Not for publication or presentation

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A G E N D A
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Salt Lake City, UT
Monday, April 25, 2022, 6:30 AM - 8:15 AM

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1. Introduction

a. Minutes from February 2021 meeting (Attachment 1)
b. Introduction of new Scientific Director: Kristin Page

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **LK15-03** Wieduwilt MJ, Stock W, Advani A, Luger S, Larson RA, Tallman M, Appelbaum F, Zhang M-J, Bo-Subait K, Wang H-L, Bhatt VR, Dholaria B, Eapen M, Hamadani M, Jamy O, Prestidge T, Pulsipher M, Ritchie D, Rizzieri D, Sharma A, Barba P, Sandmaier BM, de Lima M, Kebriaei P, Litzow M, Saber W, Weisdorf D. Superior survival with pediatric-style chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in older adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: Analysis from CALGB 10403 and the CIBMTR. ***Leukemia. 2021 Jul;35(7):2076-2085. doi: 10.1038/s41375-021-01213-5.***
b. **LK16-03** Metheny L, Callander NS, Hall AC, Zhang M-J, Bo-Subait K, Wang H-L, Agrawal V, Al-Homsi AS, Assal A, Bacher U, Beitinjaneh A, Bejanyan N, Bhatt VR, Bredeson C, Byrne M, Cairo M, Cerny J, DeFilipp Z, Perez MAD, Freytes CO, Ganguly S, Grunwald MR, Hashmi S, Hildebrandt GC, Inamoto Y, Kanakry CG, Kharfan-Dabaja MA, Lazarus HM, Lee JW, Nathan S, Nishihori T, Olsson RF, Ringdén O, Rizzieri D, Savani BN, Savoie ML, Seo S, van der Poel M, Verdonck LF, Wagner JL, Yared JA, Hourigan CS, Kebriaei P, Litzow M, Sandmaier BM, Saber W, Weisdorf D, de Lima M. Allogeneic transplantation to treat therapy-related myelodysplastic syndrome and acute myelogenous leukemia in adults. ***Transplantation and Cellular Therapy. 2021 Nov;27(11):923.e1-923.e12. doi: 10.1016/j.jtct.2021.08.010.***

c. **LK17-01** Percival M-E, Wang H-L, Zhang M-J, Saber W, de Lima M, Litzow M, Kebriaei P, Abdel-Azim H, Adekola K, Aljurf M, Bacher U, Badawy SM, Beitinjaneh A, Bejanyan N, Bhatt V, Byrne M, Cahn JY, Castillo P, Chao N, Chhabra S, Copelan E, Cutler C, DeFilipp Z, Dias A, Diaz MA, Estey E, Farhadfar N, Frangoul HA, Freytes CO, Gale RP, Ganguly S, Gowda L, Grunwald M, Hossain N, Kamble RT, Kanakry CG, Kansagra A, Kharfan-Dabaja MA, Krem M, Lazarus HM, Lee JW, Liesveld JL, Lin R, Liu H, McGuirk J, Munker R, Murthy HS, Nathan S, Nishihori T, Olsson RF, Palmisiano N, Passweg JR, Prestidge T, Ringdén O, Rizzieri DA, Rybka WB, Savoie ML, Schultz KR, Seo S, Sharma A, Solh M, Strair R, van der Poel M, Verdonck LF, Yared JA, Weisdorf D, Sandmaier BM. Impact of depth of clinical response on outcomes of acute myeloid leukemia patients in first complete remission who undergo allogeneic hematopoietic cell transplantation. ***Bone Marrow Transplantation. 2021 Sep;56(9):2108-2117. doi: 10.1038/s41409-021-01261-6.***

d. **LK17-02** Menghrajani K, Gomez-Arteaga A, Madero-Marroquin R, Zhang M-J, Bo-Subait K, Sanchez J, Wang H-L, Aljurf M, Assal A, Bacher U, Badawy SM, Bejanyan N, Bhatt VR, Bredeson CN, Byrne M, Castillo P, Chhabra S, Ciurea SO, DeFilipp Z, Farhadfar N, Gadalla SM, Gale RP, Ganguly S, Gowda L, Grunwald MR, Hashmi S, Hildebrandt GC, Kanakry CG, Kansagra A, Khimani F, Krem M, Lazarus HM, Liu H, Martino R, Michelis FV, Nathan S, Nishihori T, Olsson RF, Reshef R, Rizzieri D, Rowe JM, Savani BN, Seo S, Sharma A, Solh M, Ustun C, Verdonck LF, Hourigan CS, Sandmaier BM, Litzow MR, Kebriaei P, Weisdorf DJ, Zhang Y, Tallman MS, Saber W. Risk classification at diagnosis predicts post-HCT outcomes in intermediate-, adverse-risk, and KMT2A-rearranged AML. ***Blood Advances. 2021 Sep 22. doi: 10.1182/bloodadvances.2021004881.***

e. **LK18-01** Jimenez Jimenez AM, De Lima M, Komanduri KV, Wang TP, Zhang M-J, Chen K, Abdel-Azim H, Abid MB, Aljurf M, Alkhateeb H, Assal A, Bacher U, Baron F, Battiwalla M, Beitinjaneh A, Bejanyan N, Bhatt VR, Byrne M, Cahn J-Y, Cairo M, Castillo P, Copelan E, DeFilipp Z, Perez MAD, Elsawy M, Gale RP, George B, Grunwald MR, Hildebrandt GC, Hogan WJ, Kanakry CG, Kansagra A, Kharfan-Dabaja MA, Khera N, Krem MM, Lazaryan A, Maakaron J, Martino R, McGuirk J, Michelis FV, Milone G, Mishra A, Murthy HS, Mussetti A, Nathan S, Nishihori T, Olsson RF, Palmisiano N, Patel S, Saad A, Seo S, Sharma A, Solh M, Verdonck LF, Wirk B, Yared JA, Litzow M, Kebriaei P, Hourigan CS, Saber W, Weisdorf D. An adapted European LeukemiaNet genetic risk stratification for acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplant. A CIBMTR analysis. ***Bone Marrow Transplantation. 2021 Dec;56(12):3068-3077. doi: 10.1038/s41409-021-01450-3.***

f. **LK18-02** Wieduwilt MJ, Metheny L, Zhang MJ, Wang H-L, Estrada-Merly N, Marks DI, Al-Homsi AS, Muffly L, Chao NJ, Rizzieri D, Gale RP, Gadalla SM, Cairo MS, Mussetti A, Gore SD, Bhatt VR, Patel SS, Michelis FV, Inamoto Y, Badawy SM, Copelan E, Palmisiano N, Kharfan-Dabaja MA, Lazarus HM, Ganguly S, Bredeson CN, Diaz Perez MA, Cassaday R, Savani BN, Ballen KK, Martino R, Wirk B, Bacher U, Aljurf M, Bashey A, Murthy HS, Yared JA, Aldoss I, Farhadfar N, Liu H, Abdel-Azim H, Waller EK, Solh M, Seftel M, van der Poel MWM, Grunwald MR, Liesveld JL, Kamble RT, McGuirk JP, Munker R, Cahn J-Y, Lee JW, Freytes CO, Krem M, Winestone LE, Gergis U, Nathan S, Olsson RF, Verdonck LF, Sharma A, Ringden O, Friend BD, Cerny J, Choe HK, Chhabra S, Nishihori T, Seo S, George B, Baxter-Lowe LA, Hildebrandt GC, De Lima M, Litzow MR, Kebriaei P, Hourigan CS, Abid MB, Weisdorf DJ, Saber W. Haploidentical vs. sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia. ***Blood Advances. 2021 Sep 21. doi: 10.1182/bloodadvances.2021004916.***

g. **LK20-04** Impact of older age in allogeneic transplants for acute myeloid myelogenous leukemia in first complete remission (Maakaron J/Weisdorf D). **In press.**

h. **LK19-03** Boyiadzis M, de Lima M, Zhang M-J, Chen K, Hourigan CS, Kebriaei P, Litzow MR, Page K, Saber W, Weisdorf DJ. Prompt CR Plus Consolidation Therapy Yields Improve Survival after Allogeneic Transplantation for AML Patients Receiving Myeloablative, but Not Reduced-Intensity Conditioning: A CIBMTR Analysis. ***Oral presentation, ASH 2021.***

i. **LK19-01** Murthy H, Zhang M-J, Chen K, Ganguly S, Ahmed S, Michelis FV, Nishihori T, Deotare U, Kansagra A, Patnaik MM, Litzow MR, Kebriaei P, Hourigan CS, Page K, Kharfan-Dabaja MA, Saber W. Outcomes of Allogeneic Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm: A CIBMTR Analysis. ***Poster presentation, Tandem Meetings 2022.***

4. Studies in progress (Attachment 3)

a. **LK19-01** Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm (H Murthy/M Kharfan-Dabaja) **Manuscript preparation**
b. **LK19-02** Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era (M Krem/R Maziarz) **Analysis**
c. **LK19-03** Outcomes of allo-HCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (M Boyiadzis/M de Lima) **Manuscript preparation**
d. **LK20-01** Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (A Dias/J Yared) **Protocol development**
e. **LK20-02** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia (P Liu/L Cunningham) **Sample typing**
f. **LK20-03** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (H Murthy/M Iqbal/M Kharfan-Dabaja) **Protocol development**
g. **LK21-01** Impact of measurable residual disease status on outcomes of acute myeloid leukemia and patients 18-65 years old in first complete remission undergoing allogeneic hematopoietic cell transplantation (F El Chaer/C Hourigan) **Data file preparation**

5. Future/proposed studies

a. **PROP 2110-21/2110-168** Impact of *IDH1* and *IDH2* mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation (S Iyer/E Chen/A Jimenez/Y-B Chen) (Attachment 4)
b. **PROP 2110-29/2110-120/2110-128/2110-153/2110-204/2110-220/2110-294/2110-307/2110-326** Outcomes of allogeneic hematopoietic cell transplantation following low intensity versus high intensity therapy for AML and MDS in first complete morphologic remission (A Jimenez/T Wang/J Reagan/A Pelcovits/M Salas/A Mussetti/H Murthy/J Foran/K Sahasrabudhe/S Wall/ J Esteve/N Ali/B Sandmaier/J Ignatz-Hoover/B Tomlinson/B Wirk) (Attachment 5)
c. **PROP 2110-104/2110-216** Development of pre-transplant risk scores for patients undergoing allogeneic HCT for acute leukemia transplanted in complete remission or with relapsed/refractory disease (I Novitzky-Basso/M Walji/F Michelis/B Gyurkocza (Attachment 6)
d. **PROP 2110-121** Impact of Pretransplant Mutation Topography on Cumulative Incidence of Relapse after Allogeneic Haematopoietic Cell Transplants for T-Cell Acute Lymphoblastic Leukemia (Y Liang/ P Gale) (Attachment 7)
e. **PROP 2110-206** Comparison of transplant outcomes using fludarabine, cyclophosphamide and total body irradiation (TBI) vs. fludarabine, melphalan and TBI based reduced-intensity conditioning regimens in patients undergoing haploidentical stem cell transplant (H Alkhateeb/A Baranwal) (Attachment 8)
f. **PROP 2110-260** Outcomes of allogeneic hematopoietic cell transplantation for relapsed acute myeloid leukemia based on minimal residual disease status: CIBMTR analysis (G Murthy/W Saber) (Attachment 9)
g. **PROP 2110-293/2110-319** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms (L Williams/A-S Mirza/L Gowda/C Lai) (Attachment 10)

h. **PROP 2110-298** Impact of Pre-Transplant Extramedullary Disease on Allogeneic Transplant Outcomes in Acute Lymphoblastic Leukemia (ALL) (R Ramlal) (Attachment 11)
i. **PROP 2110-323** Allogeneic transplant for Relapsed Refractory ALL in Modern Era (L Gowda/A Zeidan) (Attachment 12)
j. **PROP 2110-347** Role of Post Remission Consolidation Therapy Prior to Haploidentical Transplantation for Patients with Acute Myeloid Leukemia (L Gowda/A-S Mirza) (Attachment 13)

Proposed studies; not accepted for consideration at this time

k. **PROP 2109-22** Utilization and outcomes of second allogeneic hematopoietic stem cell transplantation for adult for acute lymphoblastic leukemia
l. **PROP 2110-01** Outcomes of Hematopoietic Cell transplantation (HCT) for T cell Large Granular Lymphocytic Leukemia
m. **PROP 2110-10** Haploidentical SCT in pre-transplant MRD positive AML patients
n. **PROP 2110-14** Outcomes of patients with extramedullary disease with or without marrow involvement and patterns of relapse after allogeneic hematopoietic cell transplantation
o. **PROP 2110-40** Analysis of hypomethylating agent plus venetoclax and CPX-351 as a bridge to allogeneic hematopoietic stem cell transplantation in patients with secondary acute myeloid leukemia (sAML)/ AML with myelodysplastic syndrome related changes (MRC)
p. **PROP 2110-42** Developing a Super Learner Machine Learning Model and Clinical Decision Support System for Prediction of Overall Survival and Non-relapse Mortality in Patients with Acute Leukemias Undergoing Allogeneic Hematopoietic Cell Transplantation
q. **PROP 2110-78** Donor Lymphocyte infusion vs second allogeneic hematopoietic cell transplantation for relapse after transplantation for AML/MDS
r. **PROP 2110-95** Comparison of outcomes of patients with secondary, therapy-related, and antecedent-malignancy acute lymphoblastic leukemia to de novo acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation
s. **PROP 2110-105** Haploidentical transplant versus mismatched unrelated donor transplant with post-transplant cyclophosphamide for acute myeloid leukemia and myelodysplastic syndromes
t. **PROP 2110-114** Comparison Of Outcomes Between Busulfan-Based Myeloablative Conditioning Regimens With Cyclophosphamide (Bu/Cy) Or Fludarabine (Bu/Flu) For Acute Myeloid Leukemia
u. **PROP 2110-132** Thiotepa-based conditioning in pre-transplant MRD+ AML patients may improve survival outcomes due to decreased post-transplant relapse risk.
v. **PROP 2110-155** Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Therapy related Acute Lymphoblastic Leukemia (tr-ALL)
w. **PROP 2110-167** Hematopoietic Cell Transplant Outcomes in Adult Patients with Philadelphia Chromosome like Acute Lymphoblastic Leukemia
x. **PROP 2110-192** Impact of Minimal Residual Disease in Acute Lymphoblastic Leukemia patients undergoing Allogeneic Stem cell Transplant in first complete remission
y. **PROP 2110-212** Impact of MRD status < alloHCT on D+30, D+100, and D+180 post-transplant infectious complications in adults with AML, ALL, and MDS
z. **PROP 2110-221** Comparison of allogeneic hematopoietic cell transplantation following antigen-targeted salvage strategies for relapsed/refractory B-cell acute lymphoblastic leukemia
aa. **PROP 2110-235** CD19+CAR-T therapy vs allogeneic HCT for poor-risk B-cell ALL with post-induction MRD positivity
ab. **PROP 2110-236** Evaluating the Significance of Blast Maturation State as a Novel Approach to Further Risk Stratify High Risk Patients with Acute Myeloid Leukemia who are Referred for Allogeneic Hematopoietic Cell Transplantation in CR1

ac. **PROP 2110-304** The effect of the prophylactic donor lymphocyte infusion on allogeneic hematopoietic cell transplantation outcomes in patients with acute myeloid leukemia

ad. **PROP 2110-346** Role of Measurable Residual Disease in AML and MDS with reduced Intensity Allografting

6. Other business

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

Accrual Summary for the Acute Leukemia Working Committee

Characteristics of recipients of first allogeneic transplants for AML and ALL reported[a] to the CIBMTR between 2008 and 2021

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Number of patients	11887	4697
Number of centers	271	242
Age at transplant, years		
Median (range)	52 (0-88)	29 (0-79)
<10	800 (7)	843 (18)
10-17	754 (6)	746 (16)
18-29	967 (8)	798 (17)
30-39	1138 (10)	623 (13)
40-49	1740 (15)	652 (14)
50-59	2763 (23)	570 (12)
60-69	3016 (25)	426 (9)
>=70	709 (6)	39 (1)
Recipient sex		
Male	6385 (54)	2760 (59)
Female	5502 (46)	1937 (41)
HCT-CI		
0	3087 (26)	1715 (37)
1	1756 (15)	710 (15)
2	1539 (13)	579 (12)
3+	4822 (41)	1425 (30)
Missing	683 (6)	268 (6)
Disease status at time of HCT		
PIF	1428 (12)	124 (3)
CR1	7109 (60)	2669 (57)
CR2	2265 (19)	1377 (29)
>=CR3	162 (1)	316 (7)
Relapse	920 (8)	208 (4)
Missing	3 (<1)	3 (<1)
Time from diagnosis to HCT		
Median (range)	5 (0-352)	8 (1-499)
<6 months	6416 (54)	1567 (33)
6 - 12 months	2540 (21)	1233 (26)
>12 months	2544 (21)	1819 (39)

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Missing	387 (3)	78 (2)
Conditioning regimen intensity		
Myeloablative	6901 (58)	3624 (77)
Reduced intensity	3009 (25)	546 (12)
Non-myeloablative	1632 (14)	380 (8)
Missing	345 (3)	147 (3)
Graft type		
Bone marrow	1972 (17)	997 (21)
Peripheral blood	7662 (64)	2344 (50)
Umbilical cord blood	2233 (19)	1340 (29)
Missing	20 (<1)	16 (<1)
Type of donor		
HLA-identical sibling	2568 (22)	938 (20)
Identical twin	36 (<1)	25 (1)
Other relative	1916 (16)	831 (18)
Unrelated	5124 (43)	1562 (33)
Cord blood	2233 (19)	1340 (29)
Missing	10 (<1)	1 (<1)
Year of HCT		
2008-2009	2544 (21)	931 (20)
2010-2011	1418 (12)	486 (10)
2012-2013	1471 (12)	560 (12)
2014-2015	2425 (20)	960 (20)
2016-2017	1939 (16)	833 (18)
2018-2019	1415 (12)	728 (15)
2020-2021	675 (6)	199 (4)
Median follow-up of survivors (range), months	61 (2-157)	57 (1-151)

[a] Patients have available comprehensive research form (CRF) and consented for research

Characteristics of recipients of first autologous transplants for AML and ALL reported[a] to the CIBMTR between 2008 and 2021

Accrual Table 2. Autologous transplant recipients:	**AML**	**ALL**
Number of patients	170	17
Number of centers	63	10
Age at transplant, years		
Median (range)	50 (7-78)	37 (22-66)
<10	2 (1)	0 (0)
10-17	3 (2)	0 (0)
18-29	16 (9)	5 (29)
30-39	29 (17)	4 (24)
40-49	35 (21)	4 (24)
50-59	42 (25)	2 (12)
60-69	39 (23)	2 (12)
>=70	4 (2)	0 (0)
Recipient sex		
Male	83 (49)	13 (76)
Female	87 (51)	4 (24)
HCT-CI		
0	64 (38)	4 (24)
1	26 (15)	3 (18)
2	22 (13)	5 (29)
3+	56 (33)	5 (29)
Missing	2 (1)	0 (0)
Disease status at time of HCT		
CR1	112 (66)	15 (88)
CR2	54 (32)	2 (12)
>=CR3	4 (2)	0 (0)
Time from diagnosis to HCT		
Median (range)	6 (3-182)	8 (5-37)
<6 months	88 (52)	3 (18)
6 - 12 months	27 (16)	10 (59)
>12 months	55 (32)	3 (18)
Missing	0 (0)	1 (6)
Conditioning regimen intensity		
Myeloablative	153 (90)	12 (71)
Reduced intensity	7 (4)	2 (12)
Non-myeloablative	1 (1)	0 (0)

Accrual Table 2. Autologous transplant recipients:	**AML**	**ALL**
Missing	9 (5)	3 (18)
Graft type		
Bone marrow	3 (2)	0 (0)
Peripheral blood	167 (98)	17 (100)
Year of HCT		
2008-2009	90 (53)	6 (35)
2010-2011	23 (14)	2 (12)
2012-2013	26 (15)	4 (24)
2014-2015	14 (8)	1 (6)
2016-2017	11 (6)	2 (12)
2018-2019	6 (4)	2 (12)
Median follow-up of survivors (range), months	87 (2-145)	71 (13-79)

[a] Patients have available comprehensive research form (CRF) and consented for research

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	**22291**	**8204**	**4394**
Source of data			
CRF	10644 (48)	2860 (35)	2100 (48)
TED	11647 (52)	5344 (65)	2294 (52)
Number of centers	239	209	329
Disease at transplant			
AML	15294 (69)	5896 (72)	2918 (66)
ALL	6535 (29)	2123 (26)	1370 (31)
Other acute leukemia	462 (2)	185 (2)	106 (2)
AML Disease status at transplant			
CR1	8061 (53)	3434 (58)	1439 (49)
CR2	2975 (19)	1072 (18)	590 (20)
CR3+	330 (2)	95 (2)	67 (2)
Advanced or active disease	3783 (25)	1262 (21)	767 (26)
Missing	145 (1)	33 (1)	55 (2)
ALL Disease status at transplant			
CR1	3206 (49)	1180 (56)	585 (43)
CR2	1873 (29)	548 (26)	393 (29)
CR3+	558 (9)	157 (7)	139 (10)
Advanced or active disease	852 (13)	222 (10)	217 (16)
Missing	46 (1)	16 (1)	36 (3)
Recipient age at transplant			
0-9 years	1628 (7)	456 (6)	414 (9)
10-19 years	2196 (10)	608 (7)	544 (12)
20-29 years	2717 (12)	883 (11)	586 (13)
30-39 years	2624 (12)	902 (11)	565 (13)
40-49 years	3365 (15)	1168 (14)	649 (15)
50-59 years	4276 (19)	1537 (19)	744 (17)
60-69 years	4476 (20)	2088 (25)	732 (17)
70+ years	1009 (5)	562 (7)	160 (4)
Median (Range)	46 (0-84)	51 (0-82)	42 (0-77)
Recipient race/ethnicity			

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 (%)
Caucasian, non-Hispanic	18394 (83)	6781 (83)	3081 (70)
African-American, non-Hispanic	829 (4)	280 (3)	180 (4)
Asian, non-Hispanic	560 (3)	264 (3)	176 (4)
Pacific islander, non-Hispanic	28 (<1)	10 (<1)	16 (<1)
Native American, non-Hispanic	91 (<1)	27 (<1)	18 (<1)
Hispanic	1501 (7)	503 (6)	262 (6)
Missing	888 (4)	339 (4)	661 (15)
Recipient sex			
Male	12328 (55)	4538 (55)	2478 (56)
Female	9963 (45)	3666 (45)	1916 (44)
Karnofsky score			
10-80	7993 (36)	3189 (39)	1427 (32)
90-100	13531 (61)	4770 (58)	2734 (62)
Missing	767 (3)	245 (3)	233 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	18 (<1)	27 (<1)	2 (<1)
4/6	102 (<1)	52 (1)	20 (<1)
5/6	3025 (14)	936 (13)	655 (16)
6/6	18769 (86)	6427 (86)	3448 (84)
Unknown	377 (N/A)	762 (N/A)	269 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	397 (2)	67 (1)	29 (1)
6/8	856 (4)	75 (1)	74 (2)
7/8	4277 (20)	1011 (16)	675 (23)
8/8	16093 (74)	4982 (81)	2204 (74)
Unknown	668 (N/A)	2069 (N/A)	1412 (N/A)
HLA-DPB1 Match			
Double allele mismatch	6032 (29)	735 (25)	303 (26)
Single allele mismatch	10975 (54)	1519 (51)	608 (52)
Full allele matched	3499 (17)	728 (24)	266 (23)
Unknown	1785 (N/A)	5222 (N/A)	3217 (N/A)
High resolution release score			
No	2753 (12)	8177 (>99)	4297 (98)
Yes	19538 (88)	27 (<1)	97 (2)
KIR typing available			
No	13733 (62)	8195 (>99)	4365 (99)
Yes	8558 (38)	9 (<1)	29 (1)
Graft type			
Marrow	7426 (33)	2201 (27)	1584 (36)

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 (%)
PBSC	14835 (67)	5906 (72)	2799 (64)
BM+PBSC	4 (<1)	5 (<1)	2 (<1)
PBSC+UCB	17 (<1)	83 (1)	4 (<1)
Others	9 (<1)	9 (<1)	5 (<1)
Conditioning regimen			
Myeloablative	15757 (71)	5220 (64)	3106 (71)
RIC/Nonmyeloablative	6444 (29)	2965 (36)	1227 (28)
TBD	90 (<1)	19 (<1)	61 (1)
Donor age at donation			
To Be Determined/NA	238 (1)	748 (9)	57 (1)
0-9 years	6 (<1)	20 (<1)	1 (<1)
10-19 years	649 (3)	288 (4)	94 (2)
20-29 years	10374 (47)	3696 (45)	1829 (42)
30-39 years	6149 (28)	2046 (25)	1302 (30)
40-49 years	3712 (17)	1078 (13)	844 (19)
50+ years	1163 (5)	328 (4)	267 (6)
Median (Range)	30 (0-61)	29 (0-89)	32 (0-67)
Donor/Recipient CMV serostatus			
+/+	5842 (26)	2423 (30)	1147 (26)
+/-	2479 (11)	924 (11)	538 (12)
-/+	7880 (35)	2700 (33)	1439 (33)
-/-	5775 (26)	1904 (23)	1077 (25)
CB - recipient +	2 (<1)	9 (<1)	0
CB - recipient -	0	3 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Missing	313 (1)	240 (3)	193 (4)
GvHD Prophylaxis			
No GvHD Prophylaxis	73 (<1)	33 (<1)	24 (1)
TDEPLETION alone	62 (<1)	12 (<1)	17 (<1)
TDEPLETION +- other	512 (2)	137 (2)	140 (3)
CD34 select alone	132 (1)	42 (1)	26 (1)
CD34 select +- other	414 (2)	318 (4)	98 (2)
Cyclophosphamide alone	484 (2)	409 (5)	125 (3)
Cyclophosphamide +- others	1071 (5)	762 (9)	205 (5)
FK506 + MMF +- others	2289 (10)	767 (9)	291 (7)
FK506 + MTX +- others (not MMF)	10229 (46)	3546 (43)	1314 (30)
FK506 +- others (not MMF, MTX)	1174 (5)	500 (6)	161 (4)
FK506 alone	524 (2)	196 (2)	71 (2)
CSA + MMF +- others (not FK506)	1129 (5)	317 (4)	286 (7)

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 (%)
CSA + MTX +- others (not MMF, FK506)	3207 (14)	836 (10)	1224 (28)
CSA +- others (not FK506, MMF, MTX)	369 (2)	117 (1)	131 (3)
CSA alone	198 (1)	63 (1)	149 (3)
Other GVHD Prophylaxis	322 (1)	111 (1)	76 (2)
Missing	102 (<1)	38 (<1)	56 (1)
Donor/Recipient sex match			
Male-Male	8677 (39)	2997 (37)	1627 (37)
Male-Female	5998 (27)	2095 (26)	1097 (25)
Female-Male	3527 (16)	1330 (16)	814 (19)
Female-Female	3847 (17)	1390 (17)	788 (18)
CB - recipient M	7 (<1)	41 (<1)	0
CB - recipient F	10 (<1)	47 (1)	5 (<1)
Missing	225 (1)	304 (4)	63 (1)
Year of transplant			
1986-1990	132 (1)	18 (<1)	19 (<1)
1991-1995	776 (3)	190 (2)	214 (5)
1996-2000	1403 (6)	509 (6)	402 (9)
2001-2005	2554 (11)	529 (6)	781 (18)
2006-2010	4683 (21)	967 (12)	787 (18)
2011-2015	6769 (30)	1822 (22)	980 (22)
2016-2020	5476 (25)	3668 (45)	1063 (24)
2021	498 (2)	501 (6)	148 (3)
Follow-up among survivors, Months			
N Eval	8960	3802	1693
Median (Range)	60 (1-372)	26 (0-362)	37 (0-365)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006-recipient only), 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	**3536**	**899**	**880**
Source of data			
CRF	2571 (73)	634 (71)	527 (60)
TED	965 (27)	265 (29)	353 (40)
Number of centers	140	122	165
Disease at transplant			
AML	2221 (63)	529 (59)	505 (57)
ALL	1222 (35)	344 (38)	347 (39)
Other acute leukemia	93 (3)	26 (3)	28 (3)
AML Disease status at transplant			
CR1	1147 (52)	287 (54)	241 (48)
CR2	608 (27)	139 (26)	139 (28)
CR3+	62 (3)	8 (2)	22 (4)
Advanced or active disease	398 (18)	93 (18)	101 (20)
Missing	6 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	550 (45)	146 (42)	146 (42)
CR2	451 (37)	124 (36)	125 (36)
CR3+	143 (12)	51 (15)	48 (14)
Advanced or active disease	77 (6)	21 (6)	28 (8)
Missing	1 (<1)	2 (1)	0
Recipient age at transplant			
0-9 years	789 (22)	267 (30)	228 (26)
10-19 years	534 (15)	136 (15)	154 (18)
20-29 years	409 (12)	73 (8)	93 (11)
30-39 years	392 (11)	98 (11)	103 (12)
40-49 years	404 (11)	93 (10)	93 (11)
50-59 years	496 (14)	112 (12)	110 (13)
60-69 years	444 (13)	105 (12)	91 (10)
70+ years	68 (2)	15 (2)	8 (1)
Median (Range)	31 (0-83)	27 (0-76)	25 (0-78)

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 (%)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1961 (55)	513 (57)	478 (54)
African-American, non-Hispanic	438 (12)	105 (12)	87 (10)
Asian, non-Hispanic	217 (6)	57 (6)	65 (7)
Pacific islander, non-Hispanic	22 (1)	3 (<1)	8 (1)
Native American, non-Hispanic	23 (1)	5 (1)	10 (1)
Hispanic	655 (19)	148 (16)	119 (14)
Missing	220 (6)	68 (8)	113 (13)
Recipient sex			
Male	1859 (53)	479 (53)	476 (54)
Female	1677 (47)	420 (47)	404 (46)
Karnofsky score			
10-80	973 (28)	243 (27)	226 (26)
90-100	2491 (70)	625 (70)	618 (70)
Missing	72 (2)	31 (3)	36 (4)
HLA-A B DRB1 groups - low resolution			
<=3/6	60 (2)	29 (4)	9 (1)
4/6	1514 (44)	329 (44)	323 (40)
5/6	1495 (44)	307 (41)	373 (47)
6/6	358 (10)	90 (12)	97 (12)
Unknown	109 (N/A)	144 (N/A)	78 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	1741 (58)	326 (59)	353 (54)
6/8	708 (24)	128 (23)	165 (25)
7/8	383 (13)	61 (11)	99 (15)
8/8	161 (5)	35 (6)	34 (5)
Unknown	543 (N/A)	349 (N/A)	229 (N/A)
HLA-DPB1 Match			
Double allele mismatch	487 (39)	65 (47)	64 (38)
Single allele mismatch	657 (52)	59 (43)	84 (50)
Full allele matched	115 (9)	14 (10)	20 (12)
Unknown	2277 (N/A)	761 (N/A)	712 (N/A)
High resolution release score			
No	2704 (76)	855 (95)	874 (99)
Yes	832 (24)	44 (5)	6 (1)
KIR typing available			
No	2846 (80)	894 (99)	876 (>99)
Yes	690 (20)	5 (1)	4 (<1)
Graft type			

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 (%)
UCB	3339 (94)	816 (91)	818 (93)
PBSC+UCB	179 (5)	83 (9)	58 (6)
Others	18 (1)	0	4 (<1)
Number of cord units			
1	2897 (82)	0	725 (82)
2	638 (18)	0	155 (18)
3	1 (<1)	0	0
Unknown	0 (N/A)	899 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	2481 (70)	638 (71)	591 (67)
RIC/Nonmyeloablative	1047 (30)	260 (29)	287 (33)
TBD	8 (<1)	1 (<1)	2 (<1)
Donor age at donation			
To Be Determined/NA	125 (4)	58 (6)	66 (8)
0-9 years	3118 (88)	691 (77)	736 (84)
10-19 years	169 (5)	82 (9)	37 (4)
20-29 years	39 (1)	22 (2)	10 (1)
30-39 years	36 (1)	25 (3)	15 (2)
40-49 years	22 (1)	10 (1)	7 (1)
50+ years	27 (1)	11 (1)	9 (1)
Median (Range)	3 (0-72)	5 (0-73)	4 (0-67)
Donor/Recipient CMV serostatus			
+/+	894 (25)	196 (22)	185 (21)
+/-	304 (9)	88 (10)	68 (8)
-/+	697 (20)	166 (18)	167 (19)
-/-	407 (12)	97 (11)	113 (13)
CB - recipient +	804 (23)	213 (24)	208 (24)
CB - recipient -	386 (11)	115 (13)	118 (13)
CB - recipient CMV unknown	44 (1)	24 (3)	21 (2)
GvHD Prophylaxis			
No GvHD Prophylaxis	16 (<1)	7 (1)	4 (<1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	20 (1)	6 (1)	3 (<1)
CD34 select alone	0	1 (<1)	2 (<1)
CD34 select +- other	178 (5)	83 (9)	60 (7)
Cyclophosphamide alone	0	0	1 (<1)
Cyclophosphamide +- others	26 (1)	15 (2)	24 (3)
FK506 + MMF +- others	998 (28)	236 (26)	146 (17)
FK506 + MTX +- others(not MMF)	136 (4)	39 (4)	44 (5)

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 (%)
FK506 +- others(not MMF,MTX)	115 (3)	32 (4)	25 (3)
FK506 alone	77 (2)	19 (2)	10 (1)
CSA + MMF +- others(not FK506)	1681 (48)	372 (41)	431 (49)
CSA + MTX +- others(not MMF,FK506)	57 (2)	16 (2)	20 (2)
CSA +- others(not FK506,MMF,MTX)	135 (4)	53 (6)	64 (7)
CSA alone	24 (1)	12 (1)	29 (3)
Other GVHD Prophylaxis	66 (2)	7 (1)	15 (2)
Missing	6 (<1)	1 (<1)	2 (<1)
Donor/Recipient sex match			
CB - recipient M	1859 (53)	479 (53)	475 (54)
CB - recipient F	1677 (47)	420 (47)	404 (46)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	54 (2)	68 (8)	16 (2)
2006-2010	1055 (30)	228 (25)	244 (28)
2011-2015	1552 (44)	274 (30)	363 (41)
2016-2020	845 (24)	304 (34)	232 (26)
2021	30 (1)	24 (3)	22 (3)
Follow-up among survivors, Months			
N Eval	1593	428	409
Median (Range)	61 (1-196)	50 (3-213)	48 (1-199)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

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, recipient only 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	**4925**	**834**	**337**
Source of data			
CRF	1402 (28)	180 (22)	99 (29)
TED	3523 (72)	654 (78)	238 (71)
Number of centers	83	66	54
Disease at transplant			
AML	3214 (65)	506 (61)	206 (61)
ALL	1578 (32)	299 (36)	124 (37)
Other acute leukemia	133 (3)	29 (3)	7 (2)
AML Disease status at transplant			
CR1	2063 (64)	340 (67)	134 (65)
CR2	486 (15)	66 (13)	26 (13)
CR3+	38 (1)	13 (3)	1 (<1)
Advanced or active disease	619 (19)	83 (16)	45 (22)
Missing	8 (<1)	4 (1)	0
ALL Disease status at transplant			
CR1	974 (62)	195 (65)	76 (61)
CR2	437 (28)	69 (23)	31 (25)
CR3+	88 (6)	13 (4)	10 (8)
Advanced or active disease	78 (5)	22 (7)	7 (6)
Missing	1 (<1)	0	0
Recipient age at transplant			
0-9 years	330 (7)	47 (6)	22 (7)
10-19 years	545 (11)	69 (8)	32 (9)
20-29 years	521 (11)	103 (12)	34 (10)
30-39 years	498 (10)	86 (10)	42 (12)
40-49 years	707 (14)	133 (16)	41 (12)
50-59 years	1071 (22)	184 (22)	60 (18)
60-69 years	1061 (22)	177 (21)	93 (28)
70+ years	192 (4)	35 (4)	13 (4)
Median (Range)	49 (1-82)	49 (1-76)	50 (1-83)
Recipient race/ethnicity			

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 (%)
Caucasian, non-Hispanic	3103 (63)	426 (51)	208 (62)
African-American, non-Hispanic	437 (9)	68 (8)	18 (5)
Asian, non-Hispanic	225 (5)	77 (9)	19 (6)
Pacific islander, non-Hispanic	13 (<1)	1 (<1)	1 (<1)
Native American, non-Hispanic	20 (<1)	2 (<1)	1 (<1)
Hispanic	828 (17)	196 (24)	65 (19)
Missing	299 (6)	64 (8)	25 (7)
Recipient sex			
Male	2807 (57)	466 (56)	188 (56)
Female	2118 (43)	368 (44)	149 (44)
Karnofsky score			
10-80	1848 (38)	365 (44)	149 (44)
90-100	2974 (60)	458 (55)	177 (53)
Missing	103 (2)	11 (1)	11 (3)
Graft type			
Marrow	1216 (25)	153 (18)	80 (24)
PBSC	3685 (75)	674 (81)	251 (74)
UCB (related)	1 (<1)	3 (<1)	0
BM+PBSC	3 (<1)	3 (<1)	1 (<1)
BM+UCB	4 (<1)	1 (<1)	0
PBSC+UCB	0	0	5 (1)
Others	16 (<1)	0	0
Conditioning regimen			
Myeloablative	3371 (68)	555 (67)	215 (64)
RIC/Nonmyeloablative	1546 (31)	277 (33)	117 (35)
TBD	8 (<1)	2 (<1)	5 (1)
Donor age at donation			
To Be Determined/NA	4 (<1)	5 (1)	0
0-9 years	227 (5)	29 (3)	12 (4)
10-19 years	453 (9)	75 (9)	29 (9)
20-29 years	782 (16)	139 (17)	53 (16)
30-39 years	792 (16)	142 (17)	71 (21)
40-49 years	816 (17)	154 (18)	42 (12)
50+ years	1851 (38)	290 (35)	130 (39)
Median (Range)	43 (0-80)	42 (0-79)	41 (1-76)
Donor/Recipient CMV serostatus			
+/+	2081 (42)	395 (47)	147 (44)
+/-	484 (10)	67 (8)	28 (8)
-/+	1388 (28)	209 (25)	89 (26)

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 (%)
-/-	905 (18)	154 (18)	63 (19)
Missing	67 (1)	9 (1)	10 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	59 (1)	8 (1)	2 (1)
TDEPLETION alone	30 (1)	13 (2)	2 (1)
TDEPLETION +- other	33 (1)	8 (1)	3 (1)
CD34 select alone	41 (1)	9 (1)	4 (1)
CD34 select +- other	207 (4)	44 (5)	28 (8)
Cyclophosphamide alone	149 (3)	26 (3)	17 (5)
Cyclophosphamide +- others	1378 (28)	207 (25)	99 (29)
FK506 + MMF +- others	273 (6)	30 (4)	11 (3)
FK506 + MTX +- others(not MMF)	1876 (38)	250 (30)	117 (35)
FK506 +- others(not MMF,MTX)	401 (8)	172 (21)	23 (7)
FK506 alone	23 (<1)	3 (<1)	2 (1)
CSA + MMF +- others(not FK506)	60 (1)	8 (1)	4 (1)
CSA + MTX +- others(not MMF,FK506)	303 (6)	34 (4)	15 (4)
CSA +- others(not FK506,MMF,MTX)	0	2 (<1)	0
CSA alone	32 (1)	6 (1)	0
Other GVHD Prophylaxis	43 (1)	8 (1)	6 (2)
Missing	17 (<1)	6 (1)	4 (1)
Donor/Recipient sex match			
Male-Male	1596 (32)	297 (36)	110 (33)
Male-Female	1094 (22)	195 (23)	76 (23)
Female-Male	1207 (25)	164 (20)	76 (23)
Female-Female	1023 (21)	169 (20)	70 (21)
CB - recipient M	4 (<1)	2 (<1)	2 (1)
CB - recipient F	1 (<1)	2 (<1)	3 (1)
Missing	0	5 (1)	0
Year of transplant			
2006-2010	268 (5)	29 (3)	16 (5)
2011-2015	1778 (36)	266 (32)	79 (23)
2016-2020	2608 (53)	483 (58)	199 (59)
2021	271 (6)	56 (7)	43 (13)
Follow-up among survivors, Months			
N Eval	2780	469	182
Median (Range)	36 (1-148)	29 (3-122)	24 (3-121)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Acute Leukemia Working Committee Members

FROM: Kristin Page, MD, MHS; Scientific Director for the Acute Leukemia Working Committee

RE: Studies in Progress Summary

LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm (H Murthy / M Kharfan-Dabaja)
The purpose of the study is to:

(1) Describe clinical outcomes of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) undergoing allogeneic HCT (allo-HCT).
(2) Identify the impact of patient-, disease-, and transplant-related factors on disease-free survival, overall survival, relapse and non-relapse mortality of patients receiving allo-HCT for BPDCN.

The results will be presented as a poster presentation during the Tandem Meeting 2022. The manuscript is currently in progress. The plan is to finalize the manuscript and submit for publication by July 2022.

LK19-02: Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era (M Krem / R Maziarz)
The purpose of the study is to:

(1) To compare post-transplant outcomes of Ph-positive ALL patients vs Ph-negative ALL patients undergoing HCT over three time periods: 2001-2007, 2008-2019.
(2) Evaluate impact of conditioning regimen intensity, MRD status, and additional cytogenetic abnormalities on post-transplant outcomes of Ph-positive ALL patients.

Analysis is currently in progress. The plan is to finalize the analysis and submit a manuscript for publication by July 2022.

LK19-03: Outcomes of allo-HCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (M Boyiadzis / M de Lima)
The purpose of this study is to:

(1) Determine treatment-related mortality in patients who underwent allo-HCT in first CR that required 2 or more cycles of induction chemotherapy.
(2) Determine overall survival in patients who underwent allo-HCT in first CR that required 2 or more cycles of induction chemotherapy.

The results were presented at ASH 2021. The manuscript is currently in progress. The plan is to finalize the manuscript and submit for publication by July 2022.

LK20-01: Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (A Dias/J Yared)
The purpose of this study is to:

(1) Evaluate overall survival, disease-free survival, relapse, and non-relapse mortality of adult patients with AML with chromosome 17 abnormalities who received allo-HCT.
(2) Determine the effect of patient-, disease-, and transplant-related factors on these outcomes.

Protocol development is currently in progress. The plan is to finalize the study population and complete the analysis by July 2022.

LK20-02: Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia (P Liu/L Cunningham)
The purpose of this study is to:

(1) Determine the prevalence of germline RUNX1 mutations in a cohort of patients positive for RUNX1 mutations undergoing allo-HCT for AML.
(2) Describe post-HCT outcomes for patients with germline RUNX1 mutations.
(3) Compare post-HCT outcomes in AML patients with germline RUNX1 mutations vs. those with somatic RUNX1 mutations, and with age-matched controls in an AML population undergoing allogeneic HCT without RUNX1 mutations.

Patient samples are currently being sequenced. The plan is to begin analysis by July 2022.

LK20-03: Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (H Murthy/M Iqbal/M Kharfan-Dabaja)
The purpose of this study is to:

(1) Describe clinical outcomes of patients with T-cell acute lymphoblastic leukemia (T-ALL) undergoing allo-HCT.
(2) Identify the impact of patient-, disease-, and transplant-related factors on overall survival, leukemia-free survival, non-relapse mortality, and relapse after allo-HCT for T-ALL.
(3) Describe clinical outcomes of patients with early precursor T-cell acute lymphoblastic leukemia (ETP-ALL) undergoing allo-HCT.

Protocol development is currently in progress. The plan is to finalize the study population and begin analysis by July 2022.

LK21-01: Impact of measurable residual disease status on outcomes of acute myeloid leukemia and patients 18-65 years old in first complete remission undergoing allogeneic hematopoietic cell transplantation (F El Chaer/C Hourigan)
The purpose of this study is to:

(1) Evaluate the prognostic impact of measurable residual disease (MRD) status for adult patients (≥ 18 years) with AML in first complete remission prior to allo-HCT.
(2) Determine the impact of key clinical factors on the risks associated with AML MRD status.

Data file preparation is currently in progress. The plan is to complete the analysis by July 2022.

Q1 Study title: Impact of *IDH1* and *IDH2* mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation

Q2 Key words: Acute myeloid leukemia, *IDH1*, *IDH2*, hematopoietic cell transplantation

Q3 Investigators:

First and last name, degree(s)	Email	Institution	Academic rank	Q4 Junior investigator?
Sunil Iyer, MD	sunil.iyer@jhsmiami.org	University of Miami	Fellow, PGY-5	Yes
Evan Chen, MD	evan_chen@dfci.harvard.edu	Dana-Farber Cancer Institute	Fellow, PGY-6	Yes
Antonio Martin Jimenez Jimenez, MD	amjimenez@med.miami.edu	University of Miami	Assistant Professor	No
Yi-Bin Chen, MD	ychen6@partners.org	Massachusetts General Hospital	Associate Professor	No

Q12 Current Ongoing Work with CIBMTR:
AJJ: Co-author on "Outcomes after HCT for rare chronic leukemias: Evaluating outcomes of Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemias."

Q13 Proposed Working Committee:
Acute leukemia

Q14a If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:
Concept previously submitted in 2020 and deemed feasible. Did not pass final round of voting (please see Scientific Impact for justification for this year's resubmission)

Q15 Research Question:
Is there a difference in rates of disease-free survival (DFS), overall survival (OS) and relapse between patients with *IDH1*- or *IDH2*-mutated (mut*IDH1/2)* acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplantation (HCT) versus AML patients with wild- type *IDH1* and *IDH2* (wt*IDH1/2*) undergoing HCT?

Q16 Research Hypothesis:
We hypothesize that there will be no difference in rates of DFS, OS, and relapse between mut*IDH1/2* AML patients undergoing HCT versus wt*IDH1/2*AML patients undergoing HCT.

Q17 Specific Objectives/Outcomes to be Investigated:
- Primary Objective. To identify differences in the following post-transplant outcomes between mut*IDH1*, mut*IDH2* and wt*IDH1/2*patients:
  - o Overall survival (OS)

- Disease free survival (DFS)
- Cumulative incidence of relapse

- Secondary Objectives. To describe the following prognostic factors associated with post-transplant outcomes in patients with mut*IDH1/2* AML
  - CR1 vs. >CR2
  - Pre-transplant measurable residual disease (MRD positive vs. negative)
  - Conditioning intensity (reduced intensity/non-myeloablative vs. myeloablative)
  - Mutation isoform (*IDH1* vs. *IDH2*)
  - Concurrent mutations (*FLT3*-ITD, *NPM1*, *DNMT3A*)

Q18 Scientific Impact:

For many patients with acute myeloid leukemia (AML), allogeneic hematopoietic cell transplant (HCT) is an effective and potentially curative post-remission treatment.[1] However, relapse remains the major cause of treatment failure following HCT.[2,3] For patients receiving an allogeneic HCT, the 3-year overall survival is 49% and the 1-year post-relapse survival is 23%.[3,4]

Maintenance therapy after HCT may improve patient outcomes. The potential benefit of maintenance therapy has been recently demonstrated by the use of targeted inhibitors for *FLT3*-mutated AML post-HCT. A randomized phase 3 trial showed that post-HCT maintenance therapy with the *FLT3*-inhibitor sorafenib is associated with a reduced 1-year cumulative incidence of relapse (7%) compared to placebo (24.5%) without a significant increase in toxicity.[5] The phase II SORMAIN study also demonstrated a relapse-free survival benefit at 24 months with sorafenib maintenance (85%) compared to placebo (53.3%).[6]

The approval of *IDH1/2* inhibitors for AML has generated interest in their potential role as post-HCT maintenance therapy. Ivosidenib was approved for *IDH1*-mutated newly-diagnosed and relapsed AML, and enasidenib was approved for *IDH2*-mutated relapsed AML.[7-9] Early phase clinical trials investigating the role of *IDH*-inhibitors as maintenance therapy are underway (e.g. NCT03564821, NCT03515512). However, the natural history of AML patients with *IDH1* and *IDH2* mutations who undergo allogeneic HCT compared to AML patients without *IDH1/2* mutations has not been well-described. Such knowledge would provide essential historical benchmarks against which the efficacy of post-HCT maintenance *IDH*-inhibitor therapy may be interpreted and evaluated. We propose using the CIBMTR database to compare post-HCT survival outcomes between AML patients with and without *IDH1/2* mutations.

We previously submitted this proposal to the CIBMTR in 2020. It was judged to be feasible but was not selected in the final round of voting. We are eager to resubmit our project for consideration since the use of IDH-inhibitors as maintenance therapy post-HCT remains of great interest. As was discussed at the Tandem Meeting last year, clinicians are beginning to use maintenance IDH-inhibitors off-label. It is essential to assess the actual efficacy of this practice by first describing in detail, as we propose in this submission, the very outcomes of mut*IDH1/2* patients (relative to wt*IDH1/2* AML patients) after HCT that maintenance therapy seeks to improve. The window for our observational study may close with increasing off-label use of IDH-inhibitors over time, and ongoing lack of our study may limit the interpretability of current clinical trials of *IDH*-inhibitor maintenance therapy.

Q19 Scientific Justification

To our knowledge, only two peer-reviewed publications have described survival outcomes of *IDH1/2*-mutated (mut*IDH1/2*) AML patients following hematopoietic cell transplant (HCT). The first involved a small cohort of 23 patients.[10] This study was limited by its small sample size, short median follow-up duration of 7.8 months, and the fact that outcomes of *IDH1*- and *IDH2*-mutated patients were not separately described. Recently, Chen *et al.* published a multicenter retrospective study in the Journal of Transplantation and Cellular Therapy that overcame several of these shortcomings.[11] The study involved a cohort of 112 patients with a follow-up duration of 27.5 months. The authors reported a two-year progression free survival (PFS) of 58% for mut*IDH1* patients and 58% for mut*IDH2* patients. The two-year cumulative incidence of relapse was 31% and 25% for mut*IDH1* and mut*IDH2* patients, respectively. The study involved the largest cohort of mut*IDH1/2* patients to date; however, the sample size remained too small to enable meaningful multivariate analysis of prognostic factors such as co-mutations, cytogenetic abnormalities, and conditioning regimen intensity. Further, the study lacked a comparator cohort of wild-type *IDH1/2* AML patients who underwent HCT. The CIBMTR database contains these data at much larger numbers than what can be feasibly collected outside of the registry, and thus it is uniquely best-positioned to address shortcomings of currently published studies and advance our understanding of post-HCT outcomes of mut*IDH1/2* AML patients.

Q20 Participant Selection Criteria

Inclusion criteria:

- Age ≥18 years with diagnosis of AML
- Underwent first allogeneic HCT between 2010 and 2020
- Received molecular testing for *IDH1* or *IDH2* (we are interested in both *IDH1/2*-mutated and non-mutated patients)
- Consented to CIBMTR database with completed research form

Exclusion criteria:

- Received treatment with *IDH* inhibitor as maintenance therapy after HCT

Q21 Does this study include pediatric patients?

No

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

IDH inhibitors are approved only for adult patients with AML, and current clinical trials are investigating the use of *IDH* inhibitors as post-HCT maintenance therapy specifically in the adult population. To provide the appropriate retrospective cohort as a historical benchmark for comparison, we seek to also describe post-HCT outcomes of *IDH*-mutated AML in specifically adult patients. Further, *IDH* mutations are primarily seen in the adult population (up to 20% compared to 4% in pediatric AML patients).[12]

Q22 Data requirements:

Patient Specific (CIBMTR Form 2040)

- Date of birth
- Sex
- Ethnicity

- Race

Pre-HCT AML Specific (CIBMTR Form 2010 and 2402)
- Date of diagnosis
- Whether AML diagnosis is therapy-related or secondary to antecedent hematologic disorder
- Laboratory work-up at diagnosis
  - o Blasts in marrow, cytogenetic results
  - o Molecular testing results (must include testing for *IDH1* and *IDH2*)
- Pre-HCT therapy received
  - o Purpose of therapy (e.g. induction, consolidation, treatment for disease relapse)
  - o Best response to line of therapy (CR, no CR)
  - o Date of therapy response assessment
  - o Date of relapse following therapy, if any
- Laboratory work-up at the time of HCT o blasts in marrow, cytogenetic results
  - o Any and all molecular testing results (must include testing for *IDH1* and *IDH2*) HCT Specific (CIBMTR Form 2005, 2006, and 2400)
- Date of transplant
- Graft source (e.g. bone marrow, PBSC, cord blood)
- Donor-recipient HLA match
- Conditioning regimen (e.g. myeloablative, reduced-intensity/non-myeloablative)
- GVHD prophylaxis

Post-HCT AML Specific (CIBMTR Form 2100 and 2110)
- Date of ANC recovery ≥500
- Date of platelet recovery ≥50
- Best response to HCT and date of this evaluation
- Disease relapse and/or progression post-HCT and associated laboratory work-up (marrow blasts, cytogenetic results, molecular testing)
- Therapy given post-HCT and indication (e.g. as maintenance, or for relapsed/progressive disease disease) o type of therapy (e.g. donor cellular infusion, treatment for relapsed/progressive disease)
  - o Date of starting and ending therapy
  - o Best response to line of therapy (CR, no CR)
  - o Date of therapy response assessment
  - o Date of (additional) relapse following therapy, if any Outcome Measures (CIBMTR Form 2100, 2200, and 2300)
- Incidence of acute and chronic GVHD o Organ involved
  - o Maximum severity if involvement
  - o Treatment received (e.g. steroids, non-steroidal immunosuppressants)
- Primary or secondary graft failure
- Incidence of disease relapse
- Time to disease relapse
- Date of death or last known follow-up

Q23 Patient reported outcomes:

N/A

Q24 Sample requirements:
N/A

Q25 Non-CIBMTR Data Source: N/A

Q26 References:

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Table 1. Characteristics of patients age ≥ 18 receiving first allo-HCT for AML in 2013-2020, CRF track

Characteristic	mutIDH1 N (%)	mutIDH2 N (%)	mutIDH1 & mutIDH2 N (%)	wtIDH1 & wtIDH2 N (%)	IDH1/IDH2 not tested N (%)
No. of patients	150	273	42	1593	3969
No. of centers	62	74	28	131	192
Age at HCT, years					
Median (range)	62 (23-74)	61 (19-77)	58 (21-72)	58 (18-82)	56 (18-88)
18-29	5 (3)	12 (4)	5 (12)	153 (10)	423 (11)
30-39	6 (4)	13 (5)	4 (10)	157 (10)	425 (11)
40-49	16 (11)	31 (11)	4 (10)	227 (14)	602 (15)
50-59	36 (24)	71 (26)	10 (24)	374 (23)	1007 (25)
60-69	66 (44)	103 (38)	17 (40)	526 (33)	1229 (31)
70	21 (14)	43 (16)	2 (5)	156 (10)	283 (7)
Recipient sex					
Male	76 (51)	148 (54)	23 (55)	883 (55)	2162 (54)
Female	74 (49)	125 (46)	19 (45)	710 (45)	1807 (46)
Disease status at time of HCT					
PIF	18 (12)	35 (13)	7 (17)	214 (13)	488 (12)
CR1	97 (65)	198 (73)	28 (67)	1065 (67)	2459 (62)
CR2	26 (17)	30 (11)	7 (17)	210 (13)	720 (18)
≥CR3	2 (1)	2 (1)	0 (0)	7 (<1)	45 (1)
Relapse	7 (5)	8 (3)	0 (0)	96 (6)	255 (6)
Missing	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)
Karnofsky score					
<90	76 (51)	127 (47)	25 (60)	724 (45)	1616 (41)
≥90	73 (49)	142 (52)	17 (40)	841 (53)	2306 (58)
Missing	1 (1)	4 (1)	0 (0)	28 (2)	47 (1)
HCT-CI					
0	24 (16)	49 (18)	2 (5)	246 (15)	818 (21)
1	26 (17)	38 (14)	6 (14)	253 (16)	570 (14)
2	20 (13)	48 (18)	4 (10)	251 (16)	560 (14)
3+	79 (53)	135 (49)	30 (71)	811 (51)	1890 (48)
Missing	1 (1)	3 (1)	0 (0)	32 (2)	131 (3)
MRD at time of HCT					
Negative	47 (31)	90 (33)	12 (29)	696 (44)	1967 (50)
Positive	75 (50)	127 (47)	23 (55)	521 (33)	1005 (25)
Disease status not in CR	25 (17)	43 (16)	7 (17)	309 (19)	742 (19)
Missing	3 (2)	13 (5)	0 (0)	67 (4)	255 (6)
Donor type					
HLA-identical sibling	14 (9)	52 (19)	4 (10)	235 (15)	902 (23)

Characteristic	mutIDH1 N (%)	mutIDH2 N (%)	mutIDH1 & mutIDH2 N (%)	wtIDH1 & wtIDH2 N (%)	IDH1/IDH2 not tested N (%)
Other related	53 (35)	79 (29)	16 (38)	448 (28)	841 (21)
Well-matched unrelated (8/8)	38 (25)	77 (28)	10 (24)	453 (28)	1317 (33)
Partially-matched unrelated (7/8)	6 (4)	11 (4)	2 (5)	76 (5)	252 (6)
Mis-matched unrelated (<= 6/8)	0 (0)	1 (<1)	4 (10)	12 (1)	16 (<1)
Multi-donor	0 (0)	0 (0)	0 (0)	6 (<1)	11 (<1)
Unrelated (matching TBD)	15 (10)	18 (7)	4 (10)	137 (9)	97 (2)
Cord blood	24 (16)	35 (13)	2 (5)	226 (14)	533 (13)
Graft type					
Bone marrow	25 (17)	45 (16)	12 (29)	296 (19)	549 (14)
Peripheral blood	101 (67)	193 (71)	28 (67)	1071 (67)	2887 (73)
Cord blood	24 (16)	35 (13)	2 (5)	226 (14)	533 (13)
Conditioning regimen intensity					
MAC	65 (43)	105 (38)	16 (38)	767 (48)	1876 (47)
RIC	46 (31)	100 (37)	11 (26)	529 (33)	1323 (33)
NMA	35 (23)	62 (23)	10 (24)	240 (15)	591 (15)
TBD	1 (1)	2 (1)	1 (2)	17 (1)	86 (2)
Missing	3 (2)	4 (1)	4 (10)	40 (3)	93 (2)
GVHD prophylaxis					
Ex-vivo T-cell depletion	4 (3)	2 (1)	1 (2)	13 (1)	32 (1)
CD34 selection	6 (4)	8 (3)	1 (2)	95 (6)	104 (3)
Post-CY + other(s)	58 (39)	96 (35)	21 (50)	513 (32)	781 (20)
Post-CY alone	1 (1)	2 (1)	1 (2)	25 (2)	20 (1)
TAC + MMF +- other(s) (except post-CY)	12 (8)	27 (10)	1 (2)	163 (10)	545 (14)
TAC + MTX +- other(s) (except MMF, post-CY)	43 (29)	87 (32)	8 (19)	495 (31)	1345 (34)
TAC + other(s) (except MMF, MTX, post-CY)	2 (1)	11 (4)	3 (7)	62 (4)	177 (4)
TAC alone	3 (2)	3 (1)	1 (2)	44 (3)	67 (2)
CSA + MMF +- other(s) (except post-CY)	12 (8)	19 (7)	1 (2)	90 (6)	384 (10)
CSA + MTX +- other(s) (except MMF, post-CY)	3 (2)	6 (2)	0 (0)	35 (2)	325 (8)
CSA + other(s) (except MMF, MTX, post-CY)	0 (0)	0 (0)	0 (0)	2 (<1)	13 (<1)
CSA alone	0 (0)	0 (0)	0 (0)	2 (<1)	28 (1)
Other(s)	1 (1)	6 (2)	0 (0)	10 (1)	43 (1)
Missing	5 (3)	6 (2)	4 (10)	44 (3)	105 (3)
Year of HCT					

Characteristic	mutIDH1 N (%)	mutIDH2 N (%)	mutIDH1 & mutIDH2 N (%)	wtIDH1 & wtIDH2 N (%)	IDH1/IDH2 not tested N (%)
2013	2 (1)	5 (2)	1 (2)	49 (3)	797 (20)
2014	12 (8)	10 (4)	3 (7)	133 (8)	907 (23)
2015	10 (7)	22 (8)	2 (5)	165 (10)	790 (20)
2016	21 (14)	46 (17)	7 (17)	231 (15)	624 (16)
2017	16 (11)	52 (19)	10 (24)	259 (16)	379 (10)
2018	34 (23)	51 (19)	11 (26)	302 (19)	255 (6)
2019	37 (25)	58 (21)	3 (7)	295 (19)	173 (4)
2020	18 (12)	29 (11)	5 (12)	159 (10)	44 (1)
Median follow-up of survivors (range), months	24 (3-73)	25 (3-73)	34 (11-73)	27 (0-84)	57 (0-99)

COMBINED CIBMTR STUDY TITLE

Outcomes of allogeneic hematopoietic cell transplantation following low intensity versus high intensity therapy for AML and MDS in first complete morphologic remission

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KEY WORDS

Allogeneic hematopoietic cell transplantation; acute myeloid leukemia; myelodysplastic syndrome; hypomethylating agents; venetoclax; targeted agents

PROPOSED WORKING COMMITTEE

Acute leukemia

RESEARCH QUESTION

Does the intensity of remission induction therapy significantly affect outcomes following allogeneic hematopoietic cell transplantation (HCT) in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)?

RESEARCH HYPOTHESIS

We hypothesize that post-HCT clinical outcomes of AML and MDS patients achieving complete remission with low intensity therapy incorporating hypomethylating agents and novel targeted agents (venetoclax, gilteritinib, midostaurin, sorafenib, ivosidenib and enasidenib) will be comparable to high intensity therapies with an additional benefit of low non-relapse mortality (NRM).

SPECIFIC OBJECTIVES/OUTCOMES

The purpose of the proposed study will be to evaluate and compare the following post-transplant outcomes of AML and MDS patients who achieved first morphologic complete remission with low intensity vs. high intensity remission induction therapies

Primary objective:
- Overall survival (OS)

Secondary objectives:
- Relapse incidence
- Relapse free survival (RFS)
- Non-relapse mortality (NRM)
- Incidence of acute and chronic graft versus host disease (GVHD)
- Subgroup analysis stratifying patients according to:
1) Age < 60 years and ≥ 60 years
2) Venetoclax-based low intensity induction regimens vs. intensive regimens
3) European Leukemia Net (ELN) risk classification
4) Measurable residual disease (MRD)

SCIENTIFIC IMPACT

The advent of novel targeted agents (venetoclax, gilteritinib, midostaurin, sorafenib, ivosidenib and enasidenib) in combination with hypomethylating agents has been a paradigm shift in treating older or medically infirm patients with AML and/ or high risk MDS. A significant proportion of patients who achieve complete remission with these agents proceed to allogeneic HCT consolidation. There is currently lack of high quality data of survival and post-transplant outcomes of patients who receive low intensity regimens in comparison to intensive therapy. The results of this proposed CIBMTR study will answer this clinically relevant and important question. Additionally, it would aid in clinical decision making for initial choice of remission induction therapy for these patients.

SCIENTIFIC JUSTIFICATION

Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) continue to remain highly aggressive malignancies primarily affecting the elderly, who are generally ineligible for intensive cytotoxic chemotherapy, have high risk chromosomal abnormalities or molecular mutations, and higher incidence of secondary AML. Historically, hypomethylating agents (HMA) or low dose chemotherapy (e.g. cytarabine) were the mainstay of treatment. Recent advances in understanding of the molecular biology of AML and MDS has led to development of several targeted agents against putative molecular mutations implicated in the pathogenesis of these malignancies. Given the efficacy, the US Food and Drug Administration (FDA) has approved multiple new oral targeted therapies for treatment of AML in recent years. Moreover, the use of these targeted agents is being expanded to patients of all ages and fitness level as individualized care plans e.g. Leukemia & Lymphoma Society Beat AML Master trial [1].

Venetoclax is first in its class, oral selective BCL-2 inhibitor which has demonstrated significant activity against AML cells including leukemia stem cells [2]. The combination of venetoclax and HMA or low-dose cytarabine for initial treatment of AML has been a paradigm shift for older individuals and those with comorbidities [3]. The pivotal VIALE-A phase III clinical trial randomized AML patients who were ineligible for intensive therapy to azacitidine with venetoclax or placebo showing a 5-month prolongation of median overall survival (OS) favoring azacitidine-venetoclax arm [4]. These clinical trials were the basis of FDA approval of venetoclax in combination with HMAs or low dose cytarabine for newly diagnosed unfit or older AML patients for frontline therapy. Of particular interest, venetoclax-based therapies have been highly efficacious in adverse risk AML with the ability to induce complete remission (CR) rates of more than 60% including in patients harboring high risk somatic mutation. Even more encouraging are CR rates in molecular subtypes of AML with venetoclax-based regimens. DiNardo and colleagues showed CR rate of 75% in IDH1/ 2, 67% in NPM1, 55% in TP53, and 72% FLT3 mutated patients [4]. Wei and colleagues showed CR rates of 72% in IDH1/ 2, 89% in NPM1, 30% in TP53, and 44% FLT3 mutated patients [3]. Additionally, up to 23% and 6% of patients achieved measurable residual disease (MRD) negative complete remissions, respectively [3, 4]. MRD negativity has been shown by others to correlate to better outcomes post reduced intensity conditioning allograft transplant and of particular interest in an elderly population less likely to receive ablative conditioning [5].

Gilteritinib, ivosidenib and enasidenib have shown efficacy in the relapsed and refractory AML setting. They are now being evaluated in the upfront treatment of AML either alone or in combination with HMA. In an ongoing randomized phase 3 trial of frontline gilteritinib in combination with azacitidine, a superior CR rate of 58% in comparison to azacitidine alone (26.5%) was reported in 123 patients with FLT3 mutation enrolled thus far [6]. In the phase 3 ADMIRAL trial comparing gilteritinib to salvage chemotherapy in relapsed or refractory FLT3 mutated AML, 26% of patients receiving gilteritinib achieved disease response prior to on-study allogeneic hematopoietic cell transplantation (HCT) compared to 15% in the salvage chemotherapy arm. HCT was not associated with an apparent overall survival benefit [7]. In IDH1 mutated AML, DiNardo et al, reported a CR rate of 61% with upfront ivosidenib-azacitidine combination with a 1-year OS of 82%. Only 1 out of 23 patients in this study received HCT [8]. When used as monotherapy, ivosidenib induced a CR rate of 42% in a phase I trial with a median OS of 12.6 months. Of the 34 patients enrolled in this study, 9% proceeded to receive HCT [9]. In a phase 1-2 study of enasidenib-azacitidine combination in IDH2 mutated treatment naïve AML, 54% achieved CR. Again, 3 out of the 68 patients enrolled in the enasidenib-azacitidine arm received allogeneic HCT [10]. In relapsed or refractory setting, less than 10% of IDH1/2 mutated AML patients were able to proceed to transplant [11, 12].

Despite the ability to induce deeper and durable remissions with these novel agents, a significant proportion of patients with AML eventually relapse. Reduced intensity or non-myeloablative allogeneic HCT remains the only potentially curative option for such patients. While many a time, it is assumed that patients ineligible for intensive induction therapy are also ineligible for allogeneic HCT, there are patients who not only respond to less intense induction therapy, but also improve functional status and are eligible for allogeneic HCT, suggesting that less intense regimens prior to HCT may provide a path to curative therapy. It has been shown in retrospective studies that in older adults with AML, a consolidative allogeneic HCT in first complete remission was associated with decreased relapse rate and superior overall survival when compared to additional chemotherapy despite an initial increased risk of non-

relapse mortality (NRM) [13]. Indeed, NCCN guidelines now recommend consolidation with allograft transplant during the first complete remission regardless of induction chemotherapy.

There is limited data on outcomes after allogeneic HCT following low intensity induction therapies that incorporate targeted agents and HMA. One retrospective study reported outcomes on 32 AML patients who underwent allogeneic HCT following venetoclax-HMA combination. Majority were patients with relapsed or refractory disease. The 1-year OS and relapse free survival (RFS) were reported to be 62% and 49%, respectively. This is considering that approximately 60% of patients had adverse risk AML. Of note, NRM was reported to be 19% [14]. Similarly, another recent study reported a comparison of non-core binding AML patients who received allogeneic HCT (n=21) versus those who did not (n=37) following venetoclax-azacitidine combination. The OS was significantly prolonged among the transplanted patients in comparison to those without (p=0.001) [15]. To our knowledge, there are no published studies reporting post-transplant outcomes of patients who received gilteritinib, ivosidenib or enasidenib as remission induction regimens.

The proposed work seeks to utilize the CIBMTR resources to compare transplant related outcomes for AML and MDS patients in first complete morphological remission after low intensity therapy incorporating HMA and novel oral targeted agents, and a control group induced with intensive standard induction chemotherapy. Outcomes based on MRD status or molecularly defined AML subtypes such as TP53 and FLT3, can only be studied using the robust size of the CIBMTR database. We also propose inclusion of myelodysplastic syndromes with excess blasts one and two (MDS-EB1/ EB2) as these are often treated with AML induction and subsequent allograft consolidation due to their high risk of leukemic transformation. Furthermore, the optimal number of cycles of venetoclax-based therapies and the timing of allogeneic HCT is not clear. One specific concern with repeated cycles is protracted myelosuppression and risk of infections which may lead to delays in allogeneic HCT or potentially render patients ineligible for subsequent transplant. To the contrary, low intensity therapies have a favorable organ toxicity profile which may translate into less non-relapse mortality. If results favor less intensive induction therapy prior to allogeneic HCT, this could spur future randomized studies comparing intensive vs low intensity AML induction in older adults who are eligible to receive allogeneic HCT. Secondly, this could increase transplant referrals for AML and MDS in older or medically unfit adults. Finally, post-transplant outcomes of patients induced with less intense regimens may be of broader interest with pending studies delineating the role of targeted and low intensity induction in younger adults.

PARTICIPANT SELECTION CRITERIA

Inclusion:

1) Age 18 years or older
2) Patients with a diagnosis of AML and MDS-EB1/ EB2 in first complete morphologic remission (defined as CR, CR with incomplete hematological recover [CRi] and morphologic leukemia free state [<5% blasts]) who received allogeneic HCT between 2015 and 2021
3) Received either low intensity or high intensity remission induction therapy prior to allogeneic HCT, defined as:

Low intensity:

- Hypomethylating agents alone (azacitidine, decitabine, guadecitabine and decitabine-cedazuridine)
- Venetoclax plus hypomethylating agents or cytarabine
- Targeted agents (gilteritinib, midostaurin, sorafenib, ivosidenib and enasidenib) alone or in combination with hypomethylating agents

High intensity:
- Traditional standard cytotoxic chemotherapy regimens including cytarabine + daunorubicin/ idarubicin (7+3), FLAG-Ida, MEC, GLAM, liposomal daunorubicin/ cytarabine, 7+3 + midostaurin, etc.

4) First allogeneic HCT

Exclusion:
1) Age < 18 years
2) Primary refractory disease
3) Second or later complete remission
4) Prior allogeneic HCT

DATA REQUIREMENTS

For conduction of this study, the following CIBMTR data will be collected and analyzed.

Patient specific data:
Age
Gender (male/ female)
Race
Karnofsky performance status (≥ 90%, < 90%)
CMV status (positive/ negative)
HCT-comorbidity index (HCT-CI)

Disease specific data:
Disease indication for HCT (AML/ high risk MDS)
AML type (de novo, secondary, therapy related)
ELN classification (favorable/ intermediate/ adverse)
Molecular mutation
Bone marrow blast percentage for MDS
Disease status prior to HCT (CR/ CRi/ morphologic leukemia free state [< 5% blasts])
MRD status prior to transplant (MRD+/ MRD-)
Time from diagnosis to HCT

Donor specific data:
Age
Gender (male/ female)
HLA match (fully matched/ 1-alelle mismatched/ haploidentical/ umbilical cord blood)
ABO compatibility (compatible/ major mismatch/ minor mismatch)

CMV status (positive/ negative)

Transplant related data:
Conditioning regimen
Conditioning intensity (myeloablative/ reduced intensity/ non-myeloablative)
Donor type (MSD/ MUD/ haploidentical/ umbilical cord blood)
Graft source (peripheral blood/ bone marrow/ umbilical cord blood)
GVHD prophylaxis
Acute GVHD (yes/ no)
Acute GVHD grade
Chronic GVHD (yes/ no)
Chronic GVHD grade

Outcomes after transplant:
Follow up duration
Relapse (yes/ no)
Time to relapse/ relapse free survival
Death (yes/ no)
Cause of death (relapse, GVHD, treatment related)
Time to death/ overall survival

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Table 1. Characteristics of patients age ≥ 18 receiving first allo-HCT for AML in CR1 from 2015-2020, CRF track

Characteristic	High intensity N (%)	Low intensity N (%)
No. of patients	2352	240
No. of centers	168	68
Age at HCT, years		
Median (range)	57 (18-81)	67 (19-82)
18-29	241 (10)	8 (3)
30-39	209 (9)	13 (5)
40-49	332 (14)	11 (5)
50-59	602 (26)	29 (12)
60-69	790 (34)	103 (43)
≥ 70	178 (8)	76 (32)
Recipient sex		
Male	1263 (54)	153 (64)
Female	1089 (46)	87 (36)
Karnofsky score		
<90	930 (40)	102 (43)
≥ 90	1389 (59)	135 (56)
Missing	33 (1)	3 (1)
HCT-CI		
0	485 (21)	37 (15)
1	366 (16)	39 (16)
2	377 (16)	34 (14)
3+	1084 (46)	123 (51)
Missing	40 (2)	7 (3)
MRD at time of HCT		
Negative	1312 (56)	131 (55)
Positive	888 (38)	93 (39)
Missing	152 (6)	16 (7)
Donor type		
HLA-identical sibling	494 (21)	30 (13)
Other related	626 (27)	87 (36)
Well-matched unrelated (8/8)	661 (28)	56 (23)
Partially-matched unrelated (7/8)	108 (5)	5 (2)
Mis-matched unrelated (<= 6/8)	16 (1)	1 (<1)
Multi-donor	9 (<1)	0 (0)

Characteristic	High intensity N (%)	Low intensity N (%)
Unrelated (matching TBD)	140 (6)	35 (15)
Cord blood	298 (13)	26 (11)
Graft type		
Bone marrow	443 (19)	27 (11)
Peripheral blood	1611 (68)	187 (78)
Cord blood	298 (13)	26 (11)
Conditioning regimen intensity		
MAC	1089 (46)	54 (23)
RIC	802 (34)	111 (46)
NMA	410 (17)	67 (28)
TBD	38 (2)	5 (2)
Missing	13 (1)	3 (1)
GVHD prophylaxis		
Ex-vivo T-cell depletion	14 (1)	2 (1)
CD34 selection	93 (4)	7 (3)
Post-CY + other(s)	710 (30)	97 (40)
Post-CY alone	34 (1)	0 (0)
TAC + MMF +- other(s) (except post-CY)	248 (11)	28 (12)
TAC + MTX +- other(s) (except MMF, post-CY)	718 (31)	52 (22)
TAC + other(s) (except MMF, MTX, post-CY)	95 (4)	15 (6)
TAC alone	42 (2)	3 (1)
CSA + MMF +- other(s) (except post-CY)	166 (7)	19 (8)
CSA + MTX +- other(s) (except MMF, post-CY)	154 (7)	5 (2)
CSA + other(s) (except MMF, MTX, post-CY)	7 (<1)	1 (<1)
CSA alone	9 (<1)	0 (0)
Other(s)	20 (1)	1 (<1)
Missing	42 (2)	10 (4)
Year of HCT		
2015	568 (24)	31 (13)
2016	531 (23)	35 (15)
2017	429 (18)	25 (10)
2018	364 (15)	44 (18)
2019	321 (14)	57 (24)
2020	139 (6)	48 (20)
Median follow-up of survivors (range), months	36 (0-74)	24 (3-64)

Table 2. Characteristics of patients age ≥ 18 receiving first allo-HCT for MDS-EB in CR from 2015-2020, CRF track

Characteristic	High intensity N (%)	Low intensity N (%)
No. of patients	55	191
No. of centers	33	71
Age at HCT, years		
Median (range)	65 (18-81)	66 (20-77)
18-29	2 (4)	2 (1)
30-39	5 (9)	3 (2)
40-49	3 (5)	6 (3)
50-59	12 (22)	23 (12)
60-69	22 (40)	104 (54)
≥ 70	11 (20)	53 (28)
Recipient sex		
Male	36 (65)	121 (63)
Female	19 (35)	70 (37)
Karnofsky score		
<90	20 (36)	71 (37)
≥ 90	34 (62)	118 (62)
Missing	1 (2)	2 (1)
HCT-CI		
0	12 (22)	31 (16)
1	12 (22)	20 (10)
2	8 (15)	31 (16)
3+	22 (40)	102 (53)
Missing	1 (2)	7 (4)
Donor type		
HLA-identical sibling	8 (15)	32 (17)
Other related	10 (18)	30 (16)
Well-matched unrelated (8/8)	26 (47)	91 (48)
Partially-matched unrelated (7/8)	5 (9)	12 (6)
Multi-donor	0 (0)	2 (1)
Unrelated (matching TBD)	2 (4)	12 (6)
Cord blood	4 (7)	12 (6)
Graft type		
Bone marrow	6 (11)	23 (12)
Peripheral blood	45 (82)	156 (82)

Characteristic	High intensity N (%)	Low intensity N (%)
Cord blood	4 (7)	12 (6)
Conditioning regimen intensity		
MAC	21 (38)	47 (25)
RIC	19 (35)	104 (54)
NMA	12 (22)	35 (18)
TBD	2 (4)	1 (1)
Missing	1 (2)	4 (2)
GVHD prophylaxis		
CD34 selection	0 (0)	3 (2)
Post-CY + other(s)	14 (25)	46 (24)
TAC + MMF +- other(s) (except post-CY)	5 (9)	29 (15)
TAC + MTX +- other(s) (except MMF, post-CY)	14 (25)	82 (43)
TAC + other(s) (except MMF, MTX, post-CY)	3 (5)	11 (6)
TAC alone	2 (4)	2 (1)
CSA + MMF +- other(s) (except post-CY)	12 (22)	15 (8)
CSA + MTX +- other(s) (except MMF, post-CY)	2 (4)	0 (0)
Other(s)	2 (4)	0 (0)
Missing	1 (2)	3 (2)
Year of HCT		
2015	13 (24)	35 (18)
2016	8 (15)	33 (17)
2017	14 (25)	41 (21)
2018	10 (18)	42 (22)
2019	9 (16)	29 (15)
2020	1 (2)	11 (6)
Median follow-up of survivors (range), months	36 (4-73)	27 (6-63)

Study Title:

Development of pre-transplant risk scores for patients undergoing allogeneic HCT for acute leukemia transplanted in complete remission or with relapsed/refractory disease.

Key Words:

Acute myeloid leukemia, allogeneic stem cell transplant, risk stratification, complete remission, refractory disease

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Research Question:

A variety of pre-transplant comorbidity and risk scores have been developed and validated for allogeneic hematopoietic cell transplant (HCT). With improved HCT outcomes over recent years, many of these prognostication tools may be outdated. Moreover, these tools have not been assessed for specific transplant indications. We propose evaluating the impact of prognostic factors derived from CIBMTR data, including novel data, for the development of an acute leukemia (AL)-specific risk score and to compare the prognostic stratification power of the score with previously published pre-allogeneic HCT risk scores. We propose to explore these factors separately on both AL patients transplanted in complete remission and those transplanted with relapsed/refractory disease.

Research Hypothesis:

Changes in standard of care, updated molecular and cytogenetic information, and novel pre- and post-transplant therapeutic interventions have impacted allogeneic HCT outcomes for patients transplanted with AL. The Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) and other risk scores prognostic for allogeneic HCT are not disease-specific for acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) in particular, and do not reflect these changes in therapy and outcomes. Similarly, the previously published Duval score which was specific for relapsed/refractory AL patients likely does not reflect changes in practice and patient risk stratification.

In the proposed study, we will use two separate sets of data for the development of prognostic risk tools for AL patients undergoing HCT:

1. Patients with AL transplanted in complete remission (CR1, CR2 and beyond)
2. Patients transplanted for relapsed/refractory leukemia

The two separate scoring systems would allow clinicians to make informed decisions on conditioning regimens, type of transplant and post-transplant therapies in these patient populations with distinct disease kinetics and prognosis.

Specific Aims/Outcomes to be investigated:

1. Determine Overall Survival, Leukemia Free Survival, Cumulative Incidence of Relapse and Non-relapse Mortality of all AL patients whether transplanted in CR or relapsed/refractory disease
2. Assess available pre-transplant variables for their significant influence on post-transplant outcomes of both groups of AL patients
3. Using the data described above, development of a specific risk score for:
   a) AML and ALL patients transplanted in CR,
   b) AML and ALL patients transplanted with relapsed/refractory disease,
   c) comparison of the predictive power of the developed risk score with other previously published scoring systems.

Scientific Impact:

The development of AL-specific risk scores based on updated CIBMTR data would assist in improved outcome prediction; crucial for treatment modification as well as patient informed consent. Risk stratification of patients with AL either in remission or relapsed/refractory disease would determine which patients would most likely benefit from allogeneic HCT and would help us identify patients who are better suited for novel therapies, targeted agents and maintenance therapy. As the landscape of treatment and risk stratification of patients with acute leukemia has changed significantly over the years, we anticipate that previously identified risk stratification tools for allogeneic HCT are outdated, and a more refined tool is warranted.

Scientific Justification:

The most common indication for allogeneic HCT is AML [Baldomero et al, 2011], with curative potential for high-risk patients [Appelbaum et al, 1997]. Moreover, selected patients with ALL also benefit from allogeneic HCT [DeFilipp et al, 2019]. However, allogeneic HCT is associated with significant morbidity and mortality, with a variety of pre-transplant risk scores developed in order to stratify patients into prognostic risk groups. Comorbidity evaluation is considered an integral component of pre-transplant workup and determine non-relapse mortality (NRM) and overall survival (OS) [Hamadani et al, 2010

Other pre-transplant risk scores in use are the Pretransplant Assessment of Mortality (PAM) Score, which estimates the probability of 2-year survival post-HCT with myeloablative conditioning for hematologic malignancies. Sorror et al recently developed and validated a composite predictive model for AML patients undergoing allogeneic HCT that included the HCT-CI, age and cytogenetic/molecular risks [Sorror et al, 2017]. In contrast, the Disease Risk Index (DRI) developed by Armand and colleagues [Armand et al, 2012] stratified patients entirely on the basis of disease type and stage into prognostic risk groups. At the Princess Margaret Cancer Centre (Toronto, Canada), we recently demonstrated in 387 AML patients that the HCT-CI, remission status and patient age can be combined in a score predictive for OS and NRM [Michelis et al, 2015].

Relapsed/refractory acute leukemia in particular (marrow blasts ≥5%) poses a significant challenge in allogeneic HCT. Outcomes can be variable, with some patients achieving long-term remission and

survival. The Duval score was initially developed in 2010 using CIBMTR data to estimate 3-year overall survival in patients with relapsed or refractory acute leukemia [Duval et al, 2010]. The score identified high-risk factors specific for AML (CR1 < 6 months, circulating blasts, non-matched sibling donor, KPS <90 and poor-risk cytogenetics) and for ALL (first refractory or second or more relapse, ≥25% marrow blasts, CMV +ve donor and age 10 years or more). The score, however, does not take into account molecular data, the HCT-CI, conditioning intensity or use of novel agents/therapies such as donor lymphocyte infusion, hypomethylating agents and tyrosine kinase inhibitors etc. Other studies have identified the number of cycles of chemotherapy, percentage of peripheral or bone marrow blood blasts, adverse cytogenetics and patient age as significant factors in these patients [Todisco et al, 2017]. CMV seropositivity has also been shown to be a predictor of improved overall survival for primary refractory AML patients undergoing unrelated donor transplant [Craddock et al, 2011]. With significant improvements in standard of care and updated therapies available to relapsed/refractory patients, we hypothesize the Duval score is now outdated for this patient population.

There are a number of pre-allogeneic transplant risk scores that have been developed specifically for AML and ALL but are based on single center data with limited numbers of patients, some of which have not been validated. On the other hand, the large multi-center studies that have developed validated pre-transplant scoring systems are not disease-specific, which may explain in part the major discrepancies in studies that apply these scores to AML and ALL specifically. The purpose of the proposed study is to develop and validate a pre-allogeneic HCT prognostic scoring system that is specific for AL patients using data from the large CIBMTR registry: one for patients in CR and one for patients with relapsed/refractory disease. Depending on data available, separate score systems could be developed for AML vs. ALL patients, as risk factors (e.g. molecular risk factors) might be different for the two diseases. The secondary objective of the study would be to compare the prognostic power of the developed score with other established pre-transplant risk scores.

Patient Eligibility Population:

Using the CIBMTR database, patients with AML and ALL who underwent HCT between 2009 and 2019 and meet the following criteria will be identified.

Eligible patients:

Inclusion criteria (should meet all the criteria):

1. Age 18 years and older at the time of HCT
2. First allogeneic transplant
3. Diagnosis of AML or ALL, either de novo or secondary
4. Patients undergoing HCT at any stage of disease
5. Transplant from an HLA matched related donor or unrelated donor (9/10 or 10/10)

Exclusion criteria:

1. Syngeneic transplants
2. Ex vivo T cell depletion
3. Cord-blood transplants
4. Haplo-identical transplants
5. Acute promyelocytic leukemia (for AML)
6. Previous allogeneic transplant

Variables to be analyzed:

Patient-related:

- Age at HCT
- Gender
- Karnofsky Performance scores: <90 vs ≥90
- Hematopoietic cell transplant-comorbidity index (HCT-CI)[Sorror et al, 2005](depending on availability of data), as well as individual scores of the components of the HCT-CI
- FEV1 pre-transplant

Disease-related:

- Type of AL: de-novo vs. therapy-related vs. secondary
- Previous autologous transplant (yes/no)
- Cytogenetics at diagnosis vs time of HCT
- Molecular data at diagnosis vs time of HCT (NPM1, FLT3-ITD, CEBPA, MLLT3-MLL, etc.)
- Cytogenetic/molecular risk stratification (according to the European Leukemia Network criteria)
- Time from diagnosis of AL to transplant
- Disease stage: CR1 vs. >CR1 vs. no CR
- Disease Risk Index (DRI) [Armand et al, 2012]

Transplant related:

- Conditioning regimen: MAC vs. RIC vs. NMA as defined by CIBMTR
- TBI in conditioning regimen: no TBI vs. TBI with dose in cGY included
- Donor age
- Donor type: MSD vs. MMSD vs. 9/10 MUD vs 10/10 MUD
- Donor-recipient gender: F-M vs. other
- CMV status of donor and recipient: +/+ vs. +/- vs. -/+ vs. -/-
- Source of hematopoietic cells: BM vs. PBSC
- Median CD34 cell dose, x 10^6/kg
- Date of transplant
- GVHD prophylaxis: Calcineurin inhibitor (CNI) + MTX vs. CNI + MMF vs. others
- Received serotherapy with either Campath or ATG: yes/no

Other pre-transplant scores that may be calculated with existing data:

- PAM score [Parmion et al, 2006]
- HCT-CI/age index [Sorror et al, 2014]
- Modified EBMT score [Hemmati et al, 2011]

Outcomes of interest:

1. Overall Survival
2. Leukemia-free Survival
3. Cumulative incidence of Relapse
4. Cumulative incidence of NRM
5. Incidence and grade of acute GVHD
6. Incidence and grade of chronic GVHD

Statistical analysis

This is a retrospective study of CIBMTR data between 2009 and 2019. The purpose of the proposed study is to develop and validate AL-specific pre-allogeneic HCT prognostic scores for both CR and relapsed/refractory patients separately, derived from a large multi-center database such as that from the CIBMTR. Initially, the identified patient population would be randomized in such a way as to develop a training cohort and a validation cohort. Within the training cohort, OS for each individual variable will be evaluated using Kaplan-Meier survival curve and log-rank test for the univariate analysis. For the continuous variable age at transplant and for the ordinal variable HCT-CI score, binary recursive partitioning will be performed and the optimal cut-off value will be established for the effect on OS. Multivariable analysis will be performed for OS using the Cox proportional hazard regression model. Variables with a p-value ≤0.15 on univariate analysis for OS will be included in the multivariable model, and stepwise selection algorithm will be applied for variable selection using as criteria p≥0.05 for variable removal. Hazard ratios (HRs) and 95% confidence intervals (CIs) will be estimated for the significant risk factors and a weighted score will then be developed, based on the HRs which will be converted into integer weights, for the purpose of assigning patients to risk groups. The potential influence of the time period effect on the developed scoring systems may also be assessed as well, considering year of transplant as an ordinal variable. The developed scoring systems will then be applied in univariate analysis for the outcomes of CIR and NRM as well, considering competing events with Fine and Gray test. For CIR, death will be accounted as competing risk, while for NRM, relapse will be accounted as competing risk. Outcomes will then be calculated at various time points post-transplant in percentages.

Following the development of the weighted scores, the models will then be tested on the independent validation cohorts and compared. Finally, the developed scoring systems will be compared to other pre-transplant risk scores (HCT-CI, PAM, etc.) by computing the C statistic for each model, with a value of 1.0 indicating perfect predictive discrimination and a value of 0.5 indicating no ability to discriminate. P-values will be tested as two-sided and p-value <0.05 will be considered statistically significant. The further plan will be developed depending on the sample size after discussion with the statistical team at CIBMTR. The authors of this proposal suggest that at least two original research manuscripts may be derived from the separate analysis of CR and relapsed/refractory AL patients.

References:

Appelbaum FR. Allogeneic hematopoietic stem cell transplantation for acute leukemia. Semin Oncol. 1997;24:114-123.

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Todisco E, Ciceri F, Boschini C, et al. Factors predicting outcome after allogeneic transplant in refractory acute myeloid leukemia: a retrospective analysis of Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Bone Marrow Transplant. 2017 Jul;52(7):955-961.

Table 1. Characteristics of patients age ≥ 18 receiving first allo-HCT for AML or ALL in 2009-2019, CRF track

Characteristic	CR N(%)	R/R N (%)
No. of patients	4606	1008
No. of centers	194	124
Age at HCT, years		
Median (range)	52 (18-80)	54 (18-82)
18-29	648 (14)	102 (10)
30-39	578 (13)	106 (11)
40-49	864 (19)	180 (18)
50-59	1211 (26)	280 (28)
60-69	1081 (23)	283 (28)
≥70	224 (5)	57 (6)
Recipient sex		
Male	2506 (54)	568 (56)
Female	2100 (46)	440 (44)
Disease status at time of HCT		
PIF	0 (0)	651 (65)
CR1	3613 (78)	0 (0)
CR2	930 (20)	0 (0)
≥CR3	63 (1)	0 (0)
Relapse	0 (0)	357 (35)
Karnofsky score		
<90	1732 (38)	529 (52)
≥90	2827 (61)	463 (46)
Missing	47 (1)	16 (2)
HCT-CI		
0	1039 (23)	161 (16)
1	699 (15)	141 (14)
2	720 (16)	139 (14)
3+	1969 (43)	522 (52)
Missing	179 (4)	45 (4)
MRD at time of HCT		
Negative	2917 (63)	0 (0)
Positive	1346 (29)	0 (0)
Disease status not in CR	0 (0)	999 (99)
Missing	343 (7)	9 (1)
Donor type		
HLA-identical sibling	2027 (44)	371 (37)
Well-matched unrelated (8/8)	2579 (56)	637 (63)

Characteristic	CR N(%)	R/R N (%)
Graft type		
Bone marrow	681 (15)	138 (14)
Peripheral blood	3925 (85)	870 (86)
Conditioning regimen intensity		
MAC	2876 (62)	666 (66)
RIC	1402 (30)	273 (27)
NMA	201 (4)	35 (3)
TBD	57 (1)	20 (2)
Missing	70 (2)	14 (1)
GVHD prophylaxis		
Post-CY + other(s)	186 (4)	39 (4)
Post-CY alone	54 (1)	4 (<1)
TAC + MMF +- other(s) (except post-CY)	558 (12)	171 (17)
TAC + MTX +- other(s) (except MMF, post-CY)	2555 (55)	567 (56)
TAC + other(s) (except MMF, MTX, post-CY)	312 (7)	67 (7)
TAC alone	94 (2)	29 (3)
CSA + MMF +- other(s) (except post-CY)	211 (5)	46 (5)
CSA + MTX +- other(s) (except MMF, post-CY)	462 (10)	57 (6)
CSA + other(s) (except MMF, MTX, post-CY)	20 (<1)	1 (<1)
CSA alone	36 (1)	4 (<1)
Other(s)	33 (1)	9 (1)
Missing	85 (2)	14 (1)
Year of HCT		
2009	570 (12)	178 (18)
2010	442 (10)	128 (13)
2011	242 (5)	45 (4)
2012	205 (4)	38 (4)
2013	463 (10)	119 (12)
2014	706 (15)	153 (15)
2015	611 (13)	100 (10)
2016	495 (11)	118 (12)
2017	343 (7)	55 (5)
2018	327 (7)	45 (4)
2019	202 (4)	29 (3)
Median follow-up of survivors (range), months	61 (2-147)	70 (3-137)

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

Impact of Pretransplant Mutation Topography on Cumulative Incidence of Relapse after Allogeneic Haematopoietic Cell Transplants for T-Cell Acute Lymphoblastic Leukemia

Q2. Key Words

Mutation Topography; Cumulative Incidence of Relapse; Allogeneic Haematopoietic Cell Transplant; T-Cell Acute Lymphoblastic Leukemia

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Yang Liang, MD; PhD
Email address:	liangyang@sysucc.org.cn
Institution name:	Sun Yat-sen University Cancer Center
Academic rank:	Principle Investigator

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 Peter Gale, MD; PhD
Email address:	robertpetergale@alumni.ucla.edu
Institution name:	Imperial College London
Academic rank:	Visiting 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:

Yang Liang

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

- Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project

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:

- Acute Leukemia

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

- No

Q15. RESEARCH QUESTION:

Does Pretransplant Mutation Topography have Impact on Cumulative Incidence of Relapse after Allogeneic Haematopoietic Cell Transplants for T-Cell Acute Lymphoblastic Leukemia?

Q16. RESEARCH HYPOTHESIS:

Therapy of T-cell acute lymphoblastic leukemia (T-cell ALL) is often ineffective(1-3). Acquired somatic mutations drive the biology of T-cell ALL(4,5). We hypothesize pretransplant mutation topography will correlate with cumulative incidence of relapse (CIR) after allotransplants.

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

Suggested word limit of 200 words:

We will do targeted mutational genetic analysis on pretransplant blood samples from recipients with T-cell ALL enrolled in the Center for International Blood and Marrow Transplant Research Repository 2000 and 2020 and interrogate correlations with CIR after adjusting for other prognostic and predictive co-variates as primary objective. Secondary objectives including overall survival, death without relapse.

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.

If associations between mutation topography and CIR are detected these data will inform decision making regarding benefits and risk of allotransplants in persons with -cell -ALL.

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.

Sub-groups of T-cell ALL include ETP-ALL, cortical T-ALL and medullary T-ALL. These sub-groups have different immune phenotype reflecting different thymocyte developmental stages and are associated with different clinical outcomes (5). Each sub-group has a unique mutation topography. For example, early immature ETP sub-group has a lower prevalence of NOTCH1 and CDKN2A mutations compared with cortical T-ALL and medullary T-ALL but more frequent mutations in signaling factors (NRAS. FLT3), epigenetic regulators (IDH1, IDH2, DNMT3), and transcription factors regulating haematopoietic and T-cell development (RUNX1, GATA3 and ETV6) (6,7). ETP T-ALL accounts for about 10 percent of T-cell ALL in children and 40–50% in adult T-ALLs (8). ETP is considered high-risk T-cell ALL (9). Cortical T-cell ALL is associated with mutations of TLX1, TLX3, NKX2-1 and NKX2-2 homeobox genes, a high frequency of NOTCH1 and CDKN2A mutations and has a favourable prognosis (10). Medullary T-cell ALL is associated with mutations of TAL1 (11). We propose constructing a predictive model for allotransplants in T-cell ALL.

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.

Recipients with T-cell ALL receiving an allotransplant enrolled in the Center for International Blood and Marrow Transplant Research Repository 2000 and 2020.

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.**

No addition data collection is required.

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:

1. Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):580-588.
2. Litzow MR, Ferrando AA. How I treat T-cell acute lymphoblastic leukemia in adults. Blood. 2015;126(7):833-841.
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11. Ferrando AA, Neuberg DS, Staunton J, et al. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell. 2002;1(1):75-87.

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 allo-HCT for T-cell ALL in 2000-2020 with blood samples available

Characteristic	TED N (%)	CRF N (%)
No. of patients	797	472
No. of centers	143	120
Age at HCT, years		
Median (range)	29 (1-75)	27 (1-72)
<10	98 (12)	76 (16)
10-17	109 (14)	80 (17)
18-29	206 (26)	113 (24)
30-39	151 (19)	78 (17)
40-49	101 (13)	71 (15)
50-59	79 (10)	29 (6)
60-69	48 (6)	22 (5)
≥70	5 (1)	3 (1)
Recipient sex		
Male	558 (70)	328 (69)
Female	239 (30)	144 (31)
Disease status at time of HCT		
PIF	42 (5)	21 (4)
CR1	446 (56)	203 (43)
CR2	243 (30)	185 (39)
≥CR3	19 (2)	23 (5)
Relapse	47 (6)	37 (8)
Missing	0 (0)	3 (1)
Karnofsky score		
<90	239 (30)	130 (28)
≥90	539 (68)	325 (69)
Missing	19 (2)	17 (4)
HCT-CI		
0	269 (34)	134 (28)
1	109 (14)	42 (9)
2	138 (17)	60 (13)
3+	276 (35)	120 (25)
N/A	4 (1)	114 (24)
Missing	1 (<1)	2 (<1)
MRD at time of HCT		
Negative	498 (62)	216 (46)
Positive	127 (16)	71 (15)
Disease status not in CR	88 (11)	36 (8)
N/A, legacy cases	2 (<1)	109 (23)
Missing	82 (10)	40 (8)
Donor type		
HLA-identical sibling	98 (12)	31 (7)
Other related	26 (3)	27 (6)
Well-matched unrelated (8/8)	417 (52)	186 (39)
Partially-matched unrelated (7/8)	108 (14)	59 (13)
Mis-matched unrelated (<= 6/8)	8 (1)	12 (3)
Multi-donor	1 (<1)	0 (0)
Unrelated (matching TBD)	69 (9)	3 (1)

Characteristic	TED N (%)	CRF N (%)
Cord blood	70 (9)	154 (33)
Graft type		
Bone marrow	227 (28)	99 (21)
Peripheral blood	500 (63)	219 (46)
Cord blood	70 (9)	154 (33)
Conditioning regimen intensity		
MAC	668 (84)	304 (64)
RIC	89 (11)	30 (6)
NMA	15 (2)	16 (3)
TBD	21 (3)	8 (2)
Missing	4 (1)	114 (24)
GVHD prophylaxis		
Post-Cy	58 (7)	26 (6)
CNI + MMF +/- others	139 (17)	157 (33)
CNI + MTX +/- others (not MMF, post-Cy)	462 (58)	204 (43)
CNI + others (not MMF, MTX, post-Cy)	72 (9)	32 (7)
Other	30 (4)	21 (4)
Missing	36 (5)	32 (7)
Year of transplant		
2003	0 (0)	1 (<1)
2005	0 (0)	23 (5)
2006	0 (0)	47 (10)
2007	4 (1)	44 (9)
2008	20 (3)	33 (7)
2009	43 (5)	25 (5)
2010	51 (6)	18 (4)
2011	61 (8)	22 (5)
2012	72 (9)	26 (6)
2013	54 (7)	35 (7)
2014	67 (8)	49 (10)
2015	76 (10)	43 (9)
2016	58 (7)	39 (8)
2017	88 (11)	27 (6)
2018	87 (11)	22 (5)
2019	79 (10)	16 (3)
2020	37 (5)	2 (<1)
Median follow-up of survivors (range), months	49 (2-145)	61 (3-171)

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

Comparison of transplant outcomes using fludarabine, cyclophosphamide and total body irradiation (TBI) vs. fludarabine, melphalan and TBI based reduced-intensity conditioning regimens in patients undergoing haploidentical stem cell transplant.

Q2. Key Words

AML, haploidentical stem cell transplant, conditioning, melphalan, cyclophosphamide

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hassan Alkhateeb, M.D.
Email address:	Alkhateeb.hassan@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Assistant Professor of Medicine

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):	Anmol Baranwal, M.B.B.S.
Email address:	Baranwal.anmol@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Fellow, Blood and Marrow Transplant

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

- Yes

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:

Hassan Alkhateeb, M.D.

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.

NA

Q13. PROPOSED WORKING COMMITTEE:

- Acute Leukemia

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

- No

Q15. RESEARCH QUESTION:

For patients with acute myeloid leukemia (AML) undergoing a haploidentical stem cell transplant, is conditioning with fludarabine, melphalan and TBI (Flu/Mel/TBI) associated with a better relapse free survival (RFS) compared to conditioning with fludarabine, cyclophosphamide and TBI (Flu/Cy/TBI).

Q16. RESEARCH HYPOTHESIS:

Patients undergoing reduced intensity haploidentical stem cell transplant (haploSCT) for AML are at increased risk of relapse. Previous CIBMTR data suggested a better leukemia control in Melphalan based regimen in matched related and unrelated donors. Fludarabine/Melphalan/TBI may lead to less relapse risk post haploidentical transplant compared to Fludarabine/Cyclophosphamide/TBI.

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

Suggested word limit of 200 words:

Specific Aims:
1. To investigate whether Flu/Mel/TBI is associated with a better relapse free survival compared to Flu/Cy/TBI.
2. To analyze transplant-related mortality (TRM), relapse-free (RFS), and overall survival (OS) between the two treatment groups.

Definitions and Study End Points:
Primary study endpoints are-
1. 3-year relapse-free (RFS) and overall survival (OS).

Secondary study endpoints are-
1. Transplant related mortality (TRM) at day 100, 1-year and 3-years post-transplant
2. 3-year cumulative incidence of relapse
3. Time to neutrophil recovery
4. Time to platelet recovery
5. Cumulative incidence of acute GVHD grades 2-4
6. Cumulative incidence of chronic GVHD

Definitions-
1. Relapse: Disease recurrence. This event will be summarized by cumulative incidence estimate with TRM as the competing risk.
2. RFS: Survival without disease progression or relapse; patients alive without disease progression or relapse will be censored at the time of last follow-up.
3. TRM: Time to death without the evidence of disease relapse. This event will be summarized as cumulative incidence estimate with relapse as competing risk.
4. OS: Time to death, patients censored at last follow-up.
5. Time to neutrophil recovery: First of the 3 consecutive days with absolute neutrophil count of ≥ 500 neutrophils/mL post-transplant
6. Time to platelet recovery: First of the 3 consecutive days with platelet count of ≥ 20,000 x 109/L post-transplant, in the absence of platelet transfusion within the last 7 days
7. GVHD: Grades 2- 4 acute GVHD and chronic GVHD as defined [14-16].

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.

This study will help determine the optimal conditioning regimen, between Flu/Mel/TBI and Flu/Cy/TBI, for patients with AML undergoing a haploidentical stem cell transplant and will provide guidance for future transplants.

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.

For patients with high risk hematologic malignancies, hematopoietic stem cell transplant is a potentially curative therapy. The ability to perform a stem cell transplant is sometimes limited due to lack of a fully human leucocyte antigen (HLA) matched donor. Haploidentical stem cell transplant (haploSCT) is a potential option in such cases. The use of cyclophosphamide in haploSCT dates to 1999. O'Donnell et al. in 2002 showed that cyclophosphamide added on days -5 and -6 to fludarabine and TBI based conditioning followed by post-transplant cyclophosphamide (PTCy) on day +3 along with tacrolimus and mycophenolate mofetil led to improved engraftment compared to patients received cyclophosphamide in the post-transplant setting alone [1]. Subsequent trials showed that post-transplant cyclophosphamide on days +3 and +4 lead to lower incidences of GVHD and primary graft failure, and improved overall survival and event free survival [2-4].

PTCy is an established GVHD prophylaxis in haploSCT, however the conditioning regimen of choice remains undetermined and largely remains a matter of institutional preference. Although Flu/Cy/TBI remains a commonly used regimen, other regimens that have been used in haploidentical setting include fludarabine and melphalan; fludarabine and TBI; fludarabine, busulfan and cyclophosphamide; fludarabine, melphalan and TBI; fludarabine, melphalan and thiotepa; etc. Among lymphoid malignancies, data is mostly for Flu/Cy/TBI, with several studies demonstrating an incidence of acute GVHD ranging from 16-43% and a 1-year non-relapse mortality ranging from 11-16% [5-9].

Melphalan combined with fludarabine (Flu/Mel) is a commonly used reduced-intensity conditioning regimen. Damlaj et al. compared transplant outcomes of Flu/Mel with fludarabine and busulfan (Flu/Bu) in patients with AML and MDS. Melphalan based conditioning had higher 2-year progression free survival compared to busulfan based conditioning (60.5% vs. 48.7%). Likewise, Flu/Mel was associated with lower incidence of relapse at 2 years (17.3% vs. 35.6%, p=0.0058) [10]. Similar findings were reported in a CIBMTR study evaluating transplant outcomes for AML patients using Flu/Mel or Flu/Bu as conditioning regimen. Flu/Mel was associated with a significantly lower risk of relapse compared to Flu/BU (HR: 0.65, p<0.001) [11]. Melphalan is increasingly being used in conditioning regimens for patients undergoing a haploSCT. In a study by Di Stasi et al., 32 patients undergoing haploSCT received Flu/Mel with Thiotepa as conditioning regimen. The study showed a 29% cumulative incidence of acute GVHD. Non-relapse mortality at 1 year was 24% [12]. Similarly in a study by Brammer et al., 22 patients were evaluated, 11 with Flu/Mel140 and 11 with Flu/Mel100, with TBI or thiotepa. TBI was used only for patients receiving RIC Flu/Mel100. The cumulative incidence of grade II-IV acute GVHD was 51% with majority being grade II. Transplant related mortality was similar in both Flu/Mel140 and Flu/Mel100 groups (18% versus 19% respectively, P = .952). Authors concluded fludarabine and melphalan 100 mg/m2 with 2 Gy TBI or thiotepa to be a safe and promising regimen for use in haploSCT compared FluMel140 based regimen [13]. Depending on institutional preferences, Flu/Mel/TBI is being used for conditioning in patients undergoing haploSCT.

These studies are, however, limited by small sample size. Moreover, there is no head-to-head trial comparing the effectiveness and/or safety between the two commonly used regimens, ie., between Flu/Cy/TBI and Flu/Mel/TBI. Single center analyses are prone to institutional biases and are unlikely to provide meaningful guidance. Given the robust database of clinical information of the CIBMTR, we believe this study will be the most comprehensive study comparing the two widely used regimens. Overall, the proposed study has a potential to advance the field and provide guidance to future transplants in this challenging population.

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: The study will include all adult patients with acute myeloid leukemia (AML) undergoing first haploidentical allogeneic stem cell transplant between July 2007 and January 2021.

Exclusion criteria: All patients age less than 18 years should be excluded.

Q21. Does this study include pediatric patients?

- No

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

The aim of this study is to provide guidance on conditioning regimen for adult patients with AML undergoing a haploidentical stem cell transplant. Moreover, both Flu/Mel/TBI and Flu/Cy/TBI are reduced-intensity conditioning regimens and may not be suitable in pediatric patients who may tolerate myeloablative conditioning.

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 variables:
1. Age at diagnosis
2. Sex: Female vs. male
3. Age at the time of transplantation
4. Karnofsky performance score (< 70 vs. ≥ 70)

Disease related variables at diagnosis and pre-transplant treatment
1. Date of diagnosis of hematologic malignancy
2. De novo or therapy related myeloid neoplasm (t-MN)
3. Complete blood count (WBC, blasts in blood, hemoglobin, absolute neutrophil count, and platelet) at diagnosis
4. Cytogenetics at diagnosis (karyotype or FISH)
5. Extramedullary disease yes or no
6. Bone marrow blast count
7. Molecular studies
8. Systemic therapy given prior to allogeneic stem cell transplant
9. MRD status after systemic therapy
10. Best response to the systemic therapy prior to allogeneic stem cell transplant

Disease related variables prior to transplant (before initiation of conditioning regimen)
1. Disease status at stem cell transplantation; CR1 vs CR2, vs active disease.

Transplant related variables:
1. Donor type – Haploidentical
2. Conditioning regimen – for this study we will compare two RIC FluCyTBI and FluMelTBI
3. Graft source – bone marrow (BM) vs. peripheral blood stem cell (PBSC)
4. Graft manipulation, if any
5. Donor and recipient CMV serologic status
6. HCT CI score

Study variables post-transplant:
1. Time to neutrophil recovery
2. Time to platelet recovery
3. Chimerism studies
4. Acute GVHD – grade 0-I vs. grade II-IV
5. Chronic GVHD – yes vs. no
6. Post-transplant therapy; yes vs no, if yes DLI vs targeted therapy vs low dose hypomethylating agent.
7. Relapse – yes vs. no
8. Time to relapse from the date of haploSCT
9. Survival status – alive vs. dead
10. Time to death from the date of haploSCT
11. Primary cause of death

All requested data is available from existing data collection forms: Form 2010, Form 2110, Pre-TED (2400), Comprehensive Baseline (2000), Post-TED (2450), Form 2402, Form 2900, Form 2006.

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. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2002;8(7):377-86.
2. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008 Jun; 14(6):641-50.
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4. Munchel A, Kesserwan C, Symons HJ, et al. Nonmyeloablative, HLA-haploidentical bone marrow transplantation with high dose, post-transplantation cyclophosphamide. Pediatr Rep. 2011 Jun 22; 3 Suppl 2():e15.
5. Burroughs LM, O'Donnell PV, Sandmaier BM, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. Biol Blood Marrow Transplant 2008; 14: 1279– 1287.
6. Kanakry JA, Kasamon YL, Gocke CD, et al. Outcomes of related donor HLA-identical or HLA-haploidentical allogeneic blood or marrow transplantation for peripheral T cell lymphoma. Biol Blood Marrow Transplant 2013; 19: 602– 606.
7. Raiola A, Dominietto A, Varaldo R, et al. Unmanipulated haploidentical BMT following nonmyeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. Bone Marrow Transplant 2014; 49: 190– 194.
8. Castagna L, Bramanti S, Furst S, et al. Nonmyeloablative conditioning, unmanipulated haploidentical SCT and post-infusion CY for advanced lymphomas. Bone Marrow Transplant 2014; 49: 1552.
9. Kasamon YL, Bolanos-Meade J, Gladstone D, et al. Outcomes of nonmyeloablative (NMA) haploidentical blood or marrow transplantation (haploBMT) with high-dose posttransplantation cyclophosphamide (PT/Cy) for lymphoma. Blood 2013; 122.
10. Damlaj M, Alkhateeb HB, Hefazi M, et al. Fludarabine-busulfan reduced-intensity conditioning in comparison with fludarabine-melphalan is associated with increased relapse risk in spite of pharmacokinetic dosing. Biol Blood Marrow Transplant. 2016 Aug;22(8):1431-1439.
11. Zhou Z, Nath R, Cerny J, et al. Reduced intensity conditioning for acute myeloid leukemia using melphalan- vs busulfan-based regimens: a CIBMTR report. Blood Adv. 2020 Jul 14;4(13):3180-3190.
12. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. Biol Blood Marrow Transplant. 2014 Dec;20(12):1975-81.
13. Brammer JE, Khouri I, Gaballa S, et al. Outcomes of Haploidentical Stem Cell Transplantation for Lymphoma with Melphalan-Based Conditioning. Biol Blood Marrow Transplant. 2016 Mar;22(3):493-8.
14. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995 Jun;15(6):825-8.
15. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980 Aug;69(2):204-17.
16. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1.

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 ≥ 18 receiving first allo-HCT for AML with haploidentical donor in 2008-2020

Characteristic	Flu/Mel/TBI N (%)	Flu/Cy/TBI N (%)
No. of patients	208	1423
No. of centers	38	123
Age at HCT, years		
Median (range)	60 (19-76)	62 (18-81)
18-29	16 (8)	65 (5)
30-39	15 (7)	97 (7)
40-49	27 (13)	123 (9)
50-59	43 (21)	300 (21)
60-69	96 (46)	602 (42)
≥70	11 (5)	236 (17)
Reporting track		
TED	124 (60)	898 (63)
CRF	84 (40)	524 (37)
Missing	0 (0)	1 (<1)
Recipient sex		
Male	125 (60)	818 (57)
Female	83 (40)	605 (43)
Karnofsky score		
<90	83 (40)	640 (45)
≥90	117 (56)	753 (53)
Missing	8 (4)	30 (2)
HCT-CI		
0	55 (26)	321 (23)
1	34 (16)	202 (14)
2	33 (16)	184 (13)
3+	81 (39)	703 (49)
Missing	5 (2)	13 (1)
Disease status at time of HCT		
PIF	30 (14)	158 (11)
CR1	134 (64)	958 (67)
CR2	32 (15)	227 (16)
≥CR3	3 (1)	19 (1)
Relapse	9 (4)	60 (4)
Missing	0 (0)	1 (<1)
MRD at time of HCT		
Negative	91 (44)	748 (53)
Positive	64 (31)	375 (26)
Disease status not in CR	39 (19)	219 (15)
Missing	14 (7)	81 (6)

Characteristic	Flu/Mel/TBI N (%)	Flu/Cy/TBI N (%)
Graft type		
Bone marrow	70 (34)	525 (37)
Peripheral blood	138 (66)	898 (63)
GVHD prophylaxis		
Post-Cy	192 (92)	1318 (93)
CNI + MMF +/- others	1 (<1)	51 (4)
CNI + others (not MMF, MTX, post-Cy)	0 (0)	1 (<1)
Other	4 (2)	10 (1)
Missing	11 (5)	43 (3)
Year of HCT		
2008	2 (1)	20 (1)
2009	1 (<1)	36 (3)
2010	0 (0)	28 (2)
2011	0 (0)	30 (2)
2012	2 (1)	33 (2)
2013	4 (2)	66 (5)
2014	6 (3)	77 (5)
2015	23 (11)	148 (10)
2016	15 (7)	185 (13)
2017	27 (13)	194 (14)
2018	35 (17)	257 (18)
2019	43 (21)	159 (11)
2020	50 (24)	190 (13)
Median follow-up of survivors (range), months	22 (3-78)	35 (3-143)

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

Outcomes of allogeneic hematopoietic cell transplantation for relapsed acute myeloid leukemia based on minimal residual disease status: CIBMTR analysis

Q2. Key Words

Leukemia, Myeloid, Minimal residual disease, allogeneic stem cell transplantation

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Guru Subramanian Guru Murthy MD, MS
Email address:	gmurthy@mcw.edu
Institution name:	Medical College of Wisconsin
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?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Wael Saber MD, MS
Email address:	wsaber@mcw.edu
Institution name:	Medical College of Wisconsin
Academic rank:	Associate 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:

Guru Subramanian Guru Murthy MD, MS

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.

CK18-03 - PI; CK20-01- PI; DS 13-02 - PI

Q13. PROPOSED WORKING COMMITTEE:

- Acute Leukemia

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:

Wael Saber MD, MS

Q15. RESEARCH QUESTION:

In patients with relapsed acute myeloid leukemia [defined by second or greater complete remission (CR)] who undergo allogeneic hematopoietic cell transplantation (allo-HCT), does minimal residual disease (MRD) status influence outcomes ?

Q16. RESEARCH HYPOTHESIS:

We postulate that MRD status would significantly affect the outcomes of allo-HCT for patients with relapsed acute myeloid leukemia [second or greater CR at the time of allo-HCT] and positive MRD would be associated with higher relapse and worse leukemia free survival.

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

Suggested word limit of 200 words:

To compare the following clinical outcomes of allo-HCT for relapsed acute myeloid leukemia (AML) based on the MRD status:

- Overall survival (OS)
- Leukemia free survival (LFS)
- Non-relapse mortality (NRM)
- Relapse
- Incidence of acute graft versus host disease (GVHD)
- Incidence of Chronic GVHD
- GVHD-free Relapse-free survival (GRFS)

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.

Majority of the prior studies in AML have focused on the role for MRD in first CR prior to allo-HCT. Hence, our proposal will uniquely address an important area of unmet need, evaluating the role of MRD status in the setting of second or greater CR at allo-HCT. Results from our study would provide important information for the clinical decision-making process in relapsed AML and pave way for future studies.

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.

AML is a hematologic malignancy arising from clonal expansion of myeloid blasts and generally affects older adults. Despite achieving 60-80% CR with initial induction therapy, more than 50% of AML patients experience disease relapse or have refractory disease [1]. The prognosis of patients with relapsed/refractory AML is often poor and their outcomes are influenced by several factors including subsequent allo-HCT [2,3]. Among patients undergoing allo-HCT for AML, the disease status prior to transplant is an important determinant of outcomes. While disease status and response to therapy is conventionally assessed using criteria for morphologic CR (<5% blasts), there is emerging data to support to the role of minimal/measurable residual disease (MRD) analysis in AML as deeper responses correlate with improved long-term outcomes [4]. However, the role of MRD status prior to allo-HCT for relapsed/refractory AML is still unclear.

Prior studies have investigated the role of MRD status prior to allo-HCT in AML and demonstrated its independent prognostic significance over conventional pretreatment variables [5-9]. However, most of those patients studied were in first CR (CR1). A large retrospective study by Araki et al. included 359 adults with AML who underwent myeloablative allo-HCT and demonstrated a 3-year relapse rate of 67% with MRD positive CR and 22% in MRD negative CR [9]. They also showed MRD-negative CR to be associated with significantly longer overall survival and progression-free survival compared to MRD positive CR or active disease, with similar outcomes between the latter two groups. But, its application in relapsed/refractory AML population is limited as majority was in CR1. Some studies have also demonstrated the role of MRD status in second CR (CR2) for AML. A study by Walter et al. included 253 patients with AML who received myeloablative allo-HCT in CR1 (n = 183) or CR2 (n = 70) and showed higher 3-year overall survival for patients with MRD negative CR (73% and 32% for MRD negative and MRD positive CR1; 73% and 44% for MRD negative and MRD positive CR2) [10]. Similarly, higher relapse was noted in MRD positive patients (21% and 58% for MRD negative and MRD positive CR1, and 19% and 68% for MRD negative and MRD positive CR2 respectively). In another multicenter retrospective study with 54 relapsed/refractory AML patients who underwent allo-HCT, 2-year overall survival was significantly higher in patients with MRD negative CR (74%) compared to MRD positive CR (50%) or refractory disease (16%) [11]. However, these are smaller retrospective studies and there is paucity of literature from larger datasets to exclusively illustrate the role of achieving MRD negativity prior to allo-HCT in relapsed AML and how this influences aspects such as conditioning intensity and donor choices.

Hence, while the current literature signifies the role for MRD status in CR1 for AML patients undergoing allo-HCT, the role of MRD status in the setting of second or greater CR at allo-HCT still remains unclear. This justifies the need for further research in the relapsed AML population as it would be an important factor considered in the clinical decision-making process.

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.

Adults aged ≥18 with relapsed AML who underwent allo-HCT (second or greater CR at allo-HCT) between the period 2008 to 2019 and reported to CIBMTR with available information on MRD status will be included. Patients without evidence of relapsed disease (those in first CR at allo-HCT) would be excluded.

Q21. Does this study include pediatric patients?

- No

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

Given the variations in transplant practice for managing adult AML vs. pediatric AML (including the higher utilization of reduced intensity conditioning in older adults), the study is restricted to adults.

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.

Main effect:
• MRD status: MRD positive vs. MRD negative at allo-HCT
Patient-related:
• Patient age: continuous and by decades
• Gender: Males vs. females
• Race/ethnicity: Hispanic vs Non-Hispanic White vs Non-Hispanic Black/African American vs Other vs Missing
• HCT-CI: 0 vs 1 vs 2 vs 3+
• Karnofsky performance score: <90 vs 90-100
Disease-related:
• Type: primary AML vs secondary AML vs. therapy related AML
• ELN/CIBMTR risk- Favorable vs. intermediate vs. poor
• Cytogenetics
• Molecular mutations
• Time from diagnosis to transplant: (continuous) <6 months vs 6-11 months vs ≥12 months
• Disease status: CR2 vs. ≥CR3
Transplant-related:
• HLA match: Matched sibling vs. 8/8 matched unrelated donors vs. partially- unrelated 7/8 vs. mismatched unrelated (≤6/8) vs. cord blood
• Donor age: continuous and by decades
• Source of stem cell: Bone marrow vs peripheral blood
• Conditioning intensity: MAC vs. RIC/NMA
• Donor-recipient sex match: M-M vs M-F vs F-M vs F-F
• Donor-recipient CMV status: +/+ vs +/- vs -/+ vs -/- vs Missing
• Donor-recipient ABO match: Matched vs. minor vs. major vs. bidirectional mismatches
• GVHD prophylaxis: TAC based vs. CSA based vs. Post-CY based vs. others
• ATG/Campath: No vs Yes
• Year of transplant
• Center effect
STUDY DESIGN:
This is a retrospective analysis of the CIBMTR database. The study would include patients with AML who underwent allo-HCT in second or greater CR and meet the above-mentioned study criteria. MRD status at allo-HCT would be the main effect and comparisons would be done between MRD positive vs. MRD negative patients. The primary outcome will be OS and LFS. The secondary outcomes will be relapse, NRM, incidence of acute GVHD, chronic GVHD and GRFS. Patient related, donor related, and transplant related variables summarized above will be compared between two groups using chi-square test for categorical variables and the Wilcox on two sample test for continuous variables. The probabilities for OS, LFS and GRFS will be calculated using the Kaplan Meier estimator and cumulative incidence estimates will be used for competing risks outcomes, including relapse, NRM, acute GVHD, and chronic GVHD. Cox proportional hazards regression will be used to identify independent prognostic factors associated with the outcomes. The proportional hazards assumption for each factor will be checked. When the proportional hazards assumption is violated, a time-varying effect will be considered. The stepwise selection method will be used to identify significant factors associated with the outcomes at a significance level $p<0.05$. Interactions between main effects and significant factors will be tested. Center effects will be tested using the score test of homogeneity.
Additional exploratory analysis:
Prior literature suggests that MRD positive patients have worse outcomes similar to those with active disease (refractory) at the time of allo-HCT [9]. Hence, if time and resources permit, we envision a subgroup analysis to compare the outcomes of MRD positive CR patients (in second or greater CR at allo-HCT) with those who underwent allo-HCT in refractory status. This would provide important information about the value of performing allo-HCT in MRD positive patients and the potential factors that could predict better outcomes in this high risk patient population.

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:

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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 age ≥ 18 receiving first allo-HCT for AML in CR2+ in 2008-2019, CRF track

Characteristic	MRD – N (%)	MRD + N (%)	Unknown MRD status N (%)
No. of patients	1186	473	183
No. of centers	160	130	65
Age at HCT, years			
Median (range)	48 (18-77)	53 (18-78)	47 (19-75)
18-29	202 (17)	50 (11)	35 (19)
30-39	186 (16)	65 (14)	27 (15)
40-49	256 (22)	83 (18)	44 (24)
50-59	293 (25)	131 (28)	45 (25)
60-69	205 (17)	130 (27)	26 (14)
≥70	44 (4)	14 (3)	6 (3)
Recipient sex			
Male	606 (51)	245 (52)	102 (56)
Female	580 (49)	228 (48)	81 (44)
Karnofsky score			
<90	393 (33)	181 (38)	65 (36)
≥90	772 (65)	285 (60)	114 (62)
Missing	21 (2)	7 (1)	4 (2)
HCT-CI			
0	287 (24)	99 (21)	49 (27)
1	167 (14)	72 (15)	37 (20)
2	156 (13)	82 (17)	26 (14)
3+	500 (42)	195 (41)	58 (32)
Missing	76 (6)	25 (5)	13 (7)
Clinical onset of AML			
De-novo	1074 (91)	424 (90)	167 (91)
Transformed from MDS/MPS	68 (6)	32 (7)	12 (7)
Therapy linked	44 (4)	17 (4)	4 (2)
Disease status at time of HCT			
CR2	1102 (93)	441 (93)	170 (93)
≥CR3	84 (7)	32 (7)	13 (7)
Donor type			
HLA-identical sibling	228 (19)	85 (18)	38 (21)
Other related	168 (14)	97 (21)	27 (15)
Well-matched unrelated (8/8)	380 (32)	133 (28)	58 (32)
Partially-matched unrelated (7/8)	109 (9)	49 (10)	17 (9)
Mis-matched unrelated (<= 6/8)	8 (1)	3 (1)	1 (1)
Multi-donor	2 (<1)	1 (<1)	0 (0)
Unrelated (matching TBD)	11 (1)	9 (2)	2 (1)
Cord blood	280 (24)	96 (20)	40 (22)
Graft type			
Bone marrow	158 (13)	61 (13)	20 (11)
Peripheral blood	748 (63)	316 (67)	123 (67)
Cord blood	280 (24)	96 (20)	40 (22)
Conditioning regimen intensity			
MAC	728 (61)	248 (52)	121 (66)
RIC	242 (20)	143 (30)	31 (17)

Characteristic	MRD – N (%)	MRD + N (%)	Unknown MRD status N (%)
NMA	194 (16)	66 (14)	26 (14)
TBD	11 (1)	9 (2)	2 (1)
Missing	11 (1)	7 (1)	3 (2)
Year of HCT			
2008	177 (15)	43 (9)	37 (20)
2009	196 (17)	22 (5)	23 (13)
2010	108 (9)	35 (7)	25 (14)
2011	52 (4)	9 (2)	13 (7)
2012	74 (6)	12 (3)	5 (3)
2013	102 (9)	35 (7)	16 (9)
2014	111 (9)	83 (18)	8 (4)
2015	109 (9)	70 (15)	12 (7)
2016	84 (7)	58 (12)	8 (4)
2017	60 (5)	45 (10)	14 (8)
2018	73 (6)	35 (7)	13 (7)
2019	40 (3)	26 (5)	9 (5)
Median follow-up of survivors (range), months	72 (3-149)	59 (3-145)	68 (3-149)

Title: Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms

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Research Question:

1. To understand variables that predict relapse and post relapse survival for patients with MDS or AML undergoing first allogeneic hematopoietic stem cell transplant (ASCT) in the modern era
2. To characterize clonal evolution patterns before and after ASCT at the time of relapse to provide insight into prognosis and inform best future treatment strategies

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Research Hypothesis:

1. With modern advances (i.e. genomic data, targeted anti-leukemic agents, low intensity therapies, incorporation of novel diagnostic tools for measurable residual disease detection etc.) we hypothesize that post relapse survival for patients with MDS and AML undergoing first ASCT has improved substantially.
2. We anticipate that patients with relapsed AML/MDS after ASCT harbor unique molecular and cytogenetic changes compared to their original disease, permitted by immune pressure and rapid hematopoietic expansion after ASCT. We expect that better understanding of clonal evolution in AML/MDS relapse after ASCT will provide a necessary foundation to develop more effective relapse prevention and treatment strategies.

Specific Aims:

Primary Aim:

> Determine Overall Survival (OS) for patients with MDS and AML relapse following first allogeneic stem cell transplant in the modern era and describe the molecular and cytogenetic mutational landscape in AML/MDS relapse after ASCT.

Secondary Aims:

1. Identify predictors of relapse post-ASCT based on pre-transplant characteristics
2. Determine one-year progression free survival (PFS) post relapse
3. Characterize dynamic changes in clonal evolution (molecular and cytogenetics) at time of disease relapse compared to their original disease
4. Determine if pre-emptive maintenance (Y/N) impacts cumulative incidence of relapse for those who relapsed post first ASCT (stratified by disease risk group, conditioning intensity)
5. Develop predictive model for survival post relapse
6. Identify the impact of second cellular intervention (DLI or ASCT) on overall survival, acute and chronic GVHD

Scientific Impact:

Relapse reduction is the main role of consolidative ASCT and to achieve cure in select population. As the number of approved and investigational drugs to treat relapses in AML and MDS continue to increase in the modern era, it is important to characterize their benefit in ASCT recipients. Improvement in outcomes will aid in treatment decisions for patients and motivate pharmaceutical partners to develop transplant-inclusive trial designs.

There is extensive reporting of molecular cytogenetics and associated risk for newly diagnosed AML which guides treatment planning and prognosis [1]. However for AML/MDS relapse after ASCT, it is not clear how those molecular and cytogenetic changes correlate with outcomes. We do not know whether patients who have AML/MDS relapse after ASCT commonly present with the same cytogenetic and molecular abnormalities present in their original disease, or have significant clonal evolution that correlates with more refractory disease. Understanding the biology of relapse may provide novel avenues to design future relapse mitigation strategies.

Scientific Justification:

ASCT is a potentially curative therapy for many patients with AML and MDS. Relapse is still a common cause of treatment failure post ASCT. Since ASCT is a consolidation option that partially uses the benefit of chemotherapy regimens, management of relapses after transplant with chemotherapy is generally unsatisfactory owing to a relatively chemo resistant state [2]. Over the last decade our understanding about genomic and immune mediated mechanisms driving relapse post ASCT has significantly increased [3]. This has led to many novel pursuits for mechanistic drug discovery targeting leukemogenesis [4,5]. Proactively, we have also made changes to conditioning regimens to make them less toxic while facilitating engraftment and subsequently impose cellular control of leukemia with limited adverse alloimmunity. In relapsed refractory AML and MDS, pharmaceutical clinical trials using many of these new drugs were shown to be better tolerated than conventional chemotherapy with improved response rates and in some cases survival [5,6]. When these novel drugs were combined with donor lymphocyte infusions in clinical trials, the combination was well tolerated with improved response rates [7,8].

There have also been multiple trials exploring prophylactic maintenance strategies to prevent relapses [8]. While the transplant community eagerly awaits BMT-CTN 1506 results, a recent metanalysis of maintenance strategy showed benefits of this pursuit, in contrast to a randomized trial [9,10]. Collectively, these findings allude to a growing optimism that post ASCT relapses may be decreasing and are amenable for further successful salvage and improved survival. However, in multiple registration trials, relapse/refractory AML/MDS patients are grouped together in one broad inclusion group (including those post ASCT). Further, there is limited representation of post ASCT cases in registration trials, which limits our ability to inform patients on life beyond ASCT, in the event of relapse. The last CIBMTR project studying this topic only included patients that were transplanted up until 2010 and then subsequently relapsed [11]. Since the time of reporting of the above study the practice has changed substantially and a contemporary update is now warranted.

In addition to advancements in novel treatment options in MDS/AML and transplantation, there have been rapid advances in high throughput sequencing technology making genetic analysis integral to cancer diagnosis, prognostication, and treatment in the modern era. However, the molecular and cytogenetic profile of patients with AML/MDS relapse after ASCT is not well characterized in the literature. The effect of previous treatment for AML and conditioning for transplant may mediate development of cytogenetic and molecular changes that drive relapse. The molecular and cytogenetic changes at AML/MDS relapse after ASCT compared to original disease may impact outcomes and treatment selection, and should be assessed for this unique patient population. Bazarbacki et al. (2020) recently reported that survival among young patients with AML relapse after ASCT has improved from 16% in 2000-2004 to 26% in the 2015-2018 timeframe from the European Society for Blood and Marrow Transplantation data. Favorable cytogenetics at diagnosis and later year of relapse did contribute to favorable outcomes in these patients [12]. However, there was no comment about changes in molecular and cytogenetic information from original disease to relapse. For patients with AML/MDS relapse in donor-derived cells after allo-HSCT in cases reported in the literature [13], 24% of all patients harbored chromosome 7 abnormalities, a disproportionately high population given the relatively young age of

the transplanted patients. This suggests possible role of therapy-related changes after transplantation. In many of the reported cases, patients developed chromosome 7 abnormