Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Thursday, February 16, 2023 12:45 p.m. - 2:15 p.m. (EST)

Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute; Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
Co-Chair:	**Margaret MacMillan, MD, MSc; University of Minnesota, Minneapolis, MN; Telephone: 612-626-2961, E-mail: macmi002@umn.edu**
Co-Chair:	**Carrie Kitko, MD; Vanderbilt University Medical Center; Telephone: 615-936-2088, E-mail: carrie.l.kitko@vumc.org**
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8334; E-mail: sspellma@nmdp.org**
Scientific Director:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Center Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org**
Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4339; E-mail: taowang@mcw.edu**
Statistician:	**TBD**

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1. **Introduction**
   a. Minutes from April 2022 meeting (Attachment 1)
   b. Introduction of incoming co-chair, Dr. Zachariah DeFilipp.
      Thank you to Dr. Joseph Pidala for all his contributions to the GVWC.

2. **Accrual Summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   a. **GV17-03** Saliba RM, Alousi AM, Pidala J, Arora M, Spellman SR, Hemmer MT, Wang T, Abboud C, Ahmed S, Antin JH, Beitinjaneh A, Buchbinder D, Byrne M, Cahn J, Choe H, Hanna R, Hematti P, Kamble RT, Kitko CL, Laughlin M, Lekakis L, MacMillan ML, Martino R, Mehta PA, Nishihori T, Patel SS, Perales M, Rangarajan HG, Ringdén O, Rosenthal J, Savani BN, Schultz KR, Seo S, Teshmia T, Van der Poel M, Verdonck LF, Weisdorf D, Wirk B, Yared JA, Schriber J, Champlin R, Ciurea S. Characteristics of Graft-versus-Host Disease (GvHD) after Post-transplant Cyclophosphamide versus Conventional GvHD Prophylaxis. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):681-693. doi: 10.1016/j.jtct.2022.07.013.***
   b. **GV18-01a** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Auletta JJ, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Gale RP, Hashem H, Hashmi S, Hematti P, Hong S, Hossain NM, Inamoto Y, Lekakis LJ, Modi D, Patel S, Sharma A, Solomon S, Couriel DR. Association of Chronic Graft-versus-Host Disease with Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Children with Hematologic Malignancy. ***Transplantation and Cellular Therapy. 2022 Oct;28(10):712.e1-712.e8. doi: 10.1016/j.jtct.2022.07.014.***

c. **GV18-01b** Lee CJ, Wang T, Chen K, Arora M, Brazauskas R, Spellman SR, Kitko C, MacMillan ML, Pidala JA, Badawy SM, Bhatt N, Bhatt VR, Cahn J, DeFilipp Z, Diaz MA, Farhadfar N, Gadalla S, Hashmi S, Hematti P, Hossain NM, Inamoto Y, Lekakis LJ, Sharma A, Solomon S, Lee S, Couriel DR. Severity of Chronic Graft-versus-Host Disease and Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancy. ***Submitted.***

d. **GV21-01** Farhadfar N, Al-Mansour Z, Wang T, Chen K, Pidala J, MacMillan ML, Kitko CL, Spellman SR, Wingard JR, Lee SJ. Racial, Ethnic and Socioeconomic Disparity in Outcomes of Patients with Chronic Graft-Versus-Host Disease: A CIBMTR Analysis. ***Poster presentation, ASH 2022.***

4. Studies in progress (Attachment 3)

a. **GV18-02** Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease (Wallis W/ Alousi AM/ Gulbis A) **Manuscript Preparation.**

b. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A) **Manuscript Preparation.**

c. **GV20-01** Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B) **Analysis.**

d. **GV20-02** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R) **Data File Preparation.**

e. **GV21-01/GV22-03** Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z/Rashid N) **Analysis.**

f. **GV21-02** Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M) **Analysis.**

g. **GV22-01** Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (Nishitani M/ Duncan C/ Graham R/ Qayed M) **Protocol Development.**

h. **GV22-02** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (Im A/ Pavletic S) **Protocol Development.**

5. Future/proposed studies

a. **PROP 2210-62/2210-75** The Effect of Graft-Versus-Host Disease Prophylaxis on Survival after HLA-Matched Hematopoietic cell transplantation (HCT): a CIBMTR analysis (McCurdy S/ Pashna M/ Mehta R) (Attachment 4)

b. **PROP 2210-76** PTCy/CNI with or without MMF in HLA-matched donor HCT (Mehta R) (Attachment 5)

c. **PROP 2210-108** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplant (Gallogly M/ Metheny L) (Attachment 6)

d. **PROP 2210-155** ATG versus PTCy for peripheral blood matched-sibling donor hematopoietic cell transplantation (Arcuri L/ Hamerschlak N) (Attachment 7)

e. **PROP 2210-23** Post-Transplant Cyclophosphamide (PTCy) vs. Anti-Thymocyte Globulin (ATG) in Patients with Acute Leukemia (AL) and Myelodysplastic Syndrome (MDS) receiving HLA-Mismatched Unrelated Donor (MMUD) Hematopoietic Cell Transplant (HCT). A CIBMTR Analysis (Jimenez A / Shaffer B) (Attachment 8)

f. **PROP 2210-203** Allogeneic stem cell transplant (Allo- SCT) in patients older than 70 years using posttransplant cyclophosphamide (PTCy) based Graft versus Host disease (GVHD) prophylaxis: An analysis from the CIBMTR database (Nath R/ Zhou Z) (Attachment 9)

Future/proposed studies to be presented at the CIBMTR Collaborative Working Committee Study Proposals Session

g. **PROP 2209-15** Incidence of Chronic Graft Versus Host Disease in Cryopreserved Versus Fresh Peripheral Blood Allogeneic Hematopoietic Stem Cell Grafts (Maurer K/ Soiffer R) (Attachment 10)

Proposed studies; not accepted for consideration at this time

h. **PROP 2209-17** GvHD prediction using machine learning. *Overlap with CIBMTR study GV20-01; insufficient detail about methods.*

i. **PROP 2210-07** Does early phase grade 1-2 mild or moderate skin GVHD have a benefit on OS and DFS after ASCT? *Unclear comparator group; lower scientific impact relative to other proposals.*

j. **PROP 2210-54** Impact of the additional immunosuppressant option on graft versus host disease and outcomes in patients who receive post-transplant cyclophosphamide for graft versus host disease prophylaxis. *Heterogeneous population; lower scientific impact relative to other proposals.*

k. **PROP 2210-127** Outcomes of Patients with Acute Myeloid Leukemia (AML) and Measurable Residual Disease (MRD) Undergoing Allogeneic Transplantation using Post-Transplant Cyclophosphamide versus Conventional Graft-versus-Host Disease (GvHD) Prophylaxis. *Limited MRD data availability; heterogeneous population.*

l. **PROP 2210-158** Effect of chronic graft-versus-host disease treatment on primary disease relapse. *Heterogeneous population; chronic GVHD severity correlated with type and number of treatments used.*

m. **PROP 2210-294** Optimal duration of ruxolitinib after acute and chronic GVHD: real world practices after 2020. *Duration of ruxolitinib influenced by many factors; lower scientific impact relative to other proposals.*

6. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Salt Lake City, UT
Saturday, April 23, 2022 12:15 PM - 1:45 PM MDT

Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute; Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
Co-Chair:	**Margaret MacMillan, MD, MSc; University of Minnesota, Minneapolis, MN; Telephone: 612-626-2961, E-mail: macmi002@umn.edu**
Co-Chair:	**Carrie Kitko, MD; Vanderbilt University Medical Center; Telephone: 615-936-2088, E-mail: carrie.l.kitko@vumc.org**
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8334; E-mail: sspellma@nmdp.org**
Scientific Director:	**Stephanie Lee, MD, MPH, Fred Hutchinson Cancer Research Center Telephone: 206-667-6190; E-mail: sjlee@fredhutch.org**
Statistical Director:	**Tao Wang, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4339; E-mail: taowang@mcw.edu**
Statistician:	**Karen Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0834; E-mail: kachen@mcw.edu**

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1. **Introduction**
   Dr. Joseph Pidala called the meeting to order and introduced the current GVWC leadership members. Dr. Pidala discussed the goals, expectations, and limitations of the GVWC and criteria that must be met to be considered for authorship on a manuscript. Details on publicly available datasets on the CIBMTR website were discussed. Dr. Margaret MacMillan explained the proposal scoring process and guidelines.

2. **Accrual Summary**
   The accrual summary was not presented, but was made available to attendees as an attachment.

3. **Presentations, published or submitted papers**
   Details regarding presentations and publications were not presented, but were made available to attendees as an attachment.

4. **Studies in progress**
   Details regarding the studies in progress were not presented, but were made available to attendees as an attachment.

5. **Future/proposed studies**
   Drs. MacMillan and Carrie Kitko led this session, which is where the committee chose to devote its available time. Presenters were reminded to limit their presentations to 5 minutes to ensure time for discussion (5 minutes).

a. **PROP 2108-02/2109-19/2110-72:** Post-Transplant Cyclophosphamide vs *in vivo* T-Cell Depletion with Anti-Thymocyte Globulin or Alemtuzumab in Patients with Acute Leukemia or Myelodysplastic Syndrome undergoing Unrelated Donor Hematopoietic Cell Transplant (A Jimenez/L Arcuri/A Marinos/K Komanduri/N Hamerschlak/P Lulla)

Dr. Alejandro Marinos presented the proposal. The main objective of the proposed study is to compare post-transplant clinical outcomes between patients who received post-transplant cyclophosphamide (PT-Cy) with those who received anti-thymocyte globulin (ATG) or alemtuzumab. A total of 2684 patients aged 18 and older underwent first unrelated donor allo-HCT for AML, ALL, or MDS in 2010-2020, with 548 receiving PT-Cy and 2136 receiving ATG or alemtuzumab.

Questions were asked about the availability of ATG dosing and timing. Suggestions were made to do separate analyses for ATG and alemtuzumab patients, to exclude patients who received both ATG and alemtuzumab, and to consider evaluating viral infections and PTLD as outcomes.

b. **PROP 2110-193/2110-278:** Comparative analysis of the incidence of graft versus host disease by age group in pediatric hematopoietic stem cell transplant recipients and impact on non-relapse mortality (M Nishitani/C Duncan/R Graham/M Qayed)

Dr. Miki Nishitani presented the proposal. The main objective of the proposed study is to compare the incidence, severity, and risk factors for acute and chronic GVHD in patients aged 0-17 years who underwent HCT in 2002-2011 with those who underwent HCT in 2012-2020. A total of 14,234 patients aged 17 years or younger received first allo-HCT in 2002-2020, with 8437 in 2002-2011 and 5797 in 2012-2020.

Attendees suggested grouping adolescents based on sex in addition to age and adding a cohort of patients aged 18-30. Concerns were raised about the heterogeneity of the population due to the inclusion of all disease types and changes in HLA typing technology over the span of years included in the study.

c. **PROP 2108-04:** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus host disease after hematopoietic cell transplantation (A Im/S Pavletic)

Dr. Annie Im presented the proposal. The main objectives of the proposed study are to develop a risk score based on clinical factors to predict the likelihood of developing moderate to severe chronic GVHD and to validate the risk score using the CIBMTR dataset. A total of 25,457 patients who underwent first allo-HCT in 2010-2019 met the criteria for this study.

Attendees suggested developing separate risks scores for those who received traditional GVHD prophylaxis and those who received post-transplant cyclophosphamide, including factors that have not been evaluated in existing studies, and including post-HCT measurements collected before GVHD onset. Statistical questions were raised regarding the risk factor weighting and whether relapse will be a competing event for GVHD.

d. **PROP 2110-25/2110-266:** A Risk-Score for Bronchiolitis Obliterans Syndrome after Allogeneic Hematopoietic Cell Transplantation (S Patel/R Mehta/C Ustun/A Alousi)

Dr. Sagar Patel presented the proposal. The main objective of the proposed study is to identify risk factors for developing bronchiolitis obliterans (BOS) following allo-HCT with the goal of creating a risk score. A total of 72,438 patients who underwent first allo-HCT in 1996-2019 met the criteria for this study.

Concerns were raised about the quality of the BOS data due to cases of BOS reported without GVHD diagnosis. It was suggested to compare outcomes between BOS patients with GVHD and without GVHD and to include available data on respiratory viral infections.

e. **PROP 2106-01:** Incidence and Risk Factors for thromboembolism in patients with Chronic Graft-versus-Host Disease (N El Jurdi/M Arora)

Dr. Najla El Jurdi presented the proposal. The main objective of the proposed study is to evaluate the impact of GVHD and ABO mismatch on the incidence and risk factors for thromboembolism (TEE) following allo-HCT. A total of 9650 patients aged 18 years or older who underwent first allo-HCT for AML or ALL in 2008-2019 met the criteria for this study.

Attendees made several suggestions including differentiating between catheter related and spontaneous DVT and adding prior infections and TMA as risk factors. There was also interest in comparing the incidence of TEE in the CIBMTR cohort with that of the general population.

f. **PROP 2110-24:** Does race/ethnicity or socio-economic status impact the outcomes of patients with acute GVHD? (N Rashid/N Farhadfar)

Dr. Nahid Rashid presented the proposal. The main objective of the proposed study is to evaluate the impact of race, ethnicity, and socioeconomic status on long term post-transplant outcomes after onset of acute GVHD. A total of 7038 patients underwent alloHCT for AML, ALL, or MDS in the United States in 2008-2019 and subsequently developed acute GVHD. Within this cohort, 5343 identified as non-Hispanic white, 548 as non-Hispanic black, 706 as Hispanic, 318 as Asian, and 123 as either Native Hawaiian, Pacific Islander, American Indian, Alaskan Native, or multi-racial.

A comment was made that patients with acute GVHD are often admitted, so the study may not find differences in access to care due to factors such as travel distance to transplant center.

Dropped proposed studies

a. **PROP 2109-06:** Risk Factors For Engraftment Syndrome And Its Impact On Clinical Outcomes In Pediatric Allogeneic Stem Cell Transplant Recipients: A Contemporary Analysis. ***Concern about accurate capture of engraftment syndrome; lower scientific impact relative to other proposals.***

b. **PROP 2109-23:** Assessing if multiparous female donors increase the risk of graft vs host disease in HLA-Matched un-related and related allogenic stem cell transplant in the era of post-transplant cyclophosphamide. ***Need for additional data collection; lower scientific impact relative to other proposals.***

c. **PROP 2110-30:** Risk of cardiovascular disease, infections, secondary malignancies, and non-relapse mortality among patients who received sirolimus. ***Concern about study population heterogeneity and ability to isolate effect of sirolimus; unclear feasibility; lower scientific impact relative to***

other proposals.

d. **PROP 2110-70:** Comparing Patterns, Outcomes and Organ Involvement with Acute and Chronic Graft-versus-Host Disease Between Patients with Non-Malignant Diseases Undergoing Haploidentical Transplantation Using Post-Transplantation Cyclophosphamide vs. Matched Unrelated Donor Transplantation Using Calcineurin Inhibitors. ***Overlap with CIBMTR study GV17-03.***

e. **PROP 2110-97:** Is there differential benefit of alternative GVHD prophylaxis strategies among racial and ethnic groups? Graft-versus host disease-free relapse-free survival by race and ethnicity comparing post-transplant cyclophosphamide-based to calcineurin inhibitor plus methotrexate-based GVHD prophylaxis. ***Minority sample size too small; transplant approach confounded by donor availability*****.**

f. **PROP 2110-122:** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies. ***Data on ATG timing not available.***

g. **PROP 2110-169:** Comparison of survival and graft versus host disease outcomes in alternate mismatched graft sources. ***Overlap with published CIBMTR study GV16-01a.***

h. **PROP 2110-215:** Effect of Graft-Versus-Host Disease Prophylaxis on Survival after Reduced Intensity Conditioning Hematopoietic cell transplantation for Older Adults: a CIBMTR analysis. ***Overlap with CIBMTR study GV17-03.***

i. **PROP 2110-218:** To compare CD3+ T-Cell Dose for Patients Receiving Allogeneic Peripheral Blood Stem Cell Transplants from Matched Related Donors using a propensity-matched study. ***The primary single center study population is very small; lower scientific impact relative to other proposals.***

j. **PROP 2110-279:** One Year Graft vs. Host Disease Relapse Free Survival in Acute Lymphoblastic Leukemia patients undertaking Matched Related or Matched Unrelated Allogeneic Stem Cell Transplant Using Post Transplant Cytoxan compared to conventional Graft vs Host Disease prophylaxis. ***Limited sample size; overlap with published CIBMTR study GV16-01a.***

k. **PROP 2110-285:** Sirolimus versus Tacrolimus in combination with post-transplant cyclophosphamide and MMF as a GVHD prophylaxis after allogeneic hematopoietic cell transplantation in patients with hematologic malignancies. ***Limited sample size.***

l. **PROP 2110-324:** Explore the optimal dose and length of post allogeneic hematopoietic stem cell transplant prophylactic immunosuppressant use. ***Data on dosing and timing not available.***

m. **PROP 2110-329:** Immunosuppression discontinuation after allogeneic hematopoietic stem cell transplantation. ***Concern about reliability of late infection data; immunosuppression discontinuation not clearly defined at 1 and 2 years in CIBMTR database.***

6. Other Business

After the proposals were presented, meeting participants had the opportunity to rate each proposal via the Tandem mobile app. Based on the voting results, current scientific merit, available number of relevant

cases, and the impact of the study on the field, the following studies will move forward in the committee's research portfolio for the upcoming year:

- **PROP 2110-193/2110-278:** Comparative analysis of the incidence of graft versus host disease by age group in pediatric hematopoietic stem cell transplant recipients and impact on non-relapse mortality

- **PROP 2108-04:** Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus host disease after hematopoietic cell transplantation

- **PROP 2110-24:** Does race/ethnicity or socio-economic status impact the outcomes of patients with acute GVHD?

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
GV17-03: Alterations in the characteristics and outcomes of acute and chronic graft-versus-host disease following post-transplant high dose cytoxan prophylaxis for haploidentical transplantation and in patients over 60 at high risk for graft-versus-host disease	Submitted	3
GV18-01a: Comparison of late effects among pediatric allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease	Submitted	1
GV18-01b: Comparison of late effects among adult allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease	Manuscript Preparation	1
GV18-02: Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease	Manuscript Preparation	2
GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic transplants recipients	Manuscript Preparation	1
GV20-01: Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants	Analysis	3
GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq	Protocol Development	3
GV21-01: Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease	Analysis	1
GV21-02: Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study	Analysis	1
GV22-01: Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation	Protocol Pending	3

GV22-02: Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation	Protocol Pending	1
GV22-03: Does race/ethnicity or socio-economic status impact the outcomes of patients with acute GVHD?	Protocol Pending	2

Accrual Summary for the Graft-vs-Host Disease Working Committee

Characteristics of leukemia patients receiving allogeneic HCT between 2008-2022

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**6378**	**4364**	**585**	**14437**	**4858**
Number of centers	243	219	160	248	187
Age at transplant, years, median (range)	55 (0-78)	55 (0-88)	51 (1-77)	59 (0-83)	30 (0-81)
Disease					
AML	2711 (43)	2037 (47)	266 (45)	5920 (41)	2472 (51)
ALL	975 (15)	842 (19)	127 (22)	1774 (12)	1467 (30)
Other leukemia	303 (5)	162 (4)	32 (5)	657 (5)	219 (5)
MDS	1723 (27)	966 (22)	122 (21)	4359 (30)	642 (13)
MPN	666 (10)	357 (8)	38 (6)	1727 (12)	58 (1)
Sex					
Male	3747 (59)	2683 (61)	349 (60)	8523 (59)	2641 (54)
Female	2631 (41)	1681 (39)	236 (40)	5914 (41)	2217 (46)
Graft source					
BM	800 (13)	1179 (27)	84 (14)	2441 (17)	0 (0)
PBSC	5571 (87)	3151 (72)	501 (86)	11983 (83)	0 (0)
Missing	7 (0)	34 (1)	0 (0)	13 (0)	4858 (100)
GVHD prophylaxis					
Ex-vivo T-cell depletion	41 (1)	159 (4)	16 (3)	79 (1)	40 (1)
CD34 selection	99 (2)	155 (4)	14 (2)	227 (2)	265 (5)
Post-tx Cyclophosphamide +/- others	313 (5)	3320 (76)	85 (15)	1180 (8)	6 (0)
Tac + MTX	2608 (41)	90 (2)	145 (25)	5381 (37)	131 (3)
Tac + MTX + others	488 (8)	22 (1)	23 (4)	2008 (14)	44 (1)
Tac + MMF	476 (7)	213 (5)	27 (5)	1071 (7)	975 (20)
Tac + MMF + others	120 (2)	48 (1)	11 (2)	562 (4)	272 (6)
Tac	169 (3)	40 (1)	22 (4)	423 (3)	110 (2)
Tac + others	371 (6)	15 (0)	13 (2)	893 (6)	145 (3)
CsA + MTX	830 (13)	48 (1)	62 (11)	711 (5)	42 (1)
CsA + MTX + others	68 (1)	5 (0)	6 (1)	216 (1)	20 (0)
CsA + MMF	375 (6)	26 (1)	23 (4)	491 (3)	1818 (37)
CsA + MMF + others	30 (0)	4 (0)	4 (1)	268 (2)	340 (7)
CsA	87 (1)	12 (0)	21 (4)	132 (1)	281 (6)
CsA + others	21 (0)	6 (0)	1 (0)	51 (0)	55 (1)
Others	65 (1)	26 (1)	9 (2)	171 (1)	101 (2)
Missing	217 (3)	175 (4)	103 (18)	573 (4)	213 (4)
Conditioning regimen intensity					

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Myeloablative	3574 (56)	1733 (40)	306 (52)	6627 (46)	3106 (64)
Reduced intensity	2086 (33)	893 (20)	169 (29)	6036 (42)	684 (14)
Non-myeloablative	432 (7)	1492 (34)	71 (12)	1071 (7)	872 (18)
Missing	286 (4)	246 (6)	39 (7)	703 (5)	196 (4)
Acute GVHD grade					
None	3152 (49)	1917 (44)	317 (54)	5240 (36)	1935 (40)
Grade I	816 (13)	740 (17)	78 (13)	2339 (16)	645 (13)
Grade II	1161 (18)	957 (22)	68 (12)	3635 (25)	1113 (23)
Grade III	667 (10)	348 (8)	56 (10)	1552 (11)	583 (12)
Grade IV	268 (4)	155 (4)	23 (4)	913 (6)	255 (5)
Missing	314 (5)	247 (6)	43 (7)	758 (5)	327 (7)
Organ involvement of aGVHD					
Skin	271 (13)	358 (25)	23 (16)	1097 (18)	349 (18)
Skin + Liver	126 (6)	52 (4)	6 (4)	229 (4)	40 (2)
Skin + Liver + UGI	21 (1)	7 (0)	4 (3)	51 (1)	15 (1)
Skin + Liver + LGI	85 (4)	49 (3)	8 (5)	264 (4)	83 (4)
Skin + Liver + UGI + LGI	94 (4)	32 (2)	7 (5)	262 (4)	75 (4)
Skin + UGI	167 (8)	95 (7)	7 (5)	562 (9)	162 (8)
Skin + LGI	268 (13)	192 (13)	20 (14)	893 (15)	309 (16)
Liver	77 (4)	25 (2)	10 (7)	103 (2)	29 (1)
Liver + UGI	19 (1)	10 (1)	0 (0)	31 (1)	13 (1)
Liver + LGI	46 (2)	27 (2)	4 (3)	84 (1)	44 (2)
Liver + UGI + LGI	51 (2)	15 (1)	1 (1)	93 (2)	42 (2)
UGI	205 (10)	154 (11)	7 (5)	513 (8)	179 (9)
LGI	219 (10)	147 (10)	22 (15)	513 (8)	185 (10)
UGI + LGI	209 (10)	114 (8)	10 (7)	465 (8)	179 (9)
Missing	240 (11)	180 (12)	19 (13)	927 (15)	243 (12)
Incidence of cGVHD					
No	3302 (52)	3007 (69)	384 (66)	7808 (54)	3448 (71)
Yes	2926 (46)	1235 (28)	176 (30)	6186 (43)	1240 (26)
Missing	150 (2)	122 (3)	25 (4)	443 (3)	170 (3)
Maximum grade of cGVHD					
Limited	416 (14)	294 (24)	33 (19)	835 (13)	440 (35)
Extensive	2468 (84)	919 (74)	139 (79)	5237 (85)	772 (62)
Missing	42 (1)	22 (2)	4 (2)	114 (2)	28 (2)
Overall severity of cGVHD					
Mild	1054 (36)	557 (45)	54 (31)	2243 (36)	733 (59)
Moderate	1012 (35)	411 (33)	62 (35)	2180 (35)	302 (24)
Severe	780 (27)	229 (19)	53 (30)	1561 (25)	161 (13)

Accrual Table 1. Leukemia patients:	**HLA-identical sibling**	**Haplo identical**	**Other related**	**Unrelated donor**	**Cord blood**
Missing	80 (3)	38 (3)	7 (4)	202 (3)	44 (4)
Year of transplant					
2008-2009	1273 (20)	166 (4)	103 (18)	2501 (17)	1117 (23)
2010-2011	702 (11)	57 (1)	28 (5)	1296 (9)	951 (20)
2012-2013	807 (13)	238 (5)	90 (15)	1780 (12)	833 (17)
2014-2015	1372 (22)	803 (18)	106 (18)	2781 (19)	843 (17)
2016-2017	1092 (17)	1167 (27)	124 (21)	2357 (16)	671 (14)
2018-2019	754 (12)	1372 (31)	107 (18)	2039 (14)	419 (9)
2020-2022	378 (6)	561 (13)	27 (5)	1683 (12)	24 (0)
Follow-up of survivors, months, median (range)	71 (0-175)	42 (0-170)	55 (2-168)	64 (0-174)	72 (1-172)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, MDS=Myelodysplastic diseases, MPN=Myeloproliferative diseases, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Characteristics of non-leukemia patients receiving allogeneic HCT between 2008-2022

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**3590**	**2028**	**637**	**4287**	**2161**
Number of centers	220	192	145	226	169
Age at transplant, years, median (range)	18 (0-79)	21 (0-76)	19 (0-77)	25 (0-79)	5 (0-73)
Disease					
NHL	645 (18)	408 (20)	127 (20)	1073 (25)	412 (19)
HD	191 (5)	290 (14)	28 (4)	343 (8)	96 (4)
SAA	952 (27)	412 (20)	91 (14)	1020 (24)	101 (5)
MM-PCD	177 (5)	54 (3)	103 (16)	262 (6)	41 (2)
Inherited abnormalities of erythrocyte diff-or function	1074 (30)	334 (16)	146 (23)	513 (12)	329 (15)
SCID & other immune system disorders	254 (7)	313 (15)	83 (13)	630 (15)	491 (23)
Inherited abnormality of platelets	4 (0)	3 (0)	0 (0)	13 (0)	26 (1)
Histiocytic disorders	31 (1)	56 (3)	7 (1)	142 (3)	153 (7)
Inherited disorders of metabolism	24 (1)	40 (2)	11 (2)	77 (2)	470 (22)
Others	238 (7)	118 (6)	41 (6)	214 (5)	42 (2)
Sex					
Male	2125 (59)	1218 (60)	373 (59)	2650 (62)	1303 (60)
Female	1465 (41)	810 (40)	264 (41)	1637 (38)	858 (40)
GVHD prophylaxis					
Ex-vivo T-cell depletion	9 (0)	134 (7)	7 (1)	63 (1)	10 (0)
CD34 selection	45 (1)	133 (7)	23 (4)	191 (4)	51 (2)
Post-tx Cyclophosphamide +/- others	181 (5)	1250 (62)	24 (4)	293 (7)	2 (0)
Tac + MTX	664 (18)	19 (1)	36 (6)	1029 (24)	65 (3)
Tac + MTX + others	170 (5)	11 (1)	12 (2)	380 (9)	15 (1)
Tac + MMF	222 (6)	116 (6)	16 (3)	312 (7)	341 (16)
Tac + MMF + others	45 (1)	28 (1)	9 (1)	116 (3)	113 (5)
Tac	70 (2)	22 (1)	15 (2)	183 (4)	71 (3)
Tac + others	74 (2)	7 (0)	4 (1)	152 (4)	76 (4)
CsA + MTX	1034 (29)	43 (2)	121 (19)	495 (12)	57 (3)
CsA + MTX + others	68 (2)	2 (0)	8 (1)	96 (2)	10 (0)
CsA + MMF	229 (6)	51 (3)	37 (6)	338 (8)	712 (33)
CsA + MMF + others	16 (0)	2 (0)	3 (0)	75 (2)	106 (5)
CsA	223 (6)	18 (1)	42 (7)	194 (5)	300 (14)
CsA + others	27 (1)	3 (0)	4 (1)	40 (1)	44 (2)
Others	191 (5)	41 (2)	24 (4)	74 (2)	35 (2)
Missing	322 (9)	148 (7)	252 (40)	256 (6)	153 (7)

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Graft source					
BM	1982 (55)	887 (44)	269 (42)	1982 (46)	0 (0)
PBSC	1604 (45)	1136 (56)	368 (58)	2268 (53)	0 (0)
Missing	4 (0)	5 (0)	0 (0)	37 (1)	2161 (100)
Conditioning regimen intensity					
Myeloablative	1269 (35)	585 (29)	251 (39)	1210 (28)	1237 (57)
Reduced intensity	881 (25)	468 (23)	139 (22)	1475 (34)	414 (19)
Non-myeloablative	1075 (30)	733 (36)	118 (19)	1255 (29)	432 (20)
Missing	365 (10)	242 (12)	129 (20)	347 (8)	78 (4)
Acute GVHD grade					
None	2515 (70)	1111 (55)	458 (72)	2125 (50)	1111 (51)
Grade I	310 (9)	254 (13)	41 (6)	599 (14)	274 (13)
Grade II	367 (10)	315 (16)	58 (9)	727 (17)	362 (17)
Grade III	185 (5)	143 (7)	32 (5)	361 (8)	183 (8)
Grade IV	105 (3)	86 (4)	14 (2)	198 (5)	94 (4)
Missing	108 (3)	119 (6)	34 (5)	277 (6)	137 (6)
Organ involvement of aGVHD					
Skin	85 (13)	137 (25)	25 (24)	292 (23)	163 (26)
Skin + Liver	30 (5)	20 (4)	7 (7)	42 (3)	11 (2)
Skin + Liver + UGI	6 (1)	0 (0)	0 (0)	5 (0)	5 (1)
Skin + Liver + LGI	32 (5)	17 (3)	6 (6)	56 (4)	24 (4)
Skin + Liver + UGI + LGI	16 (2)	8 (1)	5 (5)	38 (3)	19 (3)
Skin + UGI	35 (5)	18 (3)	2 (2)	84 (7)	39 (6)
Skin + LGI	82 (13)	66 (12)	17 (16)	183 (14)	131 (21)
Liver	25 (4)	11 (2)	2 (2)	22 (2)	6 (1)
Liver + UGI	2 (0)	1 (0)	0 (0)	3 (0)	1 (0)
Liver + LGI	14 (2)	22 (4)	3 (3)	29 (2)	15 (2)
Liver + UGI + LGI	13 (2)	11 (2)	2 (2)	21 (2)	9 (1)
UGI	57 (9)	37 (7)	5 (5)	80 (6)	29 (5)
LGI	98 (15)	56 (10)	14 (13)	135 (11)	67 (11)
UGI + LGI	55 (8)	31 (6)	10 (10)	89 (7)	51 (8)
Missing	106 (16)	107 (20)	7 (7)	199 (16)	64 (10)
Incidence of cGVHD					
No	2695 (75)	1541 (76)	531 (83)	2768 (65)	1605 (74)
Yes	820 (23)	422 (21)	84 (13)	1369 (32)	485 (22)
Missing	75 (2)	65 (3)	22 (3)	150 (3)	71 (3)
Maximum grade of cGVHD					
Limited	204 (25)	148 (35)	30 (36)	348 (25)	212 (44)
Extensive	601 (73)	271 (64)	50 (60)	967 (71)	260 (54)

Accrual Table 2. Non-leukemia patients:	**HLA-identical sibling**	**Haplo identical**	**Other related**	**Unrelated donor**	**Cord blood**
Missing	15 (2)	3 (1)	4 (5)	54 (4)	13 (3)
Overall severity of cGVHD					
Mild	369 (45)	208 (49)	39 (46)	589 (43)	281 (58)
Moderate	237 (29)	126 (30)	25 (30)	384 (28)	119 (25)
Severe	183 (22)	74 (18)	13 (15)	325 (24)	69 (14)
Missing	31 (4)	14 (3)	7 (8)	71 (5)	16 (3)
Year of transplant					
2008-2009	554 (15)	98 (5)	107 (17)	723 (17)	502 (23)
2010-2011	65 (2)	35 (2)	45 (7)	226 (5)	412 (19)
2012-2013	189 (5)	103 (5)	75 (12)	404 (9)	379 (18)
2014-2015	730 (20)	307 (15)	128 (20)	841 (20)	404 (19)
2016-2017	692 (19)	447 (22)	118 (19)	716 (17)	288 (13)
2018-2019	786 (22)	592 (29)	108 (17)	687 (16)	163 (8)
2020-2022	574 (16)	446 (22)	56 (9)	690 (16)	13 (1)
Follow-up of survivors, months, median (range)	44 (0-171)	36 (1-169)	49 (0-169)	49 (1-171)	72 (0-171)

Abbreviations: NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, SAA=Severe aplastic anemia, MM=Multiple myeloma, SCID=Severe combined immunodeficiency, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Accrual Table 3. Unrelated donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**47323**	**19111**	**12053**
Source of data			
CRF	24443 (52)	7079 (37)	5666 (47)
TED	22880 (48)	12032 (63)	6387 (53)
Number of centers	264	241	378
Disease at transplant			
AML	16388 (35)	7160 (37)	3977 (33)
ALL	6871 (15)	2478 (13)	1928 (16)
Other leukemia	1469 (3)	423 (2)	310 (3)
CML	3528 (7)	1111 (6)	1028 (9)
MDS	6936 (15)	3307 (17)	1526 (13)
Other acute leukemia	501 (1)	230 (1)	142 (1)
NHL	4211 (9)	1361 (7)	904 (8)
Hodgkin Lymphoma	947 (2)	258 (1)	212 (2)
Plasma Cell Disorders, MM	940 (2)	292 (2)	206 (2)
Other malignancies	58 (<1)	14 (<1)	22 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1519 (3)	594 (3)	510 (4)
Inherited abnormalities erythrocyte diff fxn	728 (2)	255 (1)	231 (2)
Inherited bone marrow failure syndromes	26 (<1)	32 (<1)	20 (<1)
Hemoglobinopathies	22 (<1)	22 (<1)	15 (<1)
Paroxysmal nocturnal hemoglobinuria	4 (<1)	7 (<1)	2 (<1)
SCIDs	827 (2)	328 (2)	370 (3)
Inherited abnormalities of platelets	40 (<1)	16 (<1)	12 (<1)
Inherited disorders of metabolism	301 (1)	89 (<1)	143 (1)
Histiocytic disorders	387 (1)	125 (1)	129 (1)
Autoimmune disorders	27 (<1)	14 (<1)	11 (<1)
Other	53 (<1)	18 (<1)	25 (<1)
MPN	1507 (3)	947 (5)	297 (2)
Disease missing	26 (<1)	27 (<1)	32 (<1)
AML Disease status at transplant			
CR1	8855 (54)	4408 (62)	1974 (50)
CR2	3149 (19)	1237 (17)	782 (20)
CR3+	337 (2)	108 (2)	92 (2)
Advanced or active disease	3862 (24)	1364 (19)	984 (25)

Accrual Table 3. Unrelated donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	185 (1)	43 (1)	145 (4)
ALL Disease status at transplant			
CR1	3403 (50)	1426 (58)	814 (42)
CR2	1956 (28)	631 (25)	557 (29)
CR3+	570 (8)	167 (7)	180 (9)
Advanced or active disease	860 (13)	230 (9)	257 (13)
Missing	82 (1)	24 (1)	120 (6)
MDS Disease status at transplant			
Early	1480 (21)	609 (18)	351 (23)
Advanced	4487 (65)	2464 (75)	836 (55)
Missing	969 (14)	234 (7)	339 (22)
NHL Disease status at transplant			
CR1	598 (14)	262 (19)	125 (14)
CR2	781 (19)	259 (19)	145 (16)
CR3+	365 (9)	114 (8)	80 (9)
PR	448 (11)	112 (8)	95 (11)
Advanced	1928 (46)	588 (43)	424 (47)
Missing	71 (2)	18 (1)	32 (4)
Recipient age at transplant			
0-9 years	3974 (8)	1246 (7)	1582 (13)
10-17 years	3152 (7)	969 (5)	1122 (9)
18-29 years	5720 (12)	1928 (10)	1607 (13)
30-39 years	5327 (11)	1851 (10)	1428 (12)
40-49 years	7110 (15)	2503 (13)	1748 (15)
50-59 years	9750 (21)	3711 (19)	2071 (17)
60-69 years	10023 (21)	5257 (28)	2052 (17)
70+ years	2267 (5)	1646 (9)	443 (4)
Median (Range)	48 (0-84)	53 (0-82)	42 (0-84)
Recipient race/ethnicity			
White	39105 (83)	15871 (83)	8419 (70)
Black or African American	2150 (5)	753 (4)	555 (5)
Asian	1167 (2)	602 (3)	520 (4)
Native Hawaiian or other Pacific Islander	59 (<1)	31 (<1)	32 (<1)
American Indian or Alaska Native	172 (<1)	73 (<1)	49 (<1)
Hispanic	2873 (6)	1076 (6)	718 (6)
Missing	1797 (4)	705 (4)	1760 (15)
Recipient sex			
Male	27519 (58)	11189 (59)	7161 (59)
Female	19804 (42)	7922 (41)	4892 (41)
Karnofsky score			
10-80	16419 (35)	7366 (39)	3802 (32)

Accrual Table 3. Unrelated donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
90-100	29141 (62)	11142 (58)	7620 (63)
Missing	1763 (4)	603 (3)	631 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	31 (<1)	54 (<1)	5 (<1)
4/6	246 (1)	98 (1)	58 (1)
5/6	6320 (14)	1956 (12)	1680 (15)
6/6	39021 (86)	13671 (87)	9199 (84)
Unknown	1705 (N/A)	3332 (N/A)	1111 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	907 (2)	104 (1)	82 (1)
6/8	1783 (4)	159 (1)	224 (3)
7/8	8777 (20)	2047 (16)	1797 (23)
8/8	33290 (74)	10596 (82)	5866 (74)
Unknown	2566 (N/A)	6205 (N/A)	4084 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11284 (29)	1543 (23)	914 (26)
Single allele mismatch	20903 (54)	3374 (51)	1832 (52)
Full allele matched	6608 (17)	1716 (26)	787 (22)
Unknown	8528 (N/A)	12478 (N/A)	8520 (N/A)
High resolution release score			
No	11606 (25)	19036 (>99)	11519 (96)
Yes	35717 (75)	75 (<1)	534 (4)
KIR typing available			
No	33478 (71)	19085 (>99)	11980 (99)
Yes	13845 (29)	26 (<1)	73 (1)
Graft type			
Marrow	16451 (35)	5091 (27)	4800 (40)
PBSC	30790 (65)	13824 (72)	7191 (60)
BM+PBSC	10 (<1)	6 (<1)	1 (<1)
PBSC+UCB	38 (<1)	170 (1)	10 (<1)
Others	34 (<1)	20 (<1)	51 (<1)
Conditioning regimen			
Myeloablative	28854 (61)	10141 (53)	7518 (62)
RIC/Nonmyeloablative	18244 (39)	8909 (47)	4372 (36)
TBD	225 (<1)	61 (<1)	163 (1)
Donor age at donation			
To Be Determined/NA	396 (1)	563 (3)	147 (1)
0-9 years	5 (<1)	37 (<1)	4 (<1)
10-17 years	2 (<1)	13 (<1)	1 (<1)
18-29 years	23149 (49)	9900 (52)	5152 (43)
30-39 years	13299 (28)	4964 (26)	3623 (30)

Accrual Table 3. Unrelated donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
40-49 years	7988 (17)	2533 (13)	2357 (20)
50+ years	2484 (5)	1101 (6)	769 (6)
Median (Range)	30 (0-123)	29 (0-121)	32 (0-123)
Donor/Recipient CMV serostatus			
+/+	11583 (24)	4767 (25)	3042 (25)
+/-	5466 (12)	2181 (11)	1479 (12)
-/+	15215 (32)	5254 (27)	3593 (30)
-/-	13359 (28)	4498 (24)	3132 (26)
CB - recipient +	34 (<1)	136 (1)	9 (<1)
CB - recipient -	4 (<1)	42 (<1)	2 (<1)
CB - recipient CMV unknown	0	1 (<1)	0
Missing	1662 (4)	2232 (12)	796 (7)
GvHD Prophylaxis			
No GVHD prophylaxis	200 (<1)	94 (<1)	67 (1)
Ex vivo T-cell depletion	1160 (2)	319 (2)	408 (3)
CD34 selection	720 (2)	339 (2)	194 (2)
Post-CY + other(s)	3020 (6)	2569 (13)	743 (6)
Post-CY alone	228 (<1)	109 (1)	58 (<1)
Tacrolimus + MMF +- others	5383 (11)	1947 (10)	920 (8)
Tacrolimus + MTX +- others (except MMF)	20389 (43)	8407 (44)	3390 (28)
Tacrolimus + others (except MTX, MMF)	2432 (5)	1220 (6)	469 (4)
Tacrolimus alone	1182 (2)	484 (3)	216 (2)
CSA + MMF +- others (except Tacrolimus)	3083 (7)	909 (5)	1017 (8)
CSA + MTX +- others (except Tacrolimus, MMF)	6993 (15)	1899 (10)	3358 (28)
CSA + others (except Tacrolimus, MTX, MMF)	1089 (2)	335 (2)	452 (4)
CSA alone	482 (1)	136 (1)	402 (3)
Other GVHD prophylaxis	752 (2)	270 (1)	208 (2)
Missing	210 (<1)	74 (<1)	151 (1)
Donor/Recipient sex match			
Male-Male	19283 (41)	7409 (39)	4699 (39)
Male-Female	11786 (25)	4525 (24)	2668 (22)
Female-Male	8013 (17)	3384 (18)	2383 (20)
Female-Female	7842 (17)	3072 (16)	2157 (18)
CB - recipient M	18 (<1)	96 (1)	3 (<1)
CB - recipient F	20 (<1)	83 (<1)	8 (<1)
Missing	361 (1)	542 (3)	135 (1)
Year of transplant			
1986-1990	350 (1)	46 (<1)	106 (1)
1991-1995	1839 (4)	439 (2)	748 (6)
1996-2000	3305 (7)	1185 (6)	1215 (10)
2001-2005	5345 (11)	1074 (6)	1880 (16)

Accrual Table 3. Unrelated donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2006-2010	9622 (20)	1923 (10)	1829 (15)
2011-2015	13414 (28)	3587 (19)	2563 (21)
2016-2020	10431 (22)	7184 (38)	2758 (23)
2021-2022	3017 (6)	3673 (19)	954 (8)
Follow-up among survivors, Months			
N Eval	20064	9350	5352
Median (Range)	60 (0-385)	24 (0-362)	40 (0-372)

Unrelated Cord Blood HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Accrual Table 4. Unrelated cord blood research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**6214**	**1700**	**2170**
Source of data			
CRF	4494 (72)	1137 (67)	1068 (49)
TED	1720 (28)	563 (33)	1102 (51)
Number of centers	154	142	223
Disease at transplant			
AML	2354 (38)	580 (34)	706 (33)
ALL	1279 (21)	373 (22)	468 (22)
Other leukemia	98 (2)	30 (2)	37 (2)
CML	132 (2)	36 (2)	57 (3)
MDS	559 (9)	168 (10)	172 (8)
Other acute leukemia	96 (2)	24 (1)	44 (2)
NHL	403 (6)	98 (6)	134 (6)
Hodgkin Lymphoma	103 (2)	27 (2)	36 (2)
Plasma Cell Disorders, MM	38 (1)	12 (1)	13 (1)
Other malignancies	11 (<1)	1 (<1)	3 (<1)
SAA	97 (2)	32 (2)	49 (2)
Inherited abnormalities erythrocyte diff fxn	171 (3)	51 (3)	45 (2)
Inherited bone marrow failure syndromes	4 (<1)	3 (<1)	3 (<1)
Hemoglobinopathies	2 (<1)	1 (<1)	0
SCIDs	278 (4)	91 (5)	165 (8)
Inherited abnormalities of platelets	20 (<1)	5 (<1)	10 (<1)
Inherited disorders of metabolism	387 (6)	118 (7)	142 (7)
Histiocytic disorders	107 (2)	29 (2)	51 (2)
Autoimmune disorders	9 (<1)	0	6 (<1)
Other	10 (<1)	2 (<1)	9 (<1)
Disease missing	4 (<1)	3 (<1)	0
MPN	52 (1)	16 (1)	20 (1)
AML Disease status at transplant			
CR1	1222 (52)	324 (56)	350 (50)
CR2	636 (27)	149 (26)	188 (27)
CR3+	66 (3)	9 (2)	26 (4)
Advanced or active disease	422 (18)	96 (17)	138 (20)
Missing	8 (<1)	2 (<1)	4 (1)
ALL Disease status at transplant			
CR1	574 (45)	159 (43)	202 (43)

Accrual Table 4. Unrelated cord blood research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR2	480 (38)	137 (37)	166 (35)
CR3+	148 (12)	54 (14)	61 (13)
Advanced or active disease	76 (6)	22 (6)	38 (8)
Missing	1 (<1)	1 (<1)	1 (<1)
MDS Disease status at transplant			
Early	173 (31)	41 (24)	72 (42)
Advanced	337 (60)	113 (67)	78 (45)
Missing	49 (9)	14 (8)	22 (13)
NHL Disease status at transplant			
CR1	63 (16)	9 (9)	25 (19)
CR2	75 (19)	22 (22)	35 (26)
CR3+	45 (11)	11 (11)	12 (9)
PR	68 (17)	12 (12)	16 (12)
Advanced	149 (37)	43 (44)	42 (32)
Missing	0	1 (1)	3 (2)
Recipient age at transplant			
0-9 years	1868 (30)	612 (36)	771 (36)
10-19 years	655 (11)	158 (9)	255 (12)
20-29 years	745 (12)	152 (9)	234 (11)
30-39 years	599 (10)	150 (9)	210 (10)
40-49 years	655 (11)	172 (10)	203 (9)
50-59 years	856 (14)	210 (12)	280 (13)
60-69 years	722 (12)	212 (12)	201 (9)
70+ years	114 (2)	34 (2)	16 (1)
Median (Range)	27 (0-83)	24 (0-78)	20 (0-78)
Recipient race/ethnicity			
White	3432 (55)	996 (59)	1090 (50)
Black or African American	893 (14)	221 (13)	263 (12)
Asian	366 (6)	120 (7)	163 (8)
Native Hawaiian or other Pacific Islander	32 (1)	3 (<1)	17 (1)
American Indian or Alaska Native	45 (1)	10 (1)	19 (1)
Hispanic	1108 (18)	253 (15)	297 (14)
Missing	338 (5)	97 (6)	321 (15)
Recipient sex			
Male	3439 (55)	968 (57)	1241 (57)
Female	2775 (45)	732 (43)	929 (43)
Karnofsky score			
10-80	1647 (27)	437 (26)	556 (26)
90-100	4361 (70)	1157 (68)	1433 (66)
Missing	206 (3)	106 (6)	181 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	101 (2)	57 (4)	32 (2)

Accrual Table 4. Unrelated cord blood research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
4/6	2448 (41)	557 (40)	789 (40)
5/6	2664 (45)	596 (43)	854 (43)
6/6	750 (13)	184 (13)	294 (15)
Unknown	251 (N/A)	306 (N/A)	201 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2891 (55)	569 (55)	881 (55)
6/8	1271 (24)	248 (24)	370 (23)
7/8	730 (14)	141 (14)	221 (14)
8/8	349 (7)	70 (7)	123 (8)
Unknown	973 (N/A)	672 (N/A)	575 (N/A)
HLA-DPB1 Match			
Double allele mismatch	859 (39)	99 (38)	164 (40)
Single allele mismatch	1117 (51)	136 (52)	209 (51)
Full allele matched	202 (9)	25 (10)	33 (8)
Unknown	4036 (N/A)	1440 (N/A)	1764 (N/A)
High resolution release score			
No	4674 (75)	1650 (97)	2145 (99)
Yes	1540 (25)	50 (3)	25 (1)
KIR typing available			
No	4941 (80)	1694 (>99)	2150 (99)
Yes	1273 (20)	6 (<1)	20 (1)
Graft type			
UCB	5836 (94)	1521 (89)	2034 (94)
BM+UCB	1 (<1)	0	0
PBSC+UCB	347 (6)	170 (10)	122 (6)
Others	30 (<1)	9 (1)	14 (1)
Number of cord units			
1	5200 (84)	0	1809 (83)
2	1012 (16)	0	360 (17)
3	1 (<1)	0	0
Unknown	1 (N/A)	1700 (N/A)	1 (N/A)
Conditioning regimen			
Myeloablative	4030 (65)	1076 (63)	1346 (62)
RIC/Nonmyeloablative	2168 (35)	619 (36)	807 (37)
TBD	16 (<1)	5 (<1)	17 (1)
Donor age at donation			
To Be Determined/NA	4858 (78)	646 (38)	1741 (80)
0-9 years	1081 (17)	844 (50)	348 (16)
10-19 years	58 (1)	88 (5)	17 (1)
20-29 years	65 (1)	37 (2)	15 (1)
30-39 years	57 (1)	38 (2)	21 (1)
40-49 years	46 (1)	21 (1)	11 (1)

Accrual Table 4. Unrelated cord blood research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
50+ years	49 (1)	26 (2)	17 (1)
Median (Range)	4 (0-112)	5 (0-73)	4 (0-119)
Donor/Recipient CMV serostatus			
+/+	0	0	1 (<1)
-/-	0	0	1 (<1)
CB - recipient +	3888 (63)	1027 (60)	1306 (60)
CB - recipient -	2227 (36)	613 (36)	790 (36)
CB - recipient CMV unknown	99 (2)	60 (4)	72 (3)
GvHD Prophylaxis			
No GVHD prophylaxis (forms under review)	23 (<1)	8 (<1)	14 (1)
Ex vivo T-cell depletion	25 (<1)	9 (1)	8 (<1)
CD34 selection	213 (3)	100 (6)	61 (3)
Post-CY + other(s)	12 (<1)	9 (1)	13 (1)
Post-CY alone	0	0	1 (<1)
Tacrolimus + MMF +- others	1857 (30)	539 (32)	446 (21)
Tacrolimus + MTX +- others (except MMF)	216 (3)	56 (3)	78 (4)
Tacrolimus + others (except MTX, MMF)	225 (4)	64 (4)	84 (4)
Tacrolimus alone	153 (2)	45 (3)	30 (1)
CSA + MMF +- others (except Tacrolimus)	2847 (46)	683 (40)	1039 (48)
CSA + MTX +- others (except Tacrolimus, MMF)	101 (2)	29 (2)	50 (2)
CSA + others (except Tacrolimus, MTX, MMF)	341 (5)	117 (7)	223 (10)
CSA alone	52 (1)	18 (1)	70 (3)
Other GVHD prophylaxis	137 (2)	20 (1)	42 (2)
Missing	12 (<1)	3 (<1)	11 (1)
Donor/Recipient sex match			
Male-Female	0	0	1 (<1)
Female-Male	0	0	1 (<1)
CB - recipient M	3439 (55)	968 (57)	1239 (57)
CB - recipient F	2775 (45)	732 (43)	928 (43)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	112 (2)	86 (5)	34 (2)
2006-2010	1850 (30)	426 (25)	601 (28)
2011-2015	2682 (43)	510 (30)	839 (39)
2016-2020	1341 (22)	528 (31)	547 (25)
2021-2022	228 (4)	148 (9)	144 (7)
Follow-up among survivors, Months			
N Eval	2964	887	1105
Median (Range)	64 (0-196)	49 (0-213)	43 (0-240)

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Accrual Table 5. Related donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**11071**	**1859**	**851**
Source of data			
CRF	3500 (32)	454 (24)	281 (33)
TED	7571 (68)	1405 (76)	570 (67)
Number of centers	93	78	63
Disease at transplant			
AML	3667 (33)	605 (33)	285 (33)
ALL	1843 (17)	362 (19)	163 (19)
Other leukemia	205 (2)	41 (2)	19 (2)
CML	337 (3)	45 (2)	24 (3)
MDS	1483 (13)	226 (12)	111 (13)
Other acute leukemia	164 (1)	33 (2)	11 (1)
NHL	936 (8)	168 (9)	76 (9)
Hodgkin Lymphoma	204 (2)	40 (2)	23 (3)
Plasma Cell Disorders, MM	257 (2)	39 (2)	23 (3)
Other malignancies	24 (<1)	0	1 (<1)
Breast cancer	1 (<1)	0	0
SAA	516 (5)	81 (4)	29 (3)
Inherited abnormalities erythrocyte diff fxn	494 (4)	72 (4)	20 (2)
Inherited bone marrow failure syndromes	16 (<1)	2 (<1)	4 (<1)
Hemoglobinopathies	111 (1)	22 (1)	8 (1)
Paroxysmal nocturnal hemoglobinuria	2 (<1)	0	0
SCIDs	228 (2)	36 (2)	16 (2)
Inherited abnormalities of platelets	10 (<1)	0	0
Inherited disorders of metabolism	16 (<1)	5 (<1)	2 (<1)
Histiocytic disorders	63 (1)	9 (<1)	5 (1)
Autoimmune disorders	11 (<1)	0	1 (<1)
Other	16 (<1)	0	0
Disease missing	10 (<1)	4 (<1)	1 (<1)
MPN	457 (4)	69 (4)	29 (3)
AML Disease status at transplant			
CR1	2403 (66)	411 (68)	186 (65)
CR2	562 (15)	86 (14)	36 (13)
CR3+	44 (1)	14 (2)	1 (<1)
Advanced or active disease	651 (18)	90 (15)	62 (22)
Missing	7 (<1)	4 (1)	0

Accrual Table 5. Related donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
ALL Disease status at transplant			
CR1	1119 (61)	226 (62)	103 (63)
CR2	522 (28)	91 (25)	40 (25)
CR3+	114 (6)	19 (5)	11 (7)
Advanced or active disease	86 (5)	26 (7)	9 (6)
Missing	2 (<1)	0	0
MDS Disease status at transplant			
Early	253 (17)	31 (14)	20 (18)
Advanced	1177 (79)	183 (81)	85 (77)
Missing	53 (4)	12 (5)	6 (5)
NHL Disease status at transplant			
CR1	174 (19)	39 (23)	16 (21)
CR2	176 (19)	34 (20)	10 (13)
CR3+	100 (11)	18 (11)	4 (5)
PR	68 (7)	13 (8)	7 (9)
Advanced	409 (44)	63 (38)	39 (51)
Missing	5 (1)	0	0
Recipient age at transplant			
0-9 years	1123 (10)	180 (10)	68 (8)
10-19 years	1071 (10)	139 (7)	63 (7)
20-29 years	1257 (11)	250 (13)	90 (11)
30-39 years	865 (8)	166 (9)	88 (10)
40-49 years	1356 (12)	218 (12)	99 (12)
50-59 years	2336 (21)	401 (22)	185 (22)
60-69 years	2583 (23)	431 (23)	226 (27)
70+ years	480 (4)	74 (4)	32 (4)
Median (Range)	49 (0-82)	49 (0-76)	51 (0-83)
Recipient race/ethnicity			
White	6869 (62)	977 (53)	514 (60)
Black or African American	1373 (12)	240 (13)	81 (10)
Asian	518 (5)	138 (7)	43 (5)
Native Hawaiian or other Pacific Islander	34 (<1)	5 (<1)	2 (<1)
American Indian or Alaska Native	47 (<1)	4 (<1)	4 (<1)
Hispanic	1677 (15)	357 (19)	151 (18)
Missing	553 (5)	138 (7)	56 (7)
Recipient sex			
Male	6513 (59)	1084 (58)	496 (58)
Female	4558 (41)	775 (42)	355 (42)
Karnofsky score			
10-80	3971 (36)	745 (40)	349 (41)
90-100	6760 (61)	1052 (57)	454 (53)
Missing	340 (3)	62 (3)	48 (6)

Accrual Table 5. Related donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
HLA-A B DRB1 groups - low resolution			
<=3/6	2161 (23)	346 (26)	166 (28)
4/6	636 (7)	112 (8)	65 (11)
5/6	204 (2)	37 (3)	21 (4)
6/6	6481 (68)	861 (63)	333 (57)
Unknown	1589 (N/A)	503 (N/A)	266 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2647 (29)	416 (33)	200 (38)
6/8	118 (1)	26 (2)	14 (3)
7/8	143 (2)	26 (2)	15 (3)
8/8	6262 (68)	798 (63)	296 (56)
Unknown	1901 (N/A)	593 (N/A)	326 (N/A)
HLA-DPB1 Match			
Double allele mismatch	9 (<1)	0	0
Single allele mismatch	725 (26)	8 (18)	6 (25)
Full allele matched	2072 (74)	37 (82)	18 (75)
Unknown	8265 (N/A)	1814 (N/A)	827 (N/A)
High resolution release score			
No	4655 (42)	1830 (98)	835 (98)
Yes	6416 (58)	29 (2)	16 (2)
Graft type			
Marrow	3187 (29)	431 (23)	238 (28)
PBSC	7789 (70)	1395 (75)	599 (70)
UCB	2 (<1)	14 (1)	0
BM+PBSC	8 (<1)	4 (<1)	1 (<1)
BM+UCB	30 (<1)	9 (<1)	2 (<1)
PBSC+UCB	0	0	11 (1)
Others	55 (<1)	6 (<1)	0
Conditioning regimen			
Myeloablative	6168 (56)	1021 (55)	439 (52)
RIC/Nonmyeloablative	4849 (44)	825 (44)	395 (46)
TBD	54 (<1)	13 (1)	17 (2)
Donor age at donation			
To Be Determined/NA	15 (<1)	3 (<1)	8 (1)
0-9 years	761 (7)	119 (6)	32 (4)
10-19 years	843 (8)	139 (7)	52 (6)
20-29 years	1915 (17)	319 (17)	167 (20)
30-39 years	1633 (15)	323 (17)	161 (19)
40-49 years	1796 (16)	300 (16)	115 (14)
50+ years	4108 (37)	656 (35)	316 (37)
Median (Range)	42 (0-122)	41 (0-118)	41 (0-121)
Donor/Recipient CMV serostatus			

Accrual Table 5. Related donor research sample:	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
+/+	4485 (41)	812 (44)	288 (34)
+/-	1187 (11)	151 (8)	72 (8)
-/+	2766 (25)	443 (24)	198 (23)
-/-	2371 (21)	381 (20)	162 (19)
CB - recipient +	24 (<1)	14 (1)	7 (1)
CB - recipient -	8 (<1)	9 (<1)	6 (1)
Missing	230 (2)	49 (3)	118 (14)
GvHD Prophylaxis			
No GVHD prophylaxis (forms under review)	156 (1)	35 (2)	16 (2)
Ex vivo T-cell depletion	114 (1)	31 (2)	11 (1)
CD34 selection	119 (1)	33 (2)	13 (2)
Post-CY + other(s)	3488 (32)	547 (29)	309 (36)
Post-CY alone	76 (1)	11 (1)	8 (1)
Tacrolimus + MMF +- others	794 (7)	93 (5)	26 (3)
Tacrolimus + MTX +- others (except MMF)	4050 (37)	606 (33)	309 (36)
Tacrolimus + others (except MTX, MMF)	815 (7)	292 (16)	67 (8)
Tacrolimus alone	108 (1)	22 (1)	7 (1)
CSA + MMF +- others (except Tacrolimus)	243 (2)	38 (2)	15 (2)
CSA + MTX +- others (except Tacrolimus, MMF)	719 (6)	95 (5)	43 (5)
CSA + others (except Tacrolimus, MTX, MMF)	81 (1)	11 (1)	3 (<1)
CSA alone	85 (1)	12 (1)	4 (<1)
Other GVHD prophylaxis	148 (1)	19 (1)	15 (2)
Missing	75 (1)	14 (1)	5 (1)
Donor/Recipient sex match			
Male-Male	3666 (33)	646 (35)	285 (33)
Male-Female	2322 (21)	388 (21)	182 (21)
Female-Male	2791 (25)	415 (22)	196 (23)
Female-Female	2200 (20)	374 (20)	164 (19)
CB - recipient M	21 (<1)	16 (1)	8 (1)
CB - recipient F	11 (<1)	7 (<1)	5 (1)
Missing	60 (1)	13 (1)	11 (1)
Year of transplant			
2006-2010	601 (5)	71 (4)	61 (7)
2011-2015	3701 (33)	503 (27)	203 (24)
2016-2020	5028 (45)	894 (48)	399 (47)
2021-2022	1741 (16)	391 (21)	188 (22)
Follow-up among survivors, Months			
N Eval	6629	1113	510
Median (Range)	35 (0-150)	24 (0-124)	24 (0-148)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Graft-Versus-Host Disease Working Committee Members

FROM: Stephanie Lee, MD, MPH and Stephen Spellman, MBS; Scientific Directors for GVWC

RE: Studies in Progress Summary

GV18-02: Comparison of bacterial blood stream infection incidence in allogeneic stem cell transplantation patients with and without acute graft vs host disease (Wallis W/ Alousi AM/ Gulbis A)
This study aims to determine the incidence of bacterial bloodstream infections (BSI) in patients with acute GVHD II-IV. An existing finalized dataset from the CIBMTR's Infection Working Committee was found to be a suitable data source to address the questions posed in GV18-02. The manuscript is currently in progress and the plan is to submit by July 2023.

GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A)
This study aims to compare allo-HCT outcomes between recipients with older (≥ 55 years old) HLA-matched related donors without clonal hematopoiesis and recipients with young (< 25 years old) HLA-matched unrelated donors. Next-generation sequencing will be used to determine the prevalence of clonal hematopoiesis in the older donor samples obtained from the CIBMTR research sample repository. The manuscript is currently in progress and the plan is to submit by July 2023.

GV20-01: Machine learning models and clinical decision support tool for acute and chronic graft-versus-host disease in patients with acute myelogenous leukemia undergoing allogeneic transplants (Kindwall-Keller T/ Lobo B)
This study aims to develop a machine learning model to predict the risk of developing acute and chronic GVHD in adult AML patients based on patient, disease and transplant-specific factors. The end goal is to create a tool that will provide information to both physician and patient to support clinical decision-making regarding transplant. The analysis is currently in progress.

GV20-02: Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (Sandhu K/ Altin J/ Askar M/ Nakamura R)
This study aims to evaluate the performance of a risk score derived from the MHC-PepSeq assay in predicting the development of acute and chronic GVHD in recipients of allogeneic HCT from either an 8/8 matched donor with mismatch in HLA-DP or a 7/8 mismatched donor. The protocol was reviewed at the CIBMTR Statistical Meeting in Fall 2022 and the study population was further expanded. The plan is to have the data file prepared for analysis by July 2023.

GV21-01/GV22-03: Racial, ethnicity and socioeconomic disparity in outcome of patients with graft versus host disease (Farhadfar N/ Wingard JR/ Al-Mansour Z/Rashid N)
This study aims to compare the clinical manifestations and severity of acute/chronic GVHD between racial, ethnic, and socioeconomic groups among allogeneic HCT recipients who developed chronic

GVHD. A secondary aim is to evaluate the impact of race and socioeconomic status on long-term outcomes after diagnosis of acute/chronic GVHD. The results for the chronic GVHD cohort were presented as a poster presentation at ASH 2022. The plan is to have the analysis for the acute GVHD cohort completed by July 2023.

GV21-02: Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation: A validation study (Pidala J/ Logan B/ Martens M)
This study aims to develop and validate prediction models for immune suppression discontinuation and immune suppression discontinuation failure in patients who received allogeneic HCT for hematologic malignancies. The protocol was reviewed at the CIBMTR Statistical Meeting in January 2022. The plan is to have the analysis completed by July 2023.

GV22-01: Acute and chronic graft versus host disease in infants and toddlers following hematopoietic cell transplantation (Nishitani M/ Duncan C/ Graham R/ Qayed M)
This study aims to compare the incidence and severity of acute and chronic GVHD in children and young adults following HCT between 2002-2011 and 2012-2021 and to evaluate the impact of transplant related factors on GVHD risk. Protocol development is currently in progress. The plan is to have the protocol approved by July 2023.

GV22-02: Chronic GVHD Risk Index: A clinical risk assessment score for development of moderate-severe chronic graft-versus-host disease after hematopoietic cell transplantation (Im A/ Pavletic S)
This study aims to develop and validate a risk score based on weighted clinical factors to predict the likelihood of developing moderate-severe chronic GVHD. The protocol was reviewed at the CIBMTR Statistical Meeting in January 2023. The plan is to have the data file finalized for analysis by July 2023.

CIBMTR Study Proposal

Study Title:
The Effect of Graft-Versus-Host Disease Prophylaxis on Survival after HLA-Matched Hematopoietic cell transplantation (HCT): a CIBMTR analysis.

Key Words: Older Adults, Acute Myeloid Leukemia, Post-transplant Cyclophosphamide, Myelodysplastic Syndrome

1st PI Information:
PI Name (First, Middle, Last): Munshi, N, Pashna
Degree(s): MD
Academic Rank: Assistant Professor of Medicine, Division of Hematology/Oncology
Email Address: pashna.n.munshi@gunet.georgetown.edu
Institution Name: MedStar Georgetown University Hospital, Washington, DC

2nd PI Information:
PI Name (First, Middle, Last): Mehta, S, Rohtesh
Degree(s): MD
Academic Rank: Assistant Professor of Medicine, Division of Hematology/Oncology
Email Address: RMehta1@MDAnderson.org
Institution Name: MD Anderson, Houston, TX

3rd PI Information:
PI Name (First, Middle, Last): Shannon, Rose, McCurdy
Degree(s): MD
Academic Rank: Assistant Professor of Medicine, Division of Hematology/Oncology
Email Address: shannon.mccurdy@pennmedicine.upenn.edu
Institution Name: The University of Pennsylvania, Perelman School of Medicine

Proposed Working Committee:
Graft Sources and Manipulation

Research Questions:

1) Is there a difference in the GVHD-free relapse-free survival (GRFS) in recipients of HLA-matched donor hematopoietic cell transplantation (HCT) who received post-transplant cyclophosphamide (PTCy) / calcinuerin inhibitor (CNI)-based GVHD prophylaxis versus CNI/methotrexate (MTX)-based GVHD prophylaxis after myeloablative conditioning?
2) Does PTCy/CNI improve the long-term survival of older adults undergoing HLA-matched allogeneic transplantation by decreasing late mortality secondary to chronic graft-versus-host disease (GVHD) and improve GRFS when compared to ATG?
3) What is the impact on QoL (quality of life) for those getting PTCy versus other regimens at 6 months, 1-year, and 2-years following allo-HCT?

Research Hypotheses:

We hypothesize that post-transplant cyclophosphamide (PTCy) will be associated with improved graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS) due to less non relapse mortality (NRM) compared with other graft-versus-host disease (GVHD) prevention strategies in hematopoietic cell transplantation (HCT) recipients receiving either MAC or RIC regimens and that in older adults the 1-year improvement in GRFS demonstrated in the BMT CTN 1703 study will translate to reduced late transplant mortality and improve 2-year overall survival compared to other platforms.

Specific Objectives:

1) To determine GVHD-free-relapse-free survival (GRFS) and the overall survival (OS) in patients receiving HLA-matched (related and unrelated) allogeneic HCT in patients receiving PTCy, CNI/methotrexate or ATG based regimens following MAC or RIC.
2) To determine whether PTCy results in less late NRM, but comparable relapse, translating to improved overall survival after HCT for older recipients from years 1 to 2 after allo-HCT.
3) To determine the quality of life (QoL) at 6 months , 1 year, and 2 years following PTCy based regimen compared with MTX/CNI or ATG based regimens.

Scientific Impact:

BMT CTN 1703 (Holtan S, et al. ASH 2022) focused on PTCy efficacy in the RIC setting demonstrating an improved 1-year GRFS. However, that study did not include a comparative ATG arm, did not include a MAC subgroup, nor did it look at late outcomes in the RIC cohort exclusively in older adults. In this study, we propose evaluating PTCy efficacy compared to Tac/MTX or ATG in the MAC platform as well as late survival after RIC with PTCy. We hypothesize that the improvement in GRFS seen with PTCy in RIC regimens may also be evident in younger recipients of HLA-matched transplantation receiving MAC and that decreases in chronic GVHD will lead to improvements in late mortality after 1 year. In addition, we will evaluate the efficacy of PTCy based regimens in comparison to ATG based regimens as a subgroup analysis in patients getting any conditioning intensity.

In the primary analysis of BMT CTN 1703 (Holtan S, et al. ASH 2022), PTCy resulted in superior GRFS at 1 year (HR 0.64, $p<0.001$) with a trend towards better, but no significant improvement in OS. We suspect that this is likely due to the short follow up period. With longer follow up, OS benefit resulting from lower chronic GVHD and improved NRM, is likely to be noted in those receiving PTCy. We also predict that this difference could be more pronounced in older patients who have a higher NRM beyond year one from allo-HCT.{Imus, 2019 #205} In the BMT CTN 1703 study, the median age for patients getting PTCy was 66 years, oldest patient being 78 years of age, showing that PTCy is well tolerated by this population, yet OS benefit is not seen. We propose evaluating for outcomes in patients 60 years and older who survived to 1 year to show that PTCy may improve late mortality after HCT relative to other platforms. As more older patients receive allo-HCTs, the ideal GVHD regimen for this population remains unknown. Patients over 70 were almost never transplanted before 2007 and in 2018 they made up 9% of HCT recipients.[1] However, the number of patients over the age of 70 are still over-represented in terms of the burden of these fatal cancers and under-represented amongst patients receiving curative HCT because of its associated toxicity. Given the advent of novel effective remission-inducing therapies for older patients with hematologic malignancies, and feasibility of RIC and NMA regimens, we need to define the optimal HCT platform for this growing demographic of HCT recipient: those 60 years and older. We also need to understand the effects of different regimens on late mortality, an outcome to which older adults are particularly susceptible.

Although the BMT CTN study concluded that PTCy should be the new standard of care for RIC regimens, this question has not been answered for MAC regimens. A recent Phase II study from University of

Minnesota (Hoover A, et al. ASH 2022) in patients younger than 60 years receiving MAC regimen, showed the efficacy of PTCy with extremely low rates of cGVHD when compared to a similar cohort of patients receiving non PTCy based regimens. While the outcomes of the BMT CTN 1301 in MAC did not demonstrate a chronic GVHD-free, relapse-free survival in PTCy recipients, this platform did not include MMF or CNI as part of the PTCy platform and thus rates of GVHD were higher than seen with PTCy/CNI. Therefore, we propose to evaluate PTCy/CNI compared with Tac/MTX and ATG based platforms to establish the standard of care for younger patients receiving HLA-matched HCT.

Scientific Justification:

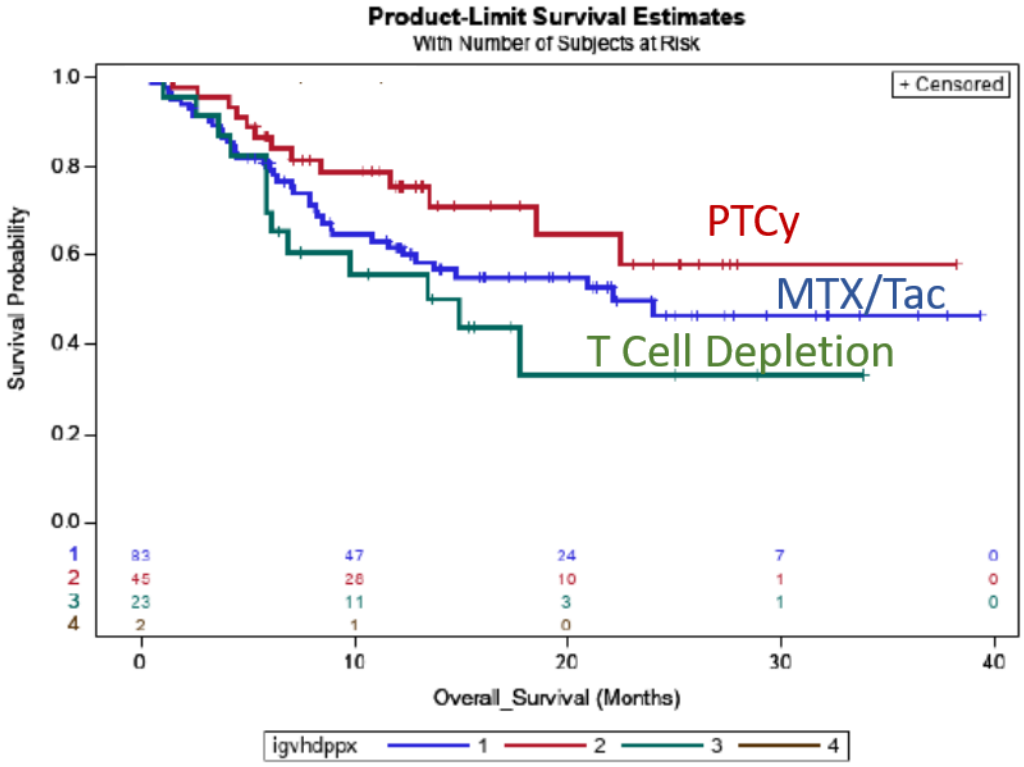
Currently, tacrolimus/methotrexate (Tac/MTX) has been the standard GVHD prophylaxis in HLA-matched donors with either MAC (BMT CTN 1301) or RIC (BMT CTN 1203) since the 1980's, and is used as a control arm in most of the BMT CTN clinical trials. The use of PTCy for GVHD prophylaxis is increasing in patients undergoing HLA-matched sibling (MSD) or unrelated (MUD) donor HCT, but data about its comparative efficacy against the traditional GVHD prophylaxis are scarce until recent BMT CTN 1703. Three registry studies by EBMT assessed the efficacy of PTCy vs conventional prophylaxis in MSD (without ATG), MSD (with ATG) and MUD (with ATG).[2-4] No such study has been done by CIBMTR yet. As practice disparities exist in the GVHD prophylaxis and conditioning regimens, among other factors, between the European and US centers, and given the rise in the use of PTCy-based prophylaxis in HLA- matched donors, such a study by the CIBMTR is timely, particularly since BMT CTN 1703 results can be practice changing.

Our study also wishes to compare MUD transplants with and without ATG based regimens to PTCy, which has not been done in the BMT CTN 1703 prospective study. An analysis of 964 patients treated at our institution with HLA-matched donors suggested that PTCy positively impact GRFS in both MSD setting (without ATG) as well as MUD setting (with ATG).[5] We found that the use of PTCy was associated with a significantly improved GRFS in both MSD (vs Tac/MTX without ATG) and MUD (vs Tac/MTX with ATG) cohorts, but the distribution of events contributing to GRFS differed by the donor type. In the MUD cohort, the use of PTCy resulted in a comparable risk of acute and chronic GVHD as Tac/MTX/ATG. However, PTCy was associated with a significantly improved PFS and lower NRM, likely related to a lower risk of viral infections and related deaths than in the ATG arm. In the MSD cohort, where no patient received ATG with Tac/MTX, the use of PTCy was associated with a significantly lower risk of cGVHD and therapy-requiring cGVHD, which resulted in superior GRFS. PTCy was also associated with a significantly lower NRM, but not in F-to-M, where PTCy was instead associated with a higher risk of NRM. The risk of NRM did not differ by gender mismatch among those who received Tac/MTX prophylaxis.[5]

PTCy has also been associated with a low NRM and safe outcomes in older HCT recipients.[6] Compared to SOC GVHD prophylaxis (tacrolimus and low-dose methotrexate), PTCy may more effectively prevent both severe acute GVHD and chronic GVHD[7] and result in low rates of NRM. This is now confirmed with the recent prospective BMT CTN 1703 (ASH 2022) study which enrolled median age 66 years patients, all receiving RIC regimens showing and met its primary endpoint of higher GRFS at 1 year (52.7% with PTCy [95% CI: 45.8%, 59.2%] vs. 34.9% for control arm [95% CI: 28.6%, 41.3%]. However, OS benefit was not seen at 1-year in the PTCy cohort and relapse rates were no different. This implies that other factors pertaining to NRM are likely underplay. Older patients tolerate the prolonged inflammatory state of

chronic GVHD poorly, with a high incidence of cardiac events and infectious death, therefore an approach that limits chronic GVHD could substantially reduce late morbidity and mortality. In addition, medications to treat or prevent GVHD such as prednisone and tacrolimus are associated with many complications, including hyperglycemia, hyperlipidemia, fractures, and kidney injury, to which older patients are more prone. Given these scenarios, we wish to study the outcomes of older patients, 60+ years, who are alive at 1 year after HCT to evaluate the effects of the GVHD prophylaxis platform on late mortality and 2-year OS. Furthermore, quality of life is critical outcome for older adults, therefore, if the data is available, we propose to also compare quality of life between the platforms.
In our preliminary work that was the foundation for this proposal, we demonstrated that PTCy was associated with improved outcomes relative to the SOC (methotrexate and tacrolimus) or T-cell depletion strategies (Figure 1). Thus, we propose to study this preliminary finding in a larger cohort.

Figure 1: Survival for Patients 60 years and Older Undergoing HCT by Graft-Versus-Host Disease Prophylaxis Strategy



Currently the combined proposal 1906-03/19-11-31/1911-139/1911-169/1911-196 is evaluating outcomes of PTCy in haplo-HCT compared to 8/8 HLA matched related and unrelated donor HCT for AML and MDS. Therefore, much of this data will be available to complete our study.The registry study by Gooptu et al.[8] looked at PTCy in haploidentical versus MUD transplants. Since this study did not address PTCy compared to SOC calcineurin inhibitor treatments, specifically in the older patients, our proposal has great value in answering that question. Furthermore, the data set from the study can be expanded from 2011 to 2021 to have a decade's worth of information comparing PTCy versus SOC in older AML/MDS patients receiving a MUD transplant.

If PTCy in this setting has similar outcomes related to GVHD and/or relapse, then patients can be spared conventional GVHD regimens using ATG, methotrexate etc. and limiting toxicities and added cost of care.

Patient Selection Criteria:
All patients in the United States or Europe receiving an HLA-matched related (MRD) or unrelated (MUD) HCT with either PTCy, methotrexate and tacrolimus, or ATG up through one year prior to the analysis.
Transplant type: MAC or RIC/NMA allo-HCTs.
Disease type: AML, MDS, ALL
Graft: PB and Bone marrow
Exclude patients with ex-vivo T cell depletion

Data Requirements:
Forms:
2000: Recipient baseline data
2005: Confirmation of HLA typing (for both donor and recipient)
2450: post-transplant essential data (for engraftment, chimerism, GVHD, relapse, non-relapse mortality, survival)
We believe the data available through the CIBMTR forms will be adequate to answer our question.

Patient-Reported Outcome (PRO) Requirements:
1. 8 PROMIS domains – Physical function, Fatigue, Sleep disturbance, Anxiety, Depression, Cognitive function, Ability to participate in social roles and activities, and Sexual function. T-scores for these domains will be used in extracts for analysis and in DBTC (data back to center) visualizations and extracts.
2. The Comprehensive Score for Financial Toxicity (COST) assessment that will have both scores and item-level data available.
3. Occupational functioning and demographic data at specified time points for specific analyses.

Sample Requirements:
No requirements for samples.

Study Design:
The primary endpoint is GRFS by GVHD prevention strategy (PTCy vs. methotrexate/tacrolimus vs. ATG). Power calculations will be based on this primary endpoint. Additional endpoints are 2-year overall survival and NRM, landmark analyses in patients surviving to 1-year post-HCT, and incidences of acute and chronic graft-versus-host disease, relapse, non-relapse mortality, CRFS, and the Kaplan-Meier progression-free survivals between the groups.

Outcomes shall be analyzed for the entire population and/or according to the following planned subgroups: 1) Diagnosis; 2) stem cell source (peripheral blood vs. bone marrow); 3) Disease risk index; 4) Age, 5) HCT-CI, 6) conditioning intensity.

<u>Variables to be analyzed for inclusion in the multivariable analysis:</u>

Patient-related:

- Age at HCT, years: <10, 10-17, 18-29, 30-39, 40-49, 50-59, 60-65, 65-69, 70-75, 76+ and continuous
- Sex: male vs female
- Karnofsky performance score: ≥90% vs. <90%
- HCT comorbidity index at transplant 0, 1, 2, and ≥ 3
- Race: White vs. Black vs. Asian/pacific islander vs. others
- CMV status: seropositive vs. seronegative.

Disease-related:

- Disease diagnosis
- Disease-Risk Index (low/intermediate vs. high/very high)
- Time from last treatment to allogeneic HCT
- Time from diagnosis to allogeneic HCT

Transplant-related:

- Bone marrow vs. peripheral blood as a graft source
- Conditioning regimen: RIC vs. NMA (using standard CIBMTR definitions).
- Year of HCT
- Donor/Recipient gender (F-to-M vs. other)
- Donor/Recipient CMV status (CMV- D/CMV+ R vs. other)
- HLA match
- Donor age – continuous and in decades
- Donor relationship
- GVHD prophylaxis used (PTCy-based, ATG-based, or methotrexate/tacrolimus)
- Viable CD34+ cells/kg of recipient infused (if available)
- TNC/kg of recipient (if available)
- CD3+/kg of recipient before thawing (if available)

Non-CIBMTR Data Source:

We would be open to potential for collaboration with the EBMT if it is determined that additional patient numbers are needed for statistical power, but this is not a requirement for the study.

References:

1. D'Souza A, Fretham C, Lee SJ, et al: Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biology of Blood and Marrow Transplantation 26:E177-E182, 2020
2. Nagler A, Labopin M, Dholaria B, et al: Graft-versus-Host Disease Prophylaxis with Post-Transplantation Cyclophosphamide versus Cyclosporine A and Methotrexate in Matched Sibling Donor Transplantation. Transplant Cell Ther 28:86 e1-86 e8, 2022
3. Battipaglia G, Labopin M, Hamladji RM, et al: Post-transplantation cyclophosphamide versus antithymocyte globulin in patients with acute myeloid leukemia undergoing allogeneic stem cell transplantation from HLA-identical sibling donors: A retrospective analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Cancer 127:209-218, 2021
4. Brissot E, Labopin M, Moiseev I, et al: Post-transplant cyclophosphamide versus antithymocyte globulin in patients with acute myeloid leukemia in first complete remission undergoing

allogeneic stem cell transplantation from 10/10 HLA-matched unrelated donors. J Hematol Oncol 13:87, 2020

5. Mehta RS, Saliba RM, Rondon G, et al: Post-Transplantation Cyclophosphamide Versus Tacrolimus and Methotrexate Graft-Versus-Host Disease Prophylaxis for HLA-Matched Donor Transplantation. Transplant Cell Ther 28:695 e1-695 e10, 2022

6. Kasamon YL, Bolanos-Meade J, Prince GT, et al: Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults. J Clin Oncol 33:3152-61, 2015

7. Kanakry CG, Fuchs EJ, Luznik L: Modern approaches to HLA-haploidentical blood or marrow transplantation. Nat Rev Clin Oncol 13:10-24, 2016

8. Gooptu M, Romee R, St Martin A, et al: HLA-haploidentical vs matched unrelated donor transplants with posttransplant cyclophosphamide-based prophylaxis. Blood 138:273-282, 2021

Conflicts of Interest:

☐ Yes

X No

No conflicts of Interest.

Table 1. Characteristics of patients receiving first alloHCT for AML/ALL/MDS with matched donor in 2010-2020, CRF track

Characteristic	ATG	PT-Cy	Tac+MTX
No. of patients	2710	624	3909
No. of centers	195	82	136
Age at HCT			
Median (min-max)	60 (0-83)	62 (2-82)	58 (1-79)
<10	116 (4)	3 (0)	95 (2)
10-17	105 (4)	4 (1)	97 (2)
18-29	198 (7)	46 (7)	272 (7)
30-39	162 (6)	40 (6)	304 (8)
40-49	249 (9)	65 (10)	483 (12)
50-59	549 (20)	101 (16)	986 (25)
60-69	1032 (38)	290 (46)	1333 (34)
>=70	299 (11)	75 (12)	339 (9)
Recipient sex			
Male	1630 (60)	383 (61)	2318 (59)
Female	1080 (40)	241 (39)	1591 (41)
Karnofsky score			
<90	1115 (41)	275 (44)	1746 (45)
>=90	1551 (57)	343 (55)	2130 (54)
Missing	44 (2)	6 (1)	33 (1)
HCT-CI			
0	712 (26)	113 (18)	759 (19)
1	362 (13)	79 (13)	571 (15)
2	367 (14)	93 (15)	581 (15)
3	453 (17)	132 (21)	718 (18)
4	289 (11)	70 (11)	498 (13)
5	214 (8)	56 (9)	288 (7)
6+	265 (10)	77 (12)	458 (12)
Missing	48 (2)	4 (1)	36 (1)
Primary disease for HCT			
AML	1146 (42)	308 (49)	1851 (47)
ALL	354 (13)	85 (14)	552 (14)
MDS	1210 (45)	231 (37)	1506 (39)
Donor type			
HLA-identical sibling	442 (16)	203 (33)	1712 (44)
Well-matched unrelated (8/8)	2268 (84)	421 (67)	2197 (56)

Characteristic	ATG	PT-Cy	Tac+MTX
Graft type			
Bone marrow	410 (15)	148 (24)	698 (18)
Peripheral blood	2300 (85)	476 (76)	3211 (82)
Conditioning intensity			
MAC	1297 (48)	274 (44)	2302 (59)
RIC	1152 (43)	249 (40)	1457 (37)
NMA	117 (4)	78 (13)	70 (2)
TBD	38 (1)	1 (0)	57 (1)
Missing	106 (4)	22 (4)	23 (1)
Year of HCT			
2010	194 (7)	0 (0)	399 (10)
2011	158 (6)	10 (2)	196 (5)
2012	182 (7)	8 (1)	244 (6)
2013	354 (13)	18 (3)	467 (12)
2014	411 (15)	31 (5)	577 (15)
2015	354 (13)	73 (12)	550 (14)
2016	353 (13)	98 (16)	455 (12)
2017	266 (10)	81 (13)	349 (9)
2018	224 (8)	102 (16)	326 (8)
2019	159 (6)	99 (16)	243 (6)
2020	55 (2)	104 (17)	103 (3)
Median follow-up of survivors (range), months	59 (3-124)	34 (2-97)	60 (3-128)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

PTCy/CNI with or without MMF in HLA-matched donor HCT

Q2. Key Words

PTCy, MMF, CNI, HLA matched donors, GVHD, relapse

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Rohtesh S. Mehta, MD MPH MS
Email address:	rmehta1@mdanderson.org
Institution name:	MD Anderson Cancer Center
Academic rank:	Associate Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	N/A
Email address:	N/A
Institution name:	N/A
Academic rank:	N/A

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

N/A

Q8. Do you identify as an underrepresented/minority?

N/A

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Stephen Spellman

Q15. RESEARCH QUESTION:

A broad question is to address the utility of adding MMF to PTCy/CNI prophylaxis with HLA-matched donor HCT.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that the addition of MMF to PTCy/CNI would be associated with a higher risk of aGVHD (mostly grade II) wit no impact on grade III-IV aGVHD, chronic GVHD or survival as compared to PTCy/CNI without MMF in patients with HLA-matched donors.
This is based on the results of our single center study that included 386 adult patients with any hematologic malignancy who underwent first allogeneic HCT using an HLA-matched donor between January 2015 and July 2020 (details below).

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

The objectives are to compare the rates of aGVHD and cGVHD, engraftment, chimerism, NRM, relapse, PFS, and OS in patients who received PTCy/CNI-prophylaxis with or without MMF after HLA-matched donor HCT.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The current PTCy-based GVHD prophylaxis regimens include a calcineurin inhibitor (CNI, such as tacrolimus) generally with mycophenolate mofetil (MMF), which was adapted from the haploidentical transplantation literature. However, no study has directly compared the benefits of adding MMF to the PTCy/CNI backbone in HLA-matched donors. The results of our single center study suggest that MMF was associated with a paradoxically higher risk of grade II aGVHD than those who did not receive MMF. These findings need to be corroborated or refuted in a larger cohort of patients, which can be only powered sufficiently through registry studies, such as the CIBMTR. If confirmed, these findings have potentially practice-changing implications.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Adapted from the haploidentical transplantation literature, the use of PTCy is increasingly being used with HLA-matched donors, generally with a calcineurin inhibitor, such as tacrolimus (Tac) with or without mycophenolate mofetil (MMF). Owing to it's immunosuppressive, potentially antitumor, and antimicrobial properties, MMF is an attractive drug; however, it remains unclear how much benefit is gained when used with PTCy/Tac. To assess that, we compared PTCy/Tac (n=242) to PTCy/Tac/MMF (n=144) in recipients of HLA-matched donors who were treated at our center. [Mehta et al. Transplant Cell Ther. 2022 Aug;28(8):500.e1-500.e10]

In multivariate analysis, we noted that the PTCy/Tac/MMF group had a significantly higher risk of grade II-IV aGVHD (HR 2.1, 95% CI 1.6-2.8, p<0.001), and steroid-refractory/dependent aGVHD (HR 4.8, 95% CI 2.4-9.6, p<0.001), yet a significantly lower risk of relapse (HR 0.5, 95% CI, 0.3-0.9, p=0.009) and better PFS (HR 0.7, 95% CI 0.5-0.9, p=0.04). There was no difference in the risk of grade III-IV acute GVHD, chronic GVHD, non-relapse mortality, or overall survival [Mehta et al. Transplant Cell Ther. 2022 Aug;28(8):500.e1-500.e10]. The higher risk of aGVHD with MMF is postulated to be related to the selective dominance of β-glucuronidase (GUS)-producing bacteria in the gut. These GUS-producing bacteria cleave glucuronic acid from glucuronide mycophenolic acid glucuronide, producing free MPA, which is toxic to the mucosa. The integrity of the GI tract plays a critical role in the pathophysiology of GVHD, and ample evidence from preclinical and clinical studies have established that the GI tract is not only a major target of GVHD, but also has a crucial role in the amplification of systemic GVHD. Thus, damage to the gut mucosa by GUS-producing bacteria (overgrowth due to the use of MMF) can trigger GVHD. This has been noticed in previous studies in solid-organ transplant. [Flannigan et al. Front Cardiovasc Med, 4 (2017), p. 17] & [taylor et al. Sci Adv, 5 (2019), p. eaax2358]. This finding was also supported in our study where stool samples at the onset of LGI aGVHD were available in a limited number of patients (n=16). We noted that the PTCy/Tac group (n = 8) had higher relative abundances of Akkermansia and Verrucomicrobiae, whereas the PTCy/Tac/MMF arm (n = 8) had higher relative abundances of Staphylococcus, Lactobacillus gasseri, and Negativicutes – all of which produce GUS. [Mehta et al. Transplant Cell Ther. 2022 Aug;28(8):500.e1-500.e10]. Another mechanism of increased GVHD related to MMF can be attributed to its inhibitory effects on NK cells and Tregs [Slight-Webb et al. JCI Insight, 4 (2019), Article e124575]. PTCy exerts its GVHD prophylaxis via preferential expansion of regulatory T cells (Tregs), which could potentially be inhibited by MMF via its inosine-5′-monophosphate dehydrogenase (IMPDH) inhibitory effect. Analysis of blood samples/PBMCs through the NMDP sample repository of patients treated on the previous CTN trials, such as the CTN 1203, CTN 1301, and CTN 1703 may provide further insights.

Overall, there is reasonable background evidence to support our hypothesis, and further studies with a larger sample size, such as through the CIBMTR, are needed to define the role of MMF with PTCy-based prophylaxis in HLA-matched donors.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

[Click here]

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

1. All ages (both peds and adults)
2. Any hematologic malignancy
3. HLA-matched donor HCT with PTCy/CNI (+/- MMF) prophylaxis
4. Include both RIC and MAC
5. Include both BM and PBPC graft
6. HCT from 2014 onwards (when PTCy use increased)
7. Exclude patients with ex-vivo T cell depletion
8. Exclude patients with ATG or alemtuzumab use

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Some of the important covariates to include in analysis:
1. Patient and donor age
2. Donor type (MSD or MUD)
3. Graft source (BM vs PBPC)
4. Gender mismatch (female-to-male)
5. Conditioning intensity (MAC vs RIC)
6. TBI vs chemotherapy
7. GVHD prophylaxis (PTCy/CNI/MMF vs PTCy/CNI)
8. DRI
9. HCT-CI
10. CMV serostatus Data Requirements:

Patient-related:
- Age at transplant
- Recipient gender
- Disease
- Disease status at HCT
- HCT-specific comorbidity index (HCT-CI)
- Revised disease risk index (DRI)
- Karnofsky performance score (KPS) HCT
- Recipient cytomegalovirus (CMV) status
- ABO typing Donor/graft-related:
- Donor age
- Donor gender
- Donor relationship
- Donor cytomegalovirus (CMV) status
- Donor ABO typing
- Graft source (PB, BM)
- Total nucleated cell (TNC) dose
- CD34 dose
- CD3 dose Transplant-related:
- Conditioning regimen intensity
- Conditioning regimen
- GVHD prophylaxis
- Year of transplant

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

N/A

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

Mehta et al. Transplant Cell Ther. 2022 Aug;28(8):500.e1-500.e10
Flannigan et al. Front Cardiovasc Med, 4 (2017), p. 17
Taylor et al. Sci Adv, 5 (2019), p. eaax2358
Slight-Webb et al. JCI Insight, 4 (2019), Article e124575

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of patients receiving first alloHCT for hematologic malignancy with matched donor in 2014-2020, CRF track

Characteristic	PTCy + MMF	CNI + MMF	PTCy (without MMF)	CNI (without MMF)
No. of patients	627	671	243	5390
No. of centers	87	92	49	195
MD Anderson patient?				
No	589 (94)	667 (99)	213 (88)	5313 (99)
Yes	38 (6)	4 (1)	30 (12)	77 (1)
Age at HCT				
Median (min-max)	62 (2-82)	60 (0-81)	56 (2-82)	58 (1-79)
<10	2 (0)	11 (2)	2 (1)	154 (3)
10-17	2 (0)	20 (3)	4 (2)	201 (4)
18-29	44 (7)	36 (5)	14 (6)	408 (8)
30-39	43 (7)	38 (6)	26 (11)	404 (7)
40-49	64 (10)	71 (11)	42 (17)	635 (12)
50-59	118 (19)	152 (23)	65 (27)	1221 (23)
60-69	275 (44)	259 (39)	69 (28)	1858 (34)
>=70	79 (13)	84 (13)	21 (9)	509 (9)
Sex				
Male	356 (57)	403 (60)	162 (67)	3245 (60)
Female	271 (43)	268 (40)	81 (33)	2145 (40)
Karnofsky score				
<90	296 (47)	336 (50)	93 (38)	2265 (42)
>=90	326 (52)	329 (49)	146 (60)	3044 (56)
Missing	5 (1)	6 (1)	4 (2)	81 (2)
HCT-CI				
0	109 (17)	142 (21)	52 (21)	1215 (23)
1	75 (12)	94 (14)	33 (14)	749 (14)
2	91 (15)	88 (13)	48 (20)	805 (15)
3+	343 (55)	329 (49)	104 (43)	2507 (47)
TBD	9 (2)	18 (2)	6 (3)	114 (2)
Disease				
AML	211 (34)	205 (31)	102 (42)	1688 (31)
ALL	53 (8)	56 (8)	31 (13)	703 (13)
OL	9 (1)	16 (2)	2 (1)	111 (2)
CML	17 (3)	15 (2)	2 (1)	131 (2)
MDS	159 (25)	251 (37)	50 (21)	1489 (28)
OAL	8 (1)	6 (1)	4 (2)	46 (1)

Characteristic	PTCy + MMF	CNI + MMF	PTCy (without MMF)	CNI (without MMF)
NHL	37 (6)	41 (6)	9 (4)	313 (6)
HD	45 (7)	12 (2)	7 (3)	95 (2)
PCD	7 (1)	7 (1)	4 (2)	99 (2)
MPN	81 (13)	62 (9)	32 (13)	715 (13)
Donor type				
HLA-identical sibling	124 (20)	345 (51)	87 (36)	2220 (41)
Well-matched unrelated (8/8)	503 (80)	326 (49)	156 (64)	3170 (59)
Graft type				
Bone marrow	104 (17)	74 (11)	116 (48)	939 (17)
Peripheral blood	523 (83)	597 (89)	127 (52)	4451 (83)
Conditioning intensity				
Myeloablative	217 (35)	280 (42)	183 (75)	2896 (54)
Reduced intensity	410 (65)	391 (58)	60 (25)	2494 (46)
Year of HCT				
2014	20 (3)	163 (24)	15 (6)	1126 (21)
2015	61 (10)	140 (21)	17 (7)	969 (18)
2016	54 (9)	112 (17)	55 (23)	902 (17)
2017	73 (12)	89 (13)	72 (30)	765 (14)
2018	128 (20)	83 (12)	49 (20)	701 (13)
2019	146 (23)	58 (9)	33 (14)	573 (11)
2020	145 (23)	26 (4)	2 (1)	354 (7)
Median follow-up of survivors (range), months	36 (0-78)	60 (3-101)	48 (2-98)	52 (0-101)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplant.

Q2. Key Words

anti-thymocyte globulin, GVHD, infection

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Molly Gallogly
Email address:	molly.gallogly@uhhospitals.org
Institution name:	University Hospitals Seidman Cancer Center
Academic rank:	Assistant Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Leland Metheny
Email address:	leland.metheny@uhhospitals.org
Institution name:	University Hospitals Seidman Cancer Center
Academic rank:	Assistant Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- Yes

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Molly Gallogly

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

What is the optimal anti-thymocyte globulin (ATG) dose based on conditioning intensity, donor choice (MRD, MUD, MMUD, CB), stem cell source (BM or PB) and risk factors for acute and chronic graft versus host disease (GVHD)?

Q16. RESEARCH HYPOTHESIS:

The optimal anti-thymocyte globulin (ATG) dosing is unknown and may be individualized based on conditioning intensity, donor choice (MRD, MUD, MMUD, CB), stem cell source (BM or PB) and risk factors for acute and chronic graft versus host disease (GVHD).

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

1. To determine the optimal dose of ATG at which the risk of acute and chronic GVHD and risk of post-HCT infectious complications and relapse are balanced as demonstrated by graft versus host disease-free relapse-free survival (GRFS)
2. To investigate the difference in overall survival (OS) in patients who underwent matched related donor (MRD), matched unrelated donor (MUD), mismatched unrelated donor (MMUD) or cord blood (CB), transplant with myeloabliative (MAC), or reduced intensity (RIC) / non-myeloablative (NMA) conditioning with varying doses of ATG.
3. To investigate the differences in treatment-related mortality (TRM), relapse incidence (RI) and disease-free survival (DFS) in these patients.
4. To investigate the differences in incidence of acute and chronic graft-versus-host-disease (GVHD) in these patients.
5. Identify whether patients with established risk factors for acute GVHD benefit from higher ATG dosing than patients without risk factors for acute GVHD.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Patients undergoing allogeneic hematopoietic cell transplantation (HCT) receive immunosuppression to facilitate engraftment and reduce the incidence and severity of acute and chronic GVHD. At many centers, in-vivo T cell depletion is routinely undertaken to reduce the incidence and severity of GVHD, however, no standardized practice exists, and clinical experience is variable. There are two major formulations of ATG and each formulation has a different recommended dose range (Baron, 2017). Currently in the United States, thymoglobulin (ATG-T) is utilized with dose range of 2.5-10mg/kg. In Europe, Neovii/Grafalon (ATG-F) is utilized as well, with a range of 15-60mg/kg. For the purposes of this study we will be dealing with ATG-T, only.

Early work established a correlation between ATG use, GVHD, and infectious complications. Initially, a total of 55 patients were randomized to 90 or 60 or 30mg/kg of rabbit ATG-F vs. no ATG. Those treated with ATG-F had significantly less grade III-IV GVHD, however, there was a higher incidence of lethal infections resulting in equivalent TRM between the two groups (Bacigalupo, 2001). Separately, in an analysis of patients undergoing matched related donor (MRD) HCT, patients received ATG-T at 2.5mg/kg for either 4, 3 or 1 days, ATG use correlated with a lower rate of aGVHD and a trend toward a higher relapse (Kroger, 2002). In the reduced intensity conditioning (RIC) MRD setting, higher ATG-T doses (7.5 to 10mg/kg) were associated significantly less GVHD at two years compared to patients receiving 2.5mg/kg of ATG (Mohty , 2003). Finally, 44% of patients receiving 4mg/kg of ATG developed acute and chronic GVHD compared to <15% of patients receiving 6-8mg/kg of ATG (Meijer, 2003).

Three retrospective analyses reported similar outcomes. In the first, Remberger and colleagues evaluated four different ATG doses in 162 patients receiving HCTs from matched unrelated donors (MUD). Lower ATG dosing was associated with a higher incidence of GVHD associated deaths whereas higher dosing was associated with more infectious deaths. Patient that received moderate doses of 6-8mg/kg experienced lower TRM and improved OS suggesting a possible target dosing range for recipients of unrelated donors(Remberger , 2004). In the second retrospective analysis, there was no significant difference in the cumulative incidence of acute GVHD, however, ATG dosing at 6mg/kg resulted in lower rates of CMV reactivation and bacterial infections, and an improved 1-year non-relapse mortality (NRM) and trend toward improved 1 year OS compared to 7.5mg/kg (Hamadani, 2009). Finally, comparisons between ATG doses of 6mgk/kg vs. 7.5mg/kg in the RIC setting showed no significant difference in acute or chronic GVHD, NRM, relapse, PFS, and OS between groups (Salem, 2015). As of yet, no large-scale analysis has been undertaken to identify the optimal dosing.

The ATG dosing question was highlighted following two large randomized studies, each with a different ATG-F dose and a different patient population. Soiffer et al. compared outcomes in the MAC MUD setting between a cohort that received a total of 60mg/kg of ATG-F with a cohort that did not received ATG (Soiffer, 2017). Although patients in the ATG cohort experienced lower grade II-IV aGVHD and moderate to severe cGVHD, the overall survival and progression free survival were lower in the ATG cohort. Kroger et al. compared outcomes in the MAC MRD setting between cohorts that received a total of 30mg/kg of ATG-F with a cohort that did not received ATG. There was no survival difference between cohorts, the rate of cGVHD was lower in the ATG cohort (Kroger, 2016). These studies do not address the utility of ATG in the RIC setting, where a greater GVL effect may be needed to supplement the conditioning regimen. It is also important to highlight that these two studies utilizes ATG-F, which is not used in the United States and therefore these studies, while interesting, do not inform US clinical practice.

Previous critiques of this proposal have focused on the lack of data on timing of ATG-T dosing before transplant. We argue that the standard practice of ATG dosing and timing is likely according to previous published studies (i.e. Walker, 2016 & Ruutu 2013), and timing of ATG-T should therefore not be a barrier. We also argue that this critique has not stopped other research bodies from publishing meaningful and practice informing results. For example, the EBMT has recently published a retrospective analysis on the effect of ATG-F with MUD PBMC vs. no ATG-F with MUD BM grafts following myeloabalative conditioning for AML (Baron , 2020). This study suggested that MUD PBSC with ATG-F have comparable, or slightly better, GRFS than MUD BM no ATG-F grafts.

We argue that given the extensive CIBMTR dataset and the statistical, scientific and clinical expertise of this working group, we can help answer a clinical question that randomized trials have failed to answer. Namely, what is the optimal dosing for ATG-T in allogeneic transplant?

Therefore, we propose to study the impact of ATG-T dosing on clinical outcomes in patients undergoing allogeneic transplant for malignant diseases. Our hypothesis is that there will be an optimal dose of ATG-T that balances the risks of both GVHD and infection, informed by transplant conditioning, graft type, and source.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

To date, a large-scale analysis to identify the optimal dose of ATG-T has not yet been undertaken. Given the heterogeneity of the patients undergoing HCT, there may not be a single, optimal dose. Instead, ATG-T dosing may depend on intensity of the preparative regimen, donor characteristics, and recipient lymphocyte counts. The number of patients required to retrospectively determine the dosing of ATG-T in relation to these characteristics would be too significant for any one institution to undertake. The CIBMTR dataset would allow such an analysis to occur. This type of study could potentially inform ATG-T dosing as well as the design of a prospective analysis with personalized ATG-T dosing.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion Criteria:
- Patients with MDS, AML, and ALL transplanted between 2005 and 2020
- Patients transplanted within the United States (due to the exclusive use of thymoglobulin, ATG-T)
- Age 1 to 75 years
- First HCT
- PBSC or BM
- HSC Sources: MUD, mMUD, MRD, CB
- Conditioning Intensity: AMAC, RIC, NMA

Exclusion Criteria:
- Ex-vivo T-cell depletion
- Haploidentical transplant
- Horse ATG
- ATG doses over 15mg/kg (to eliminate those that may have received ATG-F on a clinical trial)

Q21. Does this study include pediatric patients?

- Yes

Q22. **DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.**

Patient-related:
– Patient age at HCT: 18-29, 30-55, vs. 56-65, vs. 66-75
– Karnofsky performance score: ≥90 vs. <90
– HCT-CI: 0 vs. 1-2 vs. ≥3
– Race
Disease-related:
– Time from diagnosis to HCT, months: < 6 vs. 6 to <12 vs. ≥ 12
– AML, ALL, MDS
– Disease status at transplant: CR1 ≥ CR2 < CR
– Disease risk status (including cytogenetics)
Transplant-related:
– Graft: MRD, MUD, MMUD, CB
– Stem cell source: PBSC vs. BM
– HLA Match: 10/10 or 9/10 related, 10/10 or 9/10 unrelated
– Conditioning intensity: MAC vs. RIC/NMA
– ATG-T
o Total prescribed dose (mg/kg): less than 1mg/kg, 1-2.9mg/kg, 2-3.9mg/kg, 4-4.9mg/kg, 5-6.9mg/kg, 7-9.9mg/kg, 10-15mg/kg
– TBI-based preparative regimen
– Female Male vs. all others.
– Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
– GVHD prophylaxis
– Cell dose
Post-HCT Data:
• CMV reactivation
• EBV reactivation
• Development of PTLD
• Graft rejection rate; primary and secondary
• Acute GVHD:
o Overall grade at diagnosis
o Max grade at D+100
• Chronic GVHD:
o Chronic GVHD at 6 months, 1 year, and 2 years
o Max grade cGVHD (mild, moderate, severe)
o Limited or extensive cGVHD
• Primary cause of death
o Acute GVHD,
o Chronic GVHD,
o Infection
Not identified
Bacterial
Fungal
Viral
Protozoal
Other
o Other
• Contributing cause of death
o Acute GVHD
o Chronic GVHD
o Infection
Not identified
Bacterial
Fungal
Viral
Protozoal
Other
o Other
• Overall Survival

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

Not applicable.

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

Not applicable.

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

Not applicable.

Q26. REFERENCES:

1. Baron F, Mohty M, Blaise D, et al. Anti-thymocyte globulin as graft-versus-host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: a review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. 2017;102(2):224-234.
2. Bacigalupo A, Lamparelli T, Bruzzi P, et al. Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo Italiano Trapianti Midollo Osseo (GITMO). Blood. 2001;98(10):2942-2947.
3. Kröger N, Zabelina T, Krüger W, et al. In vivo T cell depletion with pretransplant anti-thymocyte globulin reduces graft-versus-host disease without increasing relapse in good risk myeloid leukemia patients after stem cell transplantation from matched related donors. Bone Marrow Transplant. 2002;29(8):683-689.
4. Mohty M, Bay JO, Faucher C, et al. Graft-versus-host disease following allogeneic transplantation from HLA-identical sibling with antithymocyte globulin-based reduced-intensity preparative regimen. Blood. 2003;102(2):470-476.
5. Meijer E, Cornelissen JJ, Löwenberg B, Verdonck LF. Antithymocyteglobulin as prophylaxis of graft failure and graft-versus-host disease in recipients of partially T-cell-depleted grafts from matched unrelated donors: a dose-finding study. Exp Hematol. 2003;31(11):1026-1030.
6. Remberger M, Svahn BM, Mattsson J, Ringdén O. Dose study of thymoglobulin during conditioning for unrelated donor allogeneic stem-cell transplantation. Transplantation. 2004;78(1):122-127.
7. Hamadani M, Blum W, Phillips G, et al. Improved nonrelapse mortality and infection rate with lower dose of antithymocyte globulin in patients undergoing reduced-intensity conditioning allogeneic transplantation for hematologic malignancies. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009;15(11):1422-1430.
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9. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, Randomized, Double-Blind, Phase III Clinical Trial of Anti-T-Lymphocyte Globulin to Assess Impact on Chronic Graft-Versus-Host Disease-Free Survival in Patients Undergoing HLA-Matched Unrelated Myeloablative Hematopoietic Cell Transplantation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(36):4003-4011.
10. Kroger N, Solano C, Wolschke C, et al. Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease. The New England journal of medicine. 2016;374(1):43-53.
11. Frédéric Baron, Jacques-Emmanue Galimard, Myriam Labopin, Ibrahim Yakoub-Agha, Riitta Niittyvuopio, Nicolaus Kröger, Laimonas Griskevicius, Depei Wu, Edouard Forcade, Carlos Richard, Mahmoud Aljurf, Grzegorz Helbig, Hélène Labussière-Wallet, Mohamad Mohty, Arnon Nagler. Allogeneic peripheral blood stem cell transplantation with anti-thymocyte globulin versus allogeneic bone marrow transplantation without anti-thymocyte globulin. Haematologica 2020;105(4):1138-1146; https://doi.org/10.3324/haematol.2019.227603.
12. Ruutu T, Gratwohl A, de Witte T, Afanasyev B, Apperley J, Bacigalupo A, Dazzi F, Dreger P, Duarte R, Finke J, Garderet L, Greinix H, Holler E, Kröger N, Lawitschka A, Mohty M, Nagler A, Passweg J, Ringdén O, Socié G, Sierra J, Sureda A, Wiktor-Jedrzejczak W, Madrigal A, Niederwieser D. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant. 2014 Feb;49(2):168-73. doi: 10.1038/bmt.2013.107. Epub 2013 Jul 29. Erratum in: Bone Marrow Transplant. 2014 Feb;49(2):319. Dosage error in article text. PMID: 23892326.
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Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of patients receiving first alloHCT for AML/ALL/MDS with ATG in the United States in 2008-2019, CRF track

Characteristic	Age<18	Age>=18
No. of patients	153	2346
No. of centers	32	105
Age at HCT		
Median (min-max)	11 (1-18)	60 (18-75)
<10	72 (47)	0 (0)
10-17	81 (53)	0 (0)
18-29	0 (0)	169 (7)
30-39	0 (0)	171 (7)
40-49	0 (0)	268 (11)
50-59	0 (0)	580 (25)
60-69	0 (0)	932 (40)
>=70	0 (0)	226 (10)
Recipient sex		
Male	80 (52)	1369 (58)
Female	73 (48)	977 (42)
Karnofsky score		
<90	34 (22)	983 (42)
>=90	118 (77)	1309 (56)
Missing	1 (1)	54 (2)
HCT-CI		
0	78 (51)	413 (18)
1	19 (12)	321 (14)
2	10 (7)	340 (14)
3+	31 (20)	1161 (49)
TBD	13 (8)	94 (4)
Missing	2 (3)	17 (1)
Disease		
AML	82 (54)	1072 (46)
ALL	50 (33)	253 (11)
MDS	21 (14)	1021 (44)
Donor type		
HLA-identical sibling	6 (4)	253 (11)
Well-matched unrelated (8/8)	92 (60)	1674 (71)
Partially-matched unrelated (7/8)	51 (33)	405 (17)
Mis-matched unrelated (<= 6/8)	4 (3)	14 (1)

Characteristic	Age<18	Age>=18
Graft type		
Bone marrow	105 (69)	311 (13)
Peripheral blood	48 (31)	2035 (87)
Conditioning regimen intensity		
MAC	139 (91)	1059 (45)
RIC	9 (6)	1118 (48)
NMA	5 (3)	147 (6)
TBD	0 (0)	14 (1)
Missing	0 (0)	8 (0)
Year of HCT		
2008	13 (8)	228 (10)
2009	13 (8)	233 (10)
2010	22 (14)	160 (7)
2011	3 (2)	146 (6)
2012	8 (5)	134 (6)
2013	21 (14)	252 (11)
2014	24 (16)	296 (13)
2015	26 (17)	261 (11)
2016	9 (6)	249 (11)
2017	6 (4)	170 (7)
2018	6 (4)	145 (6)
2019	2 (1)	72 (3)
Median follow-up of survivors (range), months	60 (3-123)	71 (4-152)
ATG dose (mg/kg)		
Median (min-max)	7 (0-13)	4 (0-15)
<1	3 (2)	110 (5)
1-1.9	1 (1)	57 (2)
2-2.9	7 (5)	222 (9)
3-3.9	3 (2)	434 (18)
4-4.9	33 (22)	697 (30)
5-5.9	13 (8)	355 (15)
6-6.9	16 (10)	297 (13)
7-7.9	35 (23)	143 (6)
8-8.9	19 (12)	21 (1)
9-9.9	12 (8)	5 (0)
>=10	11 (7)	5 (0)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

ATG versus PTCy for peripheral blood matched-sibling donor hematopoietic cell transplantation

Q2. Key Words

ATG; PTCy; matched-sibling donor; peripheral blood

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Leonardo Arcuri, PhD
Email address:	leonardojavier@gmail.com
Institution name:	Hospital Israelita Albert Einstein
Academic rank:	Trialist

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Nelson Hamerschlak, PhD
Email address:	hamer@einstein.br
Institution name:	Hospital Israelita Albert Einstein
Academic rank:	Head

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Leonardo Arcuri

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

None

Q13. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

Is GVHD equally mitigated by PTCy in MSD PBSC transplants, compared with ATG

Q16. RESEARCH HYPOTHESIS:

PTCy and ATG offer the same protection against GVHD in MSD PBSC transplants

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Grades II-IV aGVHD
Grades III-IV aGVHD
Chronic GVHD
Moderate/severe cGVHD
Overall survival
Relapse
Non-relapse mortality

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The benefit of ATG in peripheral blood matched-sibling donor transplants, compared with no ATG, has been demonstrated in a randomized trial. How PTCy compares with ATG has not been studied before.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The benefit of ATG in peripheral blood matched-sibling donor transplants, compared with no ATG. However, ATG is expensive and has been associated with adverse events and higher relapse incidence in reduced-intensity transplants. PTCy could substitute for ATG.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Acute leukemia or myelodysplastic syndrome
ATG or PTCy, with a calcineurin inhibitor with or without a third agent
Age 18-60 y/o
Myeloablative conditioning regimen
Peripheral blood stem cells
Matched-sibling donor

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

Pediatric patients seldom receive PTCy outside the context of haploidentical transplantation

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Age, gender, KPS, HCT-CI
Disease, disease risk index
Date of transplant
Conditioning regimen
GVHD prophylaxis
Follow-up
Date of death or last follow-up
Dead
Cause of death
II-IV aGVHD (with date)
III-IV aGVHD (with date)
cGVHD (with date)
Moderate/severe cGVHD (with date)
Relapse (with date)

Q23. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

None.

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

None.

Q25. **NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.**

None.

Q26. **REFERENCES:**

doi: 10.1016/j.jtct.2022.09.010
DOI: 10.1056/NEJMoa1506002

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of adult patients receiving first alloHCT for AML/ALL/MDS with matched donor in 2013-2020, TED and CRF tracks

Characteristic	ATG	PTCy
No. of patients	4131	1126
No. of centers	223	135
Age at HCT		
Median (min-max)	48 (18-60)	47 (18-60)
18-29	665 (16)	195 (17)
30-39	674 (16)	199 (18)
40-49	975 (24)	284 (25)
50-59	1816 (44)	448 (40)
60-69	1 (0)	0 (0)
Reporting track		
TED	3432 (83)	976 (87)
CRF	699 (17)	150 (13)
Recipient sex		
Male	2278 (55)	635 (56)
Female	1853 (45)	491 (44)
Karnofsky score		
<90	1468 (36)	424 (38)
>=90	2576 (62)	675 (60)
Missing	87 (2)	27 (2)
HCT-CI		
0	1253 (30)	273 (24)
1	634 (15)	142 (13)
2	590 (14)	205 (18)
3	766 (19)	275 (24)
4	340 (8)	96 (9)
5	231 (6)	60 (5)
6+	241 (6)	70 (6)
Missing	76 (2)	5 (0)
Primary disease for HCT		
AML	2426 (59)	655 (58)
ALL	900 (22)	286 (25)
MDS	805 (19)	185 (16)
Donor type		
HLA-identical sibling	1024 (25)	472 (42)
Well-matched unrelated (8/8)	3107 (75)	654 (58)

Characteristic	**ATG**	**PTCy**
Conditioning intensity		
MAC	3132 (76)	735 (65)
RIC	835 (20)	251 (22)
NMA	73 (2)	129 (11)
TBD	90 (2)	8 (1)
Missing	1 (0)	3 (0)
Year of HCT		
2013	421 (10)	28 (2)
2014	472 (11)	36 (3)
2015	473 (11)	60 (5)
2016	593 (14)	86 (8)
2017	542 (13)	151 (13)
2018	555 (13)	188 (17)
2019	561 (14)	237 (21)
2020	514 (12)	340 (30)
Median follow-up of survivors (range), months	36 (0-101)	24 (2-97)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Post-Transplant Cyclophosphamide (PTCy) vs. Anti-Thymocyte Globulin (ATG) in Patients with Acute Leukemia (AL) and Myelodysplastic Syndrome (MDS) receiving HLA-Mismatched Unrelated Donor (MMUD) Hematopoietic Cell Transplant (HCT). A CIBMTR Analysis

Q2. Key Words

GVHD, Cyclophosphamide, HLA-mismatch, MDS, leukemia

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Antonio Jimenez Jimenez, MD
Email address:	amjimenez@med.miami.edu
Institution name:	University of Miami
Academic rank:	Associate Professor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Brian Shaffer
Email address:	shaffeb1@mskcc.org
Institution name:	Memorial Sloan Kettering Cancer Center
Academic rank:	Assistant Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Antonio Jimenez Jimenez

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

Co-investigator for "Intensive Induction Chemotherapy vs. Hypomethylating Agent (HMA) Therapy for Older AML Patients Undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)" with ALWC

Q13. PROPOSED WORKING COMMITTEE:

- Graft Sources and Manipulation

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- Yes

Q14a. If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:

Dr. Mary Eapen (2021) and Dr. Stephanie Lee (2022). Last year, this study was combined with other proposals evaluating various T-cell depletion strategies (ATG, PTCy, alemtuzumab) in a heterogeneous patient cohort, including MUD and MMUD recipients. The combined proposal was presented at the GVHD WC meeting but was not selected to advance. Considering the emerging use of PTCy outside of the haploidentical HCT setting and the increasing utilization of MMUD grafts by the NMDP, this research question remains very relevant. For the same reasons, we believe there is merit in restricting this analysis to recipients of an MMUD graft.

Q15. RESEARCH QUESTION:

Does in vivo, graft manipulation with post-transplant cyclophosphamide (PTCy) improve clinical outcomes in MMUD recipients, compared to standard T-cell depletion with anti-thymocyte globulin (ATG)?

Q16. RESEARCH HYPOTHESIS:

When compared to anti-thymocyte globulin (ATG), in vivo graft manipulation with post-transplant cyclophosphamide (PTCy) is associated with improved clinical outcomes in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and myelodysplastic syndrome (MDS) patients undergoing HLA-mismatched unrelated donor (MMUD) transplantation.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Primary Objective:

• GVHD-free, relapse-free survival (GRFS): Will be defined as time to development of grade 3-4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death from any cause. Patients are censored at last follow-up.

Secondary Objectives:

• Overall survival (OS): time to death. Death from any cause will be considered an event. Surviving patients are censored at time of last follow-up.

• Relapse-free survival (RFS): Will be defined as time to relapse or death from any cause. Patients are censored at last follow-up.

• Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse is competing event.

• Relapse/Progression: Cumulative incidence of disease relapse/progression, with NRM as competing event.

• Incidence of acute and chronic GVHD: Cumulative incidence of acute and chronic GVHD, with death as competing risk. Patients are censored at subsequent HCT or last follow-up.

Specific Aims:

We propose to evaluate the impact of in vivo graft manipulation strategy (ATG vs. PTCy) on clinical outcomes following MMUD HCT for patients with MDS, AML and ALL. To achieve this objective, we will:

AIM 1. Identify differences in post-transplant outcomes (overall survival, leukemia-free survival, GVHD-free, relapse free survival [GRFS], non-relapse mortality, relapse and acute and chronic GVHD) in MDS, AML/ALL patients receiving in vivo graft manipulation with PTCy versus ATG, following MMUD HCT.

AIM 2. Evaluate differences in post-transplant outcomes for MDS, AML/ALL patients receiving graft manipulation with PTCy versus ATG based on graft source, degree of mismatch (7/8 vs <=6/8) and conditioning intensity.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The optimal graft manipulation strategy to prevent graft versus host disease following HCT from an HLA-MMUD remains unknown. While the current SOC following MMUD HCT is administration of tacrolimus, methotrexate and anti-thymocyte globulin (ATG) the use of post-transplant cyclophosphamide (PTCy) is an emerging prophylactic strategy that has demonstrated promise in a prospective trial for MMUD HCT and continues to be explored.

To date, comparison of both approaches has been limited to single institutions or to recipients of single-antigen MMUD grafts. Answering this research question in a large multicenter cohort, will provide HCT clinicians and scientists with critical information to improve clinical care, and will add to the current body knowledge in mismatched HCT, as emerging methodologies continue to be evaluated in this setting.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Allogeneic Hematopoietic Cell Transplant (alloHCT) continues to be the preferred consolidation strategy for most hematologic malignancies, but unfortunately, many patients cannot find an HLA-matched donor. Mismatched unrelated donors (MMUD) are frequently the sole graft source for patients without matched or other alternative donor options. Historically, MMUD HCT has been associated with poor outcomes given increased rates of GvHD, graft failure, and infection, all resulting in high non-relapse mortality (NRM). The post-transplant cyclophosphamide (PTCy) platform has successfully overcome barriers related to HLA-mismatching in the haploidentical donor setting and is being increasingly recognized as a suitable strategy for MMUD HCT.

PTCy-based GvHD prophylaxis in the MMUD HCT setting has shown to be safe and feasible in single-institution studies. A recent prospective phase-II, multi-center NMDP® trial (15-MMUD) demonstrated the effectiveness of PTCy in a cohort of 80 patients with hematologic malignancies receiving an MMUD bone marrow HCT, with one-year OS of 76% and satisfactory rates of NRM, RFS, GRFS, and GVHD.

We retrospectively evaluated the outcomes of 128 adult patients (~70% with a diagnosis of acute leukemia or MDS) who received an MMUD (>=1 mismatch at -A, -B, -C, -DRB1 alleles) at the University of Miami and MSKCC. Patients were stratified based on graft manipulation strategy, conditioning intensity, graft source, and degree of mismatch. PTCy prophylaxis resulted in superior OS (75% vs. 45%, P<0.001), RFS, GRFS, and lower NRM compared to ATG-based T-cell depletion. A large multi-center retrospective study evaluating the role of alternative donor HCT (including 9/10 MMUD recipients, N=125) for ALL demonstrated no differences in post-HCT outcomes among all donor sources. Data from the Acute Leukemia Working Party of the EBMT, showed superior results for PTCy recipients (vs. ATG) in a cohort of 272 patients with AML, following a single-antigen (9/10) MMUD HCT. The cohort included patients with DQ mismatched grafts and various GVHD prophylactic regimens following transplantation.

We propose a retrospective cohort study to evaluate differences in post-HCT outcomes for acute leukemia (AML/ALL) and MDS patients receiving graft manipulation with PTCy versus ATG following a <=7/8 MMUD HCT. To our knowledge, no large, multi-center studies addressing this important question have been conducted to date.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion Criteria

• Patients with a diagnosis of AML, ALL and MDS in CR

• Ages 18 and older

• Recipients of a MMUD graft (>=1 mismatch at -A, -B, -C, -DRB1 alleles) between 2010-2021, receiving GVHD prophylaxis with CNI+MTX (ATG cohort) or CNI+MMF (PTCy cohort)

Exclusion Criteria

• In vivo graft manipulation other than ATG or PTCy

• Ex vivo TCD

• Recipients of a single-antigen DQ mismatch graft

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

Pediatric patients with high-risk acute leukemias are more likely to receive transplant consolidation with haploidentical or CBT units (vs. MMUDs) if a fully-matched donor is not available. MDS remains primarily a disease of the elderly with a median age at diagnosis of 71 years and occurs rarely in the pediatric population. We therefore suspect that numbers will not be sufficient to answer the research question. NMDP's ongoing ACCESS study (21-MMUD) will evaluate post-HCT outcomes (OS and EFS) following MMUD BM transplantation in pediatric and AYA patients

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Study main effect: Choice of in vivo graft manipulation (PTCy vs. ATG) following MMUD HCT.
Patient-related:
• Age at transplant
• Patient gender
• Race
• Ethnicity: Hispanic vs. Non-Hispanic
• Karnofsky performance status at transplant: ≥ 90 vs. < 90
• HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3
Disease-related:
• Blast percentage at diagnosis
• CR status: CR1 vs >CR2
• Time to achieve CR
• MRD prior to transplant
• CRi prior to transplant
• Extramedullary disease
AML Patients:
• Clinical onset of AML: de novo vs. transformed from MDS/MPN vs. therapy related
• ELN genetic stratification
• White blood count at diagnosis: <10 vs. 10-100 vs. >100 x10^9/L
ALL Patients:
• Genetic stratification
• Lineage: B-cell vs T-cell
• Hyperleukocytosis at diagnosis (>30,000 for B-ALL, >100,000 for T-ALL)
• Ph+ status
MDS Patients:
• Clinical onset of MDS: De novo vs. therapy related
• Blast percentage at HCT (<5, 5-10)
• IPSS-R at diagnosis
• Cytogenetic Classification per IPSS
Transplant related:
• Conditioning intensity: Myeloablative conditioning (MAC) vs. reduced-intensity /non-myeloablative conditioning (RIC/NMA)
• Graft source: bone marrow vs. peripheral blood
• Degree of HLA mismatch (7/8 or <7/8)
• Donor age
• Donor-recipient sex match
• Donor-recipient CMV status
• Time from diagnosis to HCT
• Year of transplant

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

NA

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

NA

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

NA

Q26. REFERENCES:

1. Gragert, L., et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med 371, 339-348 (2014).
2. Anasetti C, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol 1990; 29:79.
3. Lee, S. J. et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 110, 4576–4583 (2007).
4. Mehta R, et al. Post-transplantation cyclophosphamide versus conventional graft-versus-host disease prophylaxis in mismatched unrelated donor haematopoietic cell transplantation. BJH Mar 2016, 173(3):444-455
5. Kasamon, Y.L., et al. Prospective study of nonmyeloablative, HLA-mismatched unrelated BMT with high-dose posttransplantation cyclophosphamide. Blood Adv 1, 288-292 (2017).
6. Al Malki, M., et al. A Phase II Trial of Post-Transplant Cyclophosphamide As Graft-Versus-Host Disease Prophylaxis in HLA-Mismatched Unrelated Donor Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 26, S188 (supplement) (2020).
7. Shaw B et al. Transplantation Using Bone Marrow from a (very) HLA Mismatched Unrelated Donor in the Setting of Post-Transplant Cyclophosphamide Is Feasible and Expands Access to Underserved Minorities. Biol Blood Marrow Transplant 26, S283-284 (supplement) (2020).
8. Shaw BE, Jimenez-Jimenez AM, Burns LJ, et al: National Marrow Donor Program–Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide. Journal of Clinical Oncology 39:1971-1982, 2021
9. Jimenez-Jimenez A, Komanduri K, Shaffer B, et al: Improved GRFS after posttransplant cyclophosphamide-based vs ATG-based HLA-mismatched unrelated donor transplant. Blood Adv 2022; 6 (15): 4491–4500.
10. Giorgia Battipaglia, Arnon Nagler, Mohamad Mohty et al; Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation. Blood 2019; 134 (11): 892–899.
11. Woolfrey A, Klein JP, Haagenson M, et al: HLA-C antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 17:885-92, 2011
12. Brissot, E., Labopin, M., Russo, D. et al. Alternative donors provide comparable results to matched unrelated donors in patients with acute lymphoblastic leukemia undergoing allogeneic stem cell transplantation in second complete remission: a report from the EBMT Acute Leukemia Working Party. Bone Marrow Transplant 55, 1763–1772 (2020).

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of adult patients receiving first alloHCT for AML/ALL/MDS and received ATG or PTCy in 2008-2020, CRF track

Characteristic	ATG	PTCy
No. of patients	620	164
No. of centers	110	43
Age at HCT		
Median (min-max)	52 (19-81)	60 (18-78)
18-29	85 (14)	7 (4)
30-39	84 (14)	11 (7)
40-49	112 (18)	23 (14)
50-59	154 (25)	40 (24)
60-69	156 (25)	68 (41)
>=70	29 (5)	15 (9)
Recipient sex		
Male	335 (54)	73 (45)
Female	285 (46)	91 (55)
Karnofsky score		
<90	203 (33)	75 (46)
>=90	402 (65)	87 (53)
Missing	15 (2)	2 (1)
HCT-CI		
0	78 (51)	413 (18)
1	19 (12)	321 (14)
2	10 (7)	340 (14)
3+	31 (20)	1161 (49)
TBD	13 (8)	94 (4)
Missing	2 (2)	7 (1)
Primary disease for HCT		
AML	332 (54)	74 (45)
ALL	84 (14)	32 (20)
MDS	204 (33)	58 (35)
Donor type		
Partially-matched unrelated (7/8)	588 (95)	139 (85)
Mis-matched unrelated (<= 6/8)	32 (5)	25 (15)
Graft type		
Bone marrow	92 (15)	64 (39)
Peripheral blood	528 (85)	100 (61)
Conditioning intensity		

Characteristic	ATG	PTCy
MAC	358 (58)	64 (39)
RIC	208 (34)	55 (34)
NMA	29 (5)	40 (24)
TBD	8 (1)	1 (1)
Missing	17 (3)	4 (2)
Year of HCT		
2008	91 (15)	2 (1)
2009	94 (15)	0 (0)
2010	55 (9)	1 (1)
2011	31 (5)	1 (1)
2012	32 (5)	2 (1)
2013	71 (11)	1 (1)
2014	67 (11)	8 (5)
2015	67 (11)	12 (7)
2016	47 (8)	19 (12)
2017	34 (5)	33 (20)
2018	15 (2)	53 (32)
2019	15 (2)	32 (20)
2020	1 (0)	0 (0)
Median follow-up of survivors (range), months	72 (3-147)	31 (3-60)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Allogeneic stem cell transplant (Allo- SCT) in patients older than 70 years using posttransplant cyclophosphamide (PTCy) based Graft versus Host disease (GVHD) prophylaxis: An analysis from the CIBMTR database.

Q2. Key Words

Allogeneic Stem Cell Transplant; Age over 70 years; Post transplant Cyclophosphamide

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Rajneesh Nath,MD
Email address:	Rajneesh.Nath@bannerhealth.com
Institution name:	Banner MD Anderson Cancer Center
Academic rank:	Chief, Stem Cell Transplant & Cellular Therapy

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Zheng Zhou, MD PhD
Email address:	zzhou4@tuftsmedicalcenter.org
Institution name:	Tufts Medical Center
Academic rank:	Assistant Professor of Medicine

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

N/A

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Graft vs Host Disease

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

To evaluate from the CIBMTR database the frequency and outcomes of Allo-SCT performed in patients over age 70 years using PTCy based GVHD prophylaxis.

Q16. RESEARCH HYPOTHESIS:

PTCy based graft versus host disease (GVHD) prophylaxis is being increasingly used in patients over age 70 years undergoing Allo-SCT. This regimen will favorably impact overall survival and reduce the incidence and severity of acute and chronic GVHD in this patient population.

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

The aim of the study would be to evaluate from the CIBMTR data base
1. Frequency of PTCy based GVHD prophylaxis in patients over age 70 undergoing Allo-SCT.
2. Disease and transplant characteristics of patients over age 70 undergoing PTCy based GVHD prophylaxis.
3. Day 100 , 1-year and 3 year overall survival, GVHD free relapse free survival (GRFS) at one year and cumulative incidence of acute and chronic GVHD.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

The results of the current study will give guidance to the transplant community regarding appropriate GVHD prophylaxis in elderly patients undergoing Allo-SCT.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

Allo-SCT is curative treatment modality for patients with high risk, relapsed or refractory hematological malignancies. Since the median age of most hematological malignancies is over 65 years a significant number of patients affected are over age 70 years. In the last decade there have been numerous single institution and registry reports of allogeneic SCT in patients over the age of 70 years. Post-transplant cyclophosphamide (PTCy) based GVHD prophylaxis was pioneered by the Hopkins group about 15 years ago. Though initially developed for haploidentical SCT, PTCy is now increasingly used for matched sibling and unrelated donor SCT. The current literature of GVHD prophylaxis in the elderly is mostly limited to CNI-MTX/MMF +/- TCD. The only study of PTCy as GVHD prophylaxis in Allo-SCT recipients over the age of 70 is in haploidentical SCT using non-myeloablative conditioning from the Hopkins group. The study showed a respectable 2-year survival of 53% with the cumulative incidence of 2- year non-relapse mortality and relapse risk of 27% and 30 % respectively. We wish to delve more deeply into the impact of this GVHD prophylactic regimen on those patients over age 70 receiving an Allo-SCT from any stem cell source with this analysis.

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

N/A

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Study population will include all patients 70 years who received Allo -SCT with PTCy based GVHD prophylaxis and who have the data reported to CIBMTR.

Q21. Does this study include pediatric patients?

- No

Q21a. If this study does not include pediatric patients, please provide justification:

This study is being restricted to the elderly population and pediatric patients are not included.

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Data Variables:
I) Patient related:
- Age at HCT: continuous
- Gender: male vs. female
- HSCT comorbidity index
- Karnofsky performance score, %: ≥90 vs. <90 and continuous.
- Race: White vs. Others

II) Disease related:
- Type of hematological malignancies (AML, MDS, MPN, Other)
- Disease status prior to transplant (CR, CR1, less than CR) *
- Lines of therapy before Allo-SCT
- Time from diagnosis to Allo-SCT (months)*

III) Transplant related:
- Year of Transplant* (adjust for time effect)
- Conditioning regimen (RIC, NMA)
- Donor type: Haploidentical, MUD, MMUD (Partially matched, mismatched); ?MSD
- Donor age,
- Donor & recipient (D/R) gender match
- Donor & recipient (D/R) CMV status
- Donor & recipient (D/R) ABO blood type
- Graft type: bone marrow vs peripheral blood
- GVHD prophylaxis regimen:

i) PT-Cy* based or Non PTCy based

IV) Outcome related:
- Overall survival (OS) at different time points (day 100, 1 year and 3 years)
- GVHD and Relapse free survival, GRFS*
- Time to Relapse
- Non-relapse mortality, NRM
- Time to Neutrophil engraftment time
- Time to Platelet engraftment time
- Immune recovery (objective measures, including CD4 counts recovery)
- Chimerism at 30 days, 6 months and 1 year
- Acute GVHD, organ involved and grade
- Chronic GVHD, organ involved and grade
- Post-transplant infection (bacteria, fungal and/or viral)
- Post-transplant maintenance therapy

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

Biological specimens are not required.

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

1. Zeina Al-Mansour, Jan Cerny, Muthalagu Ramanathan, Glen Raffel, Mridula George, Laura Petrillo-Deluca, Lindsey Shanahan, Jayde Bednarik, Zankar Desai, Aimee Kroll-Desrosiers, Rajneesh Nath. Allogenic (Allo) Stem Cell Transplant (SCT) in Patients over Age 70 Years: A Single Center's Experience. Biology of Blood and Marrow Transplant, 2014 Vol. 20, Issue 2, S242

2. Andrew M. Brunner, Haesook T. Kim, Erin Coughlin, Edwin P. Alyea, Philippe Armand, Karen K. Ballen, Corey Cutler, Bimalangshu R. Dey, Brett Glotzbecker, John Koreth, Steven L. McAfee, Thomas R. Spitzer, Robert J. Soiffer, Joseph H. Antin, Vincent T. Ho, Yi-Bin Chen,Outcomes in Patients Age 70 or Older Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies. Biology of Blood and Marrow Transplantation, 2013Volume 19, Issue 9, 1374-1380

3. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130(9):1156-1164. doi:10.1182/blood-2017-03-772368

4. Ringden O, Boumendii A, Labopin M et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myelogenous leukemia: on behalf of the acute leukemia working party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019; 25: 1979-1988

5. Imus PH, Tsai HL, Luznik L, Fuchs EJ, Huff CA, Gladstone DE, Lowery P, Ambinder RF, Borrello IM, Swinnen LJ, Wagner-Johnston N, Gocke CB, Ali SA, Bolaños-Meade FJ, Varadhan R, Jones RJ. Haploidentical transplantation using posttransplant cyclophosphamide as GVHD prophylaxis in patients over age 70. Blood Adv. 2019 Sep 10;3(17):2608-2616.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- No, I do not have any conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of patients age >=70 years receiving first alloHCT with PTCy in 2008-2020, CRF track

Characteristic	N (%)
No. of patients	439
No. of centers	87
Age at HCT	72 (70-88)
Recipient sex	
Male	293 (67)
Female	146 (33)
Karnofsky score	
<90	233 (53)
>=90	197 (45)
Missing	9 (2)
HCT-CI	
0	78 (51)
1	19 (12)
2	10 (7)
3+	31 (20)
TBD	13 (8)
Missing	2 (2)
Primary disease for HCT	
AML	164 (37)
ALL	14 (3)
OL	6 (1)
CML	1 (0)
MDS	181 (41)
OAL	4 (1)
NHL	12 (3)
PCD	1 (0)
SAA	5 (1)
MPN	51 (12)
Donor type	
HLA-identical sibling	12 (3)
Other related	309 (70)
Well-matched unrelated (8/8)	92 (21)
Partially-matched unrelated (7/8)	21 (5)
Mis-matched unrelated (<= 6/8)	3 (1)
Unrelated (matching TBD)	1 (0)

Characteristic	N (%)
Cord blood	1 (0)
Graft type	
Bone marrow	105 (24)
Peripheral blood	333 (76)
Cord blood	1 (0)
Conditioning intensity	
MAC	44 (10)
RIC	138 (31)
NMA	233 (53)
TBD	6 (1)
Missing	13 (3)
N/A, non-malignant disease	5 (1)
Year of HCT	
2008	3 (1)
2009	2 (0)
2010	1 (0)
2011	3 (1)
2012	5 (1)
2013	9 (2)
2014	17 (4)
2015	41 (9)
2016	51 (12)
2017	62 (14)
2018	74 (17)
2019	104 (24)
2020	67 (15)
Median follow-up of survivors (range), months	25 (2-144)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Incidence of Chronic Graft Versus Host Disease in Cryopreserved Versus Fresh Peripheral Blood Allogeneic Hematopoietic Stem Cell Grafts

Q2. Key Words

Cryopreservation, cGVHD

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Katie Maurer, MD, PhD
Email address:	alexandria_maurer@dfci.harvard.edu
Institution name:	Dana-Farber Cancer Institute
Academic rank:	Instructor

Q4. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- Yes

Q5. Do you identify as an underrepresented/minority?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Robert Soiffer, MD
Email address:	Robert_soiffer@dfci.harvard.edu
Institution name:	Dana-Farber Cancer Institute
Academic rank:	Professor

Q7. Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)

- No

Q8. Do you identify as an underrepresented/minority?

- No

Q9. We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:

Katie Maurer, MD, PhD

Q10. If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:

N/A

LETTER OF COMMITMENT:

Please note: *A letter of commitment will be signed by Lead and Last authors as it describes the expectations for filling that role. By signing the letter of commitment, the authors accept their responsibilities and will be held accountable for timely completion of all steps in the project. More details regarding author responsibilities can be found here:* *https://www.cibmtr.org/Studies/Observational/StudyManagement/p*

Q12. CURRENT ONGOING WORK WITH CIBMTR: Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Graft Sources and Manipulation

Q14. Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.

- No

Q15. RESEARCH QUESTION:

What impact does cryopreservation of peripheral blood stem cells (PBSCs) have on development of chronic graft-versus-host disease (cGVHD) in matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplantation (HCT)? If there are sufficient numbers of cryopreserved bone marrow (BM) MUDs, cGVHD will be evaluated in this setting as well.

Q16. RESEARCH HYPOTHESIS:

Cryopreservation of PBSCs (or BM) reduces incidence of cGVHD in MUD compared to HCT using fresh PBSCs (or BM).

Q17. SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.)

Suggested word limit of 200 words:

Primary: Overall incidence of chronic GVHD after HCT with fresh versus cryopreserved PBSC (or BM) in MUD HCT
Secondary: Incidence of moderate/severe chronic GVHD with fresh vs cryopreserved PBSC (or BM) in MUD HCT
Secondary: Rate of GVHD-free-relapse-free survival (GRFS) with fresh vs cryopreserved PBSC (or BM) in MUD HCT

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Preliminary data suggests that MUD HCT using cryopreserved PBSCs results in lower incidence of cGVHD and moderate/severe cGVHD compared to HCT with fresh PBSCs, particularly in patients receiving GVHD prophylaxis without PTCY (see section IX Scientific Justification). Verifying these results in a larger cohort may impact national and international practices surrounding PBSC cryopreservation as well as choice of GVHD prophylaxis regimen.

Q19. SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

The COVID-19 pandemic spurred renewed interest in the question of safety of cryopreservation after the National Marrow Donor Program (NMDP) mandated cryopreservation of unrelated donor (MUD) PBSCs at the site of collection or infusion between March and August 2020 (1). Although the cryopreservation mandate was lifted after August 2020, there continues to be heterogeneity between transplant centers regarding cryopreservation practices. We previously reported similar short-term clinical outcomes including overall survival (OS), progression free survival (PFS), relapse, and non-relapse mortality (NRM) but lower T-cell chimerism at day 30 and 100 in adult recipients of cryopreserved compared to fresh MUD PBSCs (2, 3). Further, some studies have reported increased moderate/severe chronic graft versus host disease (cGVHD) after HCT with cryopreserved PBSCs (4, 5) whereas others have reported equivalent or slightly reduced cGVHD incidence with cryopreservation (6, 7), although differences in GVHD prophylaxis regimen and small sample sizes may account for these discrepancies. We performed a single-institution analysis of two-year clinical outcomes including incidence and severity of cGVHD in 136 patients receiving cryopreserved MUD PBSC versus 251 recipients of fresh. 2-year incidence of cGVHD and moderate/severe cGVHD was lower in patients receiving cryopreserved stem cells versus fresh (cGVHD: 28% vs 52%, p=0.00001; moderate/severe cGVHD: 9% vs 24%, p=0.00016; unpublished data). This difference in GVHD incidence was restricted to patients who received a tacrolimus based GVHD prophylaxis regimen (cGVHD: 29% cryopreserved vs 57% fresh, p=0.000016; moderate/severe cGVHD: 16% vs 34%, p=0.0006). Larger patient cohorts are needed to confirm these observations. Additionally, this prior work was limited to MUD HSCT, but the impact of cryopreservation in MRD HCT on cGVHD. Here we propose to compare incidence and severity of cGVHD after MRD and MUD HCT to assess the impact of cryopreservation in the context of GVHD prophylaxis with or without PTCY. The results from this study will inform future practice around cryopreservation of PBSCs. These data will also aid in generating hypotheses for future basic and translational proposals aimed at understanding mechanisms of cGVHD

Q19a. SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF)

[Click here]

Q20. PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Inclusion Criteria
1. First 8/8 MRD or 8/8 MUD HCT in the US 2011-2022 for:
a) AML
b) MDS
c) ALL
d) MDS/MPN
e) MPN
f) NHL
g) CML
h) Other leukemia
2. PBSCs as stem cell source
a) Cryopreserved
b) Fresh
Exclusion Criteria
1. In-vivo T-cell depletion with ATG or Campath (can be included if there are sufficient numbers for analysis)
2. Ex-vivo T-cell depletion with CD34+ selection
3. BM as stem cell source (can be included if there are sufficient numbers for analysis)

Q21. Does this study include pediatric patients?

- Yes

Q22. DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion-variables to be considered in the multivariate analyses. Data collection forms available at: http://www.cibmtr.org/DataManagement/DataCollectior Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

Patient-related:
1. Age
2. Sex: male vs female
3. Caucasian vs other
4. Karnofsky Performance Score:
5. HCT-CI
6. CMV Serostatus: Positive vs. negative

Donor-related:
1. Age
2. Sex: male vs female
3. CMV serostatus: positive vs negative

Transplant related:
1. Conditioning intensity: MAC vs RIC/NMA
2. GVHD prophylaxis regimen: with PTCY vs without PTCY, with ATG vs without ATG (if sufficient numbers)

Cell therapy product:
1. PBSCs: Cryopreserved vs Fresh
2. Total number of CD34+ cells (if available)
3. % viability of CD34+ cells (if available)

Post-infusion follow up
1. Vital status: alive vs dead
2. Date of death or date last known alive
a) Cause of death
3. Granulopoiesis/neutrophil recovery: yes vs no vs N/A
a) Date of ANC>500/mm3
4. Megakaryopoiesis/platelet recovery: yes vs no vs N/A
a) Date of platelet count > 109/L
5. WBC count after HCT (and date checked) (if available)
6. Lymphocyte count after HCT (and date checked) (if available)
a) CD3+ counts
b) CD4+ counts
c) CD8+ counts
7. Chimerism after HCT (if available)
8. Relapse
a) Date of relapse
9. Need for subsequent CD34+ boost
10. Need for subsequent DLI
11. Incidence and max grade of Acute GVHD
12. Incidence and max grade of Chronic GVHD
13. Did patient require subsequent HCT?
a) Indication for subsequent HCT

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

Q24. **SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary of the investigator's previous experience with the proposed assay systems. PIs should be encouraged to review the inventory details, sample types collected and reach out to research_repos@nmdp.org with any questions.**

More information can be found at: https://www.cibmtr.org/Samples/Inventory/Pages/index

N/A

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.

N/A

Q26. REFERENCES:

Devine SM. Transplantation of allogeneic cryopreserved hematopoietic cell grafts during the Covid-19 pandemic: A National Marrow Donor Program perspective. Am J Hematol. 2021;96(2):169-71.
2. Maurer K, Kim HT, Kuczmarski TM, Garrity HM, Weber A, Reynolds CG, et al. Impact of cryopreservation and transit times of allogeneic grafts on hematopoietic and immune reconstitution. Blood Adv. 2021;5(23):5140-9.
3. Maurer K, Saucier A, Kim HT, Acharya U, Mo CC, Porter J, et al. COVID-19 and hematopoietic stem cell transplantation and immune effector cell therapy: a US cancer center experience. Blood Adv. 2021;5(3):861-71.
4. Alotaibi AS, Prem S, Chen S, Lipton JH, Kim DD, Viswabandya A, et al. Fresh vs. frozen allogeneic peripheral blood stem cell grafts: A successful timely option. Am J Hematol. 2021;96(2):179-87.
5. Medd P, Nagra S, Hollyman D, Craddock C, Malladi R. Cryopreservation of allogeneic PBSC from related and unrelated donors is associated with delayed platelet engraftment but has no impact on survival. Bone Marrow Transplant. 2013;48(2):243-8.
6. Kim DH, Jamal N, Saragosa R, Loach D, Wright J, Gupta V, et al. Similar outcomes of cryopreserved allogeneic peripheral stem cell transplants (PBSCT) compared to fresh allografts. Biol Blood Marrow Transplant. 2007;13(10):1233-43.
7. Hamadani M, Zhang MJ, Tang XY, Fei M, Brunstein C, Chhabra S, et al. Graft Cryopreservation Does Not Impact Overall Survival after Allogeneic Hematopoietic Cell Transplantation Using Post-Transplantation Cyclophosphamide for Graft-versus-Host Disease Prophylaxis. Biol Blood Marrow Transplant. 2020;26(7):1312-7.

Q27. CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:

1. Employment (such as an independent contractor, consultant or providing expert testimony)?
2. Relationships (such as executive and advisory committee positions, medical consultant, speaker's bureau)?
3. Ownership (such as equity, ownership or financial interests)?
4. Transactions (such as honoraria, patents, royalties and licenses)?
5. Legal (such as pending or current arbitration or legal proceedings)?

- Yes, I have conflicts of interest pertinent to this proposal

Q27a. If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.

1. K.M. has no COI to report
2. R.S. has the following COI to report: Consulting for Vor Biopharma, Neovii, CSL Behring, Bluesphere Bio, Cugene, Jasper, Smart Immune; data safety monitoring board for Juno Therapeutics//BMS/Celgene USA; board of directors, Be the Match//National Marrow Donor Program

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

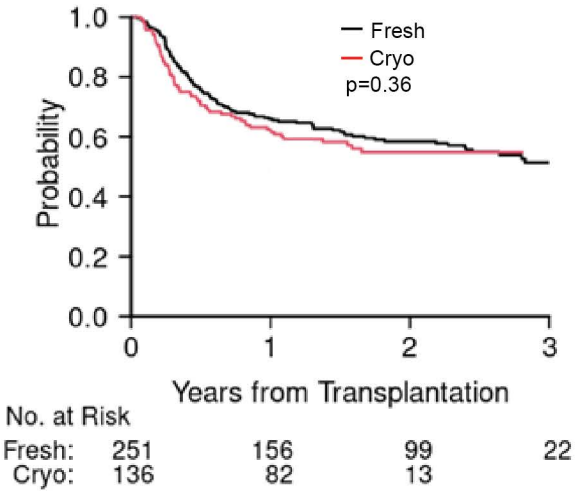
Embedded Data:

N/A

Figure 1

A

PFS

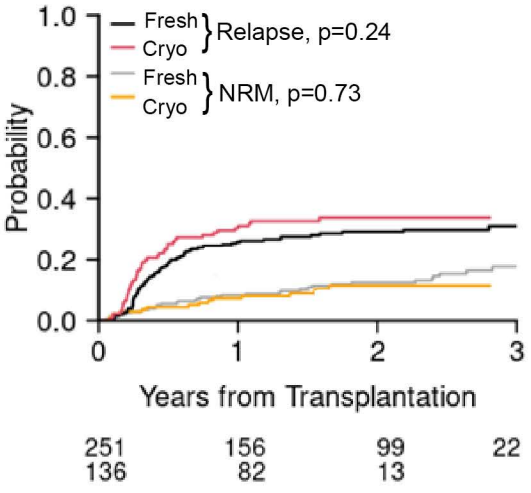


No. at Risk

Fresh:	251	156	99	22
Cryo:	136	82	13	

B

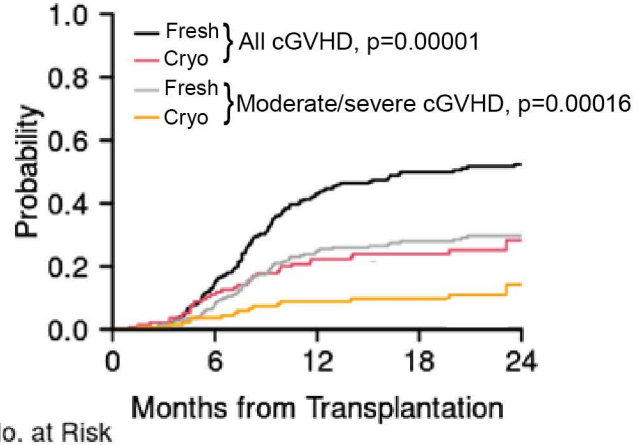
Relapse and NRM



251	156	99	22	
136	82	13		

C

Incidence of Chronic GVHD
All patients

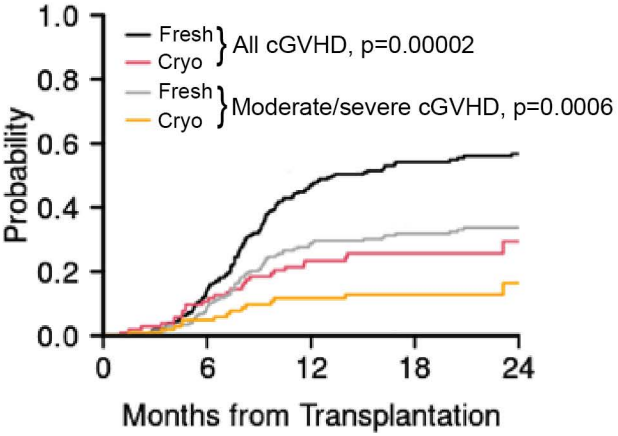


No. at Risk

Fresh:	251	164	79	45	32
Cryo:	136	84	61	36	7

D

Incidence of Chronic GVHD
Tacrolimus-based GVHD prophyalxis



205	133	57	34	25	
104	62	42	24	4	