:

Cyclophosphamide, Fludarabine, Melphalan, MESNA, Rituximab

Proposed Treatment/Study Plan:

Patients will be treated on 4 groups: Group 1 – Haploidentical transplant patients; Group 2– One antigen mismatched related or unrelated; Group 3 - Matched unrelated donor (MUD) and Group 4 Second transplant.

Patients with lymphoma will be treated with the reduced intensity regimen (#2).

Patients < 55 years will receive the myeloablative regimen (#1).

Patients age ≥ 55 and ≤ 65 years old or that in the opinion of the investigator(s) would preclude myeloablative therapy may receive the reduced intensity regimen (#2).

Patients with CLL or low-grade lymphoma may be treated with the reduced-intensity conditioning regimen even if less than 55 years at the discretion of the treating physician.

For matched unrelated donor transplants only: Peripheral blood stem cells may be used if donor is unavailable for bone marrow harvest or if adequate bone marrow cannot be collected.

Overweight patients may receive peripheral blood instead of bone marrow stem cells due to low CD34+ cell numbers per kilogram that can be collected from the donor. Peripheral blood collection is recommended for obese individuals (if patient's weight is ≥ 1.5 x the donor weight).

Myeloablative Regimen #1 with Rituximab

Day -13	**Rituximab 375mg/m ²
Day -9	Admit / Hydration IV (Sunday - Wednesday)
Day -8	Melphalan 140 mg/m ² (Patients <12 kg receive 4.6 mg/kg)
Day -7	Thiotepa 5 mg/kg
Day -6	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day) **Rituximab 1000mg/m ²
Day -5	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -4	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -3	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -2	Rest
Day -1	Rest

Day 0 Stem Cell Infusion

Day +1 **Rituximab 1000mg/m²

Day +3 Cyclophosphamine 50 mg/kg/day

Day +4 Cyclophosphamine 50 mg/kg/day

Day +5 Tacrolimus start 0.015 mg/kg/day IV or po for 3 months
MMF 15 mg/kg/dose po TID to Day +100 or otherwise indicated

Day +7 Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)

+8 **Rituximab 1000mg/m²

**CD20+ lymphoid malignancies: Rituximab 375mg/m² on day -13 followed by 1000mg/m² on day -6, +1, and +8. Prophylaxis according to BMT standard practice

Myeloablative Regimen #1 without Rituximab

Day -9 Admit / Hydration IV (Sunday - Wednesday)

Day -8 Melphalan 140 mg/m² (Patients <12 kg receive 4.6 mg/kg)

Day -7 Thiotepa 5 mg/kg

Day -6 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)

Day -5 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)

Day -4 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)

Day -3 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)

Day -2 Rest

Day -1 Rest

Day 0 Stem Cell Infusion

Day +3 Cyclophosphamine 50 mg/kg/day

Day +4 Cyclophosphamine 50 mg/kg/day

Day +5 Tacrolimus start 0.015 mg/kg/day IV or po for 3 months
MMF 15 mg/kg/dose po TID to Day +100 or otherwise indicated

Day +7 Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)

Reduced Intensity Regimen #2 with Rituximab

Day -13	**Rituximab 375mg/m ²
Day -9	Admit / Hydration IV (Sunday - Wednesday)
Day -8	Melphalan 100 mg/m ² (Patients <12 kg receive 4.6 mg/kg)
Day -7	Thiotepa 5 mg/kg
Day -6	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day) **Rituximab 1000mg/m ²
Day -5	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -4	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -3	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -2	Rest
Day -1	Rest
Day 0	Stem Cell Infusion
Day +1	**Rituximab 1000mg/m ²
Day +3	Cyclophosphamine 50 mg/kg/day
Day +4	Cyclophosphamine 50 mg/kg/day
Day +5	Tacrolimus start 0.015 mg/kg/day IV or po for 3 months MMF 15 mg/kg/dose po TID to Day +100 or otherwise indicated
Day +7	Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)
Day +8	**Rituximab 1000mg/m ²

**CD20+ lymphoid malignancies: Rituximab 375mg/m² on day -13 followed by 1000mg/m² on day -6, +1, and +8. Prophylaxis according to BMT standard practice

Reduced Intensity Regimen #2 without Rituximab

Day -9	Admit / Hydration IV (Sunday - Wednesday)
Day -8	Melphalan 100 mg/m ² (Patients <12 kg receive 4.6 mg/kg)
Day -7	Thiotepa 5 mg/kg
Day -6	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -5	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)

Day -4	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -3	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
Day -2	Rest
Day -1	Rest
Day 0	Stem Cell Infusion
Day +3	Cyclophosphamine 50 mg/kg/day
Day +4	Cyclophosphamine 50 mg/kg/day
Day +5	Tacrolimus start 0.015 mg/kg/day IV or po for 3 months MMF 15 mg/kg/dose po TID to Day +100 or otherwise indicated
Day +7	Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)

Treatment Plans for use when thiotepa is not available:

Myeloablative Regimen #1 with Rituximab (For use when thiotepa is not available**)**

-13	**Rituximab 375 mg/m ²
-7	Admit / Hydration IV (Tuesday - Friday)
-6	Melphalan 140 mg/m ² (Patients <12 kg receive 4.6 mg/kg) **Rituximab 1000 mg/m ²
-5	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-4	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-3	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-2	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-1	TBI 200 cGy
0	Stem Cell Infusion
+1	**Rituximab 1000 mg/m ²
+3	Cyclophosphamide 50 mg/kg/day
+4	Cyclophosphamide 50 mg/kg/day
+5	Tacrolimus start 0.015 mg/kg/day IV or po for 3 months MMF 15 mg/kg/dose po TID to D+100 or otherwise indicated
+7	Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)
+8	**Rituximab 1000 mg/m ²

Myeloablative Regimen #1 without Rituximab (For use when Thiotepa is not available**)**

- 7 Admit / Hydration IV (Tuesday - Friday)
- 6 Melphalan 140 mg/m² (Patients <12 kg receive 4.6 mg/kg)
- 5 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 4 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 3 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 2 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 1 TBI 200 cGy
- 0 **Stem Cell Infusion**
- +3 Cyclophosphamide 50 mg/kg/day
- +4 Cyclophosphamide 50 mg/kg/day
- +5 Tacrolimus start 0.015 mg/kg/day IV or po for 3 months
MMF 15 mg/kg/dose po TID to D+100 or otherwise indicated
- +7 Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)

Reduced Intensity Regimen #2 with Rituximab (For use when thiotepa is not available**)**

- 13 **Rituximab 375 mg/m²
- 7 Admit / Hydration IV (Tuesday - Friday)
- 6 Melphalan 100 mg/m² (Patients <12 kg receive 4.6 mg/kg)
 **Rituximab 1000 mg/m²
- 5 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 4 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 3 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 2 Fludarabine 40 mg/m² (Patients <12 kg receive 1.3 mg/kg/day)
- 1 TBI 200 cGy
- 0 **Stem Cell Infusion**
- +1 **Rituximab 1000 mg/m²
- +3 Cyclophosphamide 50 mg/kg/day
- +4 Cyclophosphamide 50 mg/kg/day
- +5 Tacrolimus start 0.015 mg/kg/day IV or po for 3 months
 MMF 15 mg/kg/dose po TID to D+100 or otherwise indicated
- +7 Start G-CSF 5 mcg/kg/day (rounded up to the nearest vial)
- +8 **Rituximab 1000 mg/m²

Reduced Intensity Regimen #2 without Rituximab (For use when thiotepa is not available**)**

-7	Admit / Hydration IV (Tuesday - Friday)
-6	Melphalan 100 mg/m ² (Patients <12 kg receive 4.6 mg/kg)
-5	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-4	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-3	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-2	Fludarabine 40 mg/m ² (Patients <12 kg receive 1.3 mg/kg/day)
-1	TBI 200 cGy
0	Stem Cell Infusion
+3	Cyclophosphamide 50 mg/kg/day
+4	Cyclophosphamide 50 mg/kg/day
+5	Tacrolimus start 0.015 mg/kg/day IV or po for 3 months MMF 15 mg/kg/dose po TID to D+100 or otherwise indicated
+7	Start G-CSF 5mcg/kg/day (rounded up to the nearest vial)

Statistical Considerations:

General

This is a six group phase II study with primary objectives of determining the safety and NRM of using high-dose post-transplant cyclophosphamide and a T-cell replete (TCR) mismatched graft for patients with hematologic malignancies. The six groups are: 1) Haploidentical related, 2) One antigen mismatched related or unrelated, 3) Matched unrelated donor (MUD), 4) Second transplant haploidentical donor, 5) Myelofibrosis, and 6) Elderly patients. The trial was originally designed with the first two groups; the third, fourth, fifth, and sixth were added after the protocol had begun. Secondary objectives include assessing engraftment, incidence of GVHD, disease-free survival, overall survival, and characterizing immunologic reconstitution in this setting.

The maximum total sample size will be 337 patients, 122 in the first group, 98 in the second group, 48 in the third group, 24 in the fourth group, 21 in the fifth group, and 24 in the sixth group, with accrual estimated to take 3 years. Of the patients in the study, in groups 1-5, we expect approximately 75% in each group to be < 55 years of age, while we expect 25% to be > 55. In each group, we wish to ensure a 2:1 ratio of patients in remission to patients not in remission at the time of transplant. If in any group, we have filled the quota of either patients in remission or patients not in remission, we will enroll only patients in the group with remaining slots.

Study Monitoring

This study will be monitored for the safety endpoint non-relapse mortality (NRM) at 100 days. A Bayesian monitoring scheme described in Thall, Simon, and Estey (1996) will be employed to perform interim monitoring of the data during the course of the trial separately within each group. For the first three groups, separate rules are provided for patients who are less than 55 years old and without significant comorbidities, at the time of transplant and those who are greater than or equal to 55. In the first group, we expect to enroll 92 patients < 55 years old and 30 patients > 55 (or with significant co-morbidities). In the second group, we expect to enroll 74 patients < 55 years old and 24 patients > 55 (or with significant co-morbidities). In the third group, we expect to enroll 36 patients < 55 years old and 12 patients > 55 (or with significant co-morbidities). For the fourth, fifth, and sixth groups, separate monitoring rules will be provided for patients regardless of age.

Group 1. Patients < 55 Years of Age.

For patients who are less than 55 years old at the time of transplant, and who do not have significant comorbidities, we desire the 100-day NRM rate to be no more than 25%; if there is a high probability that it is greater, we will terminate entry of patients < 55 onto the group. As noted above, we expect to enroll 92 patients in this group. We will use the following rule to monitor the rate of NRM in patients < 55 in this treatment group during the course of the trial: we will stop enrollment of these patients into the group if at any time

$\Pr\{100\text{-day NRM rate in patients } < 55 \text{ years old } > 25\% \mid \text{data from patients } < 55 \text{ evaluated at } 100 \text{ days}\} > 0.975$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients < 55 in the first treatment group exceeds 25% is greater than 97.5%, we will stop the group. We will assume a Beta(0.5,1.5) prior distribution for the NRM rate. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients under 55 into this group if:

$(\# \text{ patients } < 55 \text{ with NRM in a group}) / (\# \text{ patients } < 55 \text{ evaluated at 100 days in that group})$
>= 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, 7/11, 7/12, 7/13, 8/14, 8/15, 8/16, 9/17, 9/18, 9/19, 10/20, 10/21, 11/22, 11/23, 11/24, 12/25, 12/26, 12/27, 13/28, 13/29, 13/30, 13/31, 14/32, 14/33, 14/34, 15/35, 15/36, 15/37, 16/38, 16/39, 16/40, 17/41, 17/42, 17/43, 18/44, 18/45, 18/46, 19/47, 19/48, 19/49, 20/50, 20/51, 20/52, 20/53, 21/54, 21/55, 21/56, 22/57, 22/58, 22/59, 23/60, 23/61, 23/62, 23/63, 24/64, 24/65, 24/66, 25/67, 25/68, 25/69, 26/70, 26/71, 26/72, 27/73, 27/74, 27/75, 27/76, 28/77, 28/78, 28/79, 29/80, 29/81, 29/82, 29/83, 30/84, 30/85, 30/86, 31/87, 31/88, 31/89, 32/90, or 32/91

If we enroll more than 92 patients < 55 years old, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for each group based upon 10,000 simulations of the trial in the table below. For different assumptions for the "true" NRM rate in this treatment group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients < 55 years old on a group is 25%, then enrollment of patients < 55 into the group will stop early approximately 13% of the time. If the true rate is 15%, it will stop early approximately 1% of the time, and if the true rate is 45%, it will stop early more than 99% of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
5%	<0.1%	92	92	92
15%	0.8%	92	92	92
25%	12.8%	92	92	92
35%	71.4%	19	49	92
45%	99.1%	8	16	31

Group 2. Patients < 55 Years of Age.

For patients who are less than 55 years old at the time of transplant, and who do not have significant comorbidities, we desire the 100-day NRM rate in this group to be no more than 25%; if there is a high probability that it is greater, we will terminate entry of patients < 55 onto the group. As noted above, we expect to enroll 74 patients in this group. We will use the following rule to monitor the rate of NRM in patients < 55 during the course of the trial: we will stop enrollment of these patients into the group if at any time

$\Pr\{100\text{-day NRM rate in patients } < 55 \text{ years old } > 25\% \mid \text{data from patients } < 55 \text{ evaluated at 100 days}\} > 0.975$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients < 55 in this treatment group exceeds 25% is greater than 97.5%, we will stop the group. We will assume a Beta(0.5,1.5) prior distribution for the NRM rate. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients under 55 into the group if:

$(\# \text{ patients } < 55 \text{ with NRM in a group}) / (\# \text{ patients } < 55 \text{ evaluated at 100 days in that group}) \geq 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, 7/11, 7/12, 7/13, 8/14, 8/15, 8/16, 9/17, 9/18, 9/19, 10/20, 10/21, 11/22, 11/23, 11/24, 12/25, 12/26, 12/27, 13/28, 13/29, 13/30, 13/31, 14/32, 14/33, 14/34, 15/35, 15/36, 15/37, 16/38, 16/39, 16/40, 17/41, 17/42, 17/43, 18/44, 18/45, 18/46, 19/47, 19/48, 19/49, 20/50, 20/51, 20/52, 20/53, 21/54, 21/55, 21/56, 22/57, 22/58, 22/59, 23/60, 23/61, 23/62, 23/63, 24/64, 24/65, 24/66, 25/67, 25/68, 25/69, 26/70, 26/71, 26/72, \text{ or } 27/73$

If we enroll more than 74 patients < 55 years old in this group, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for this group based upon 10,000 simulations of the trial in the table below. For different assumptions for the “true” NRM rate in the group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients < 55 years old in this group is 25%, then enrollment of patients < 55 into the group will stop early less than 10% of the time. If the true rate is 15%, it will stop early less than 1% of the time, and if the true rate is 45%, it will stop early more than 95% of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
5%	<0.1%	74	74	74
15%	0.8%	74	74	74
25%	11.9%	74	74	74
35%	63.6%	19	49	74
45%	97.4%	8	16	31

Group 3. Patients < 55 Years of Age.

For patients who are less than 55 years old at the time of transplant, and who do not have significant comorbidities, we desire the 100-day NRM rate in either group to be no more than 25%; if there is a high probability that it is greater, we will terminate entry of patients < 55 onto the group. As noted above, we expect to enroll 36 patients in this group. We will use the following rule to monitor the rate of NRM in patients < 55 separately by treatment group during the course of the trial: we will stop enrollment of these patients into the group if at any time

$\Pr\{100\text{-day NRM rate in patients } < 55 \text{ years old } > 25\% \mid \text{data from patients } < 55 \text{ evaluated at } 100 \text{ days}\} > 0.975$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients < 55 in a treatment group exceeds 25% is greater than 97.5%, we will stop the group. We will assume a Beta(0.5,1.5) prior distribution for the NRM rate. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients under 55 into a group if:

$(\# \text{ patients } < 55 \text{ with NRM in a group}) / (\# \text{ patients } < 55 \text{ evaluated at } 100 \text{ days in that group}) \geq 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, 7/11, 7/12, 7/13, 8/14, 8/15, 8/16, 9/17, 9/18, 9/19, 10/20, 10/21, 11/22, 11/23, 11/24, 12/25, 12/26, 12/27, 13/28, 13/29, 13/30, 13/31, 14/32, 14/33, 14/34, \text{ or } 15/35$

If we enroll more than 36 patients < 55 years old in an group, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for each group based upon 10,000 simulations of the trial in the table below. For different assumptions for the "true" NRM rate in a treatment group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients < 55 years old on a group is 25%, then enrollment of patients < 55 into the group will stop early less than 10% of the time. If the true rate is 15%, it will stop early less than 1% of the time, and if the true rate is 45%, it will stop early more than 80% of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
5%	<0.1%	36	36	36
15%	0.8%	36	36	36
25%	9.0%	36	36	36
35%	40.5%	19	36	36
45%	80.5%	8	16	31

Group 1: Patients ≥ 55 Years of Age (or with significant co-morbidities)

For patients in the first treatment group who are ≥ 55 years of age at the time of transplant or with significant co-morbidities, we desire the 100-day NRM rate to be no more than 30%. Similar to the rule above, if there is a high probability that the NRM rate is greater than 30%, we will terminate entry of patients ≥ 55 onto the group. We will use the following rule to monitor the rate of NRM in patients ≥ 55 in this treatment group during the course of the trial: we will stop entry onto the group if at any time

$\Pr\{100\text{-day NRM rate in patients } \geq 55 \text{ years old} > 30\% \mid \text{data from patients } \geq 55 \text{ evaluated at 100 days}\} > 0.95$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients ≥ 55 in this treatment group exceeds 30% is greater than 95%, we will stop enrollment of these patients onto the group. We expect to enroll 30 patients ≥ 55 years old in this group. We will assume a Beta(0.6,1.4) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients ≥ 55 years old into the group if:

$(\# \text{ patients } \geq 55 \text{ with NRM in a group}) / (\# \text{ patients } \geq 55 \text{ evaluated at 100 days in that group}) \geq 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, 7/10, 7/11, 7/12, 8/13, 8/14, 8/15, 9/16, 9/17, 9/18, 10/19, 10/20, 11/21, 11/22, 11/23, 12/24, 12/25, 13/26, 13/27, 13/28, \text{ or } 14/29$

If we enroll more than 30 patients ≥ 55 years old into this group, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for the group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in the group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients ≥ 55 on the group is 30%, then enrollment into the group in these patients will stop early about 15% of the time. If the true rate is 10%, it will stop early less than 1% of the time, and if the true rate is 50%, it will stop early more than three-quarters of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
10%	0.1%	30	30	30
20%	2.5%	30	30	30
30%	14.9%	30	30	30
40%	46.2%	12	30	30
50%	80.8%	7	12	23

Group 2: Patients ≥ 55 Years of Age (or with significant co-morbidities)

For patients who are ≥ 55 years of age at the time of transplant or with significant co-morbidities, we desire the 100-day NRM rate in the group to be no more than 30%. Similar to the rule above, if there is a high probability that the NRM rate is greater than 30%, we will terminate entry of patients ≥ 55 onto the group. We will use the following rule to monitor the rate of NRM in patients ≥ 55 separately by treatment group during the course of the trial: we will stop entry onto the group if at any time

$\Pr\{100\text{-day NRM rate in patients } \geq 55 \text{ years old} > 30\% \mid \text{data from patients } \geq 55 \text{ evaluated at 100 days}\} > 0.95$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients ≥ 55 in this treatment group exceeds 30% is greater than 95%, we will stop enrollment of these patients onto the group. We expect to enroll 24 patients ≥ 55 years old in this group. We will assume a Beta(0.6,1.4) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients ≥ 55 years old into the group if:

$(\# \text{ patients } \geq 55 \text{ with NRM in the group}) / (\# \text{ patients } \geq 55 \text{ evaluated at 100 days in the group}) \geq 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, 7/11, 7/12, 8/13, 8/14, 8/15, 9/16, 9/17, 9/18, 10/19, 10/20, 11/21, 11/22, \text{ or } 11/23$

If we enroll more than 24 patients ≥ 55 years old in this group, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for this treatment group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in the group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients ≥ 55 on a group is 30%, then enrollment into the group in these patients will stop early about 14% of the time. If the true rate is 10%, it will stop early less than 1% of the time, and if the true rate is 50%, it will stop early more than three-quarters of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
10%	0.2%	24	24	24
20%	2.4%	24	24	24
30%	13.9%	24	24	24
40%	41.9%	12	24	24
50%	75.3%	7	12	23

Group 3: Patients ≥ 55 Years of Age (or with significant co-morbidities)

For patients who are ≥ 55 years of age at the time of transplant or with significant co-morbidities, we desire the 100-day NRM rate in this group to be no more than 30%. Similar to the rule above, if there is a high probability that the NRM rate is greater than 30%, we will terminate entry of patients ≥ 55 onto the group. We will use the following rule to monitor the rate of NRM in patients ≥ 55 in this treatment group during the course of the trial: we will stop entry of this into the group if at any time

$\Pr\{100\text{-day NRM rate in patients } \geq 55 \text{ years old} > 30\% \mid \text{data from patients } \geq 55 \text{ evaluated at 100 days}\} > 0.95$

In other words, if at any time during the trial we determine that the probability that the NRM rate in patients ≥ 55 in this treatment group exceeds 30% is greater than 95%, we will stop enrollment of these patients onto the group. We expect to enroll 12 patients ≥ 55 years old in each group. We will assume a Beta(0.6,1.4) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients ≥ 55 years old into the group if:

$(\# \text{ patients } \geq 55 \text{ with NRM in a group}) / (\# \text{ patients } \geq 55 \text{ evaluated at 100 days in that group}) \geq 3/3, 4/5, 5/6, 5/7, 5/8, 6/9, 6/10, \text{ or } 7/11$

If we enroll more than 12 patients ≥ 55 years old in a group, additional stopping boundaries will be calculated and applied as necessary. Following these stopping boundaries, we summarize operating characteristics for each group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in a treatment group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in patients ≥ 55 on a group is 30%, then enrollment into the group in these patients will stop early less than 1% of the time. If the true rate is 10%, it will stop early less than 1% of the time, and if the true rate is 50%, it will stop early nearly half of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
10%	0.2%	12	12	12
20%	2.0%	12	12	12
30%	8.9%	12	12	12
40%	23.8%	12	12	12
50%	45.9%	7	12	12

Group 4: Second Transplants

For the fourth group, we desire the 100-day NRM rate to be no more than 40%. Similar to the rules above, if there is a high probability that the NRM rate in this group is greater than 40%, we will terminate entry of patients onto the group. We will use the following rule to monitor the rate of NRM in patients and stop new patient entry in this group during the course of the trial:

$$\Pr\{100\text{-day NRM rate} > 40\% \mid \text{data from patients evaluated at 100 days}\} > 0.975$$

In other words, if at any time during the trial we determine that the probability that the NRM rate in this group exceeds 40% is greater than 97.5%, we will stop enrollment of these patients onto the group. We expect to enroll 24 patients into this group. We will assume a Beta(0.8,1.2) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients into this group if:

$$\frac{(\# \text{ patients with NRM})}{(\# \text{ patients evaluated at 100 days})} \geq 4/4, 6/7, 7/8, 7/9, 8/10, 8/11, 9/12, 9/13, 10/14, 10/15, 11/16, 12/17, 12/18, 13/19, 13/20, 14/21, 14/22, \text{ or } 15/23$$

Following these stopping boundaries, we summarize operating characteristics for this group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in this group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in this group is 40%, then enrollment into the group in these patients will stop early less than 10% of the time. If the true rate in this group is 20%, it will stop early less than 1% of the time, and if the true rate is 60%, it will stop early more than half of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
20%	0.2%	24	24	24
30%	1.6%	24	24	24
40%	8.2%	24	24	24
50%	26.9%	20	24	24
60%	58.7%	9	18	24

Group 5: Myelofibrosis

For the fifth group, we desire the 100-day NRM rate to be no more than 30%. Similar to the rules above, if there is a high probability that the NRM rate in this group is greater than 30%, we will terminate entry of patients into this group. We will use the following rule to monitor the rate of NRM in patients and stop new patient entry in this group during the course of the trial:

$$\Pr\{100\text{-day NRM rate} > 30\% \mid \text{data from patients evaluated at 100 days}\} > 0.975$$

In other words, if at any time during the trial we determine that the probability that the NRM rate in group 5 exceeds 30% is greater than 97.5%, we will stop enrollment of these patients onto the group. We expect to enroll 21 patients in this group. We will assume a Beta(0.6,1.4) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients into this group if:

$$\begin{aligned} & (\# \text{ patients} \geq 55 \text{ with NRM}) / (\# \text{ patients evaluated at 100 days}) \\ & \geq 3/3, 4/5, 5/6, 5/7, 6/8, 6/9, 7/10, 7/11, 8/12, 8/13, 9/14, 9/15, 9/16, 10/17, 10/18, 11/19, \text{ or} \\ & 11/20 \end{aligned}$$

Following these stopping boundaries, we summarize operating characteristics for this group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in this group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in this group is 30%, then enrollment into the group in these patients will stop early less than 10% of the time. If the true rate is 20%, it will stop early less than 2% of the time, and if the true rate is 50%, it will stop early more than half of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
10%	0.1%	21	21	21
20%	1.6%	21	21	21
30%	8.2%	21	21	21
40%	26.6%	18	21	21
50%	56.5%	7	16	21

Group 6: Elderly Patients (ages 65-75)

For the sixth group, we desire the 100-day NRM rate to be no more than 35%. Similar to the rules above, if there is a high probability that the NRM rate in this group is greater than 35%, we will terminate entry of patients onto the group. We will use the following rule to monitor the rate of NRM in patients and stop new patient entry in this group during the course of the trial:

$$\Pr\{100\text{-day NRM rate} > 35\% \mid \text{data from patients evaluated at 100 days}\} > 0.975$$

In other words, if at any time during the trial we determine that the probability that the NRM rate in this group exceeds 35% is greater than 97.5%, we will stop enrollment of these patients onto the group. We expect to enroll 24 patients into this group. We will assume a Beta(0.7, 1.3) prior distribution for the NRM rate in these patients. This decision rule leads to the following stopping boundaries: we will stop enrollment of patients into this group if:

$$\frac{(\# \text{ patients with NRM})}{(\# \text{ patients evaluated at 100 days})} \geq \frac{4}{4}, \frac{5}{6}, \frac{6}{7}, \frac{6}{8}, \frac{7}{9}, \frac{7}{10}, \frac{8}{11}, \frac{8}{12}, \frac{9}{13}, \frac{9}{14}, \frac{10}{15}, \frac{10}{16}, \frac{11}{17}, \frac{11}{18}, \frac{12}{19}, \frac{12}{20}, \frac{12}{21}, \frac{13}{22}, \text{ or } \frac{13}{23}$$

Following these stopping boundaries, we summarize operating characteristics for this group based upon 10,000 simulations of the trial in the table below. For different assumptions for the true NRM rate in this group, presented are the proportion of times that the group is stopped early and the median and quartiles for the total sample size. If the true NRM rate in this group is 35%, then enrollment into the group in these patients will stop early less than 8% of the time. If the true rate in this group is 25%, it will stop early less than 2% of the time, and if the true rate is 55%, it will stop early more than half of the time.

Operating Characteristics

True 100-Day NRM Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
15%	0.1%	24	24	24
25%	1.3%	24	24	24
35%	8.0%	24	24	24
45%	29.1%	21	24	24
55%	63.0%	8	18	24

Analyses

The proportions of patients with donor-derived neutrophil engraftment and with non-relapse mortality (NRM) at 100 days and at 6 months will be reported along with 95% confidence intervals. The cumulative incidence of grade III-IV acute (within 100 days of transplant) and chronic (between 100 days and one year) GVHD will be estimated using the method of Gooley et al (1999).

NRM, treatment-related mortality (TRM), overall survival (OS), and disease-free survival (DSS) will be estimated using the Kaplan-Meier method. Analyses of the association between time-to-event factors and covariates of interest will be assessed using Cox proportional hazards regression models.

The reconstitution of T-cell subsets will be summarized at one year after transplant with descriptive statistics.

All analyses will be performed overall and separately by group. Analyses will then be repeated for the two subsets of patients < 55 years old at the time of transplant and ≥ 55 at transplant.

Where Will Participants Be Enrolled:

Only at MDACC

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Estimated Accrual:

Total Accrual at MDACC: 337
Estimated monthly accrual at MDACC: 4

Accrual Comments:

The maximum total sample size will be 337 patients, 122 in the first group, 98 in the second group, 48 in the third group, 24 in the fourth group, 21 in the fifth group, and 24 in the sixth group, with accrual estimated to take 3 years.

Do you expect your target population to include non-english speaking participants? Yes

Please select expected languages of non-English speaking participants. (Select all that apply)
Expected languages of non-English speaking participants:

Spanish

Location of Treatment:

This protocol is performed on an Inpatient AND Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

Duration of hospitalization is the standard duration for patients receiving a stem cell transplant (approximately 30 days).

Return Visits: How often must participants come to MDACC?

Frequent visits initially to Ambulatory Treatment Center up to 100 days after transplant followed by periodic clinic visits.

Home Care: Specify what, if any, treatment may be given at home.

N/A

Name of Person at MDACC Responsible for Data Management: [Patricia Cole](#)

Prior protocol at M. D. Anderson:

Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
No

Data Monitoring Committee:

Is treatment assignment randomized? No

Is this a blinded or double-blinded study? No

Does this protocol have a schedule for interim and final analysis? Yes

Please describe:

We will monitor the data continuously (using a Bayesian method); there is a final analysis of this study.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? No

Please confirm that the protocol meets all criteria for exemption according to 21CFR 312.2(b), noted below:

- (b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
- (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
 - (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
 - (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
 - (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
 - (v) The investigation is conducted in compliance with the requirements of 312.7.

Rationale for Exemption:

Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

Drugs are commercially available and have been used in stem cell transplantation conditioning.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	_____	_____
Dose:	_____	_____
Route of Administration:	_____	_____

Investigational Device:

Is the Investigational Device approved by the FDA? N/A

Is the Investigational Device being used in the manner approved by the FDA? N/A

Has the Investigational Device been modified in a manner not approved by the FDA? N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder:

IDE Number:

Risk Assessment:

Please answer the following questions regarding the Investigational Device.

Intended as an implant? No

Purported or represented to be for use supporting or sustaining human life? No

For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health? No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? No

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve stem cells? Yes

Please Explain: [The study involves infusion of hematopoietic stem cells/progenitor cells after high dose chemotherapy.](#)

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No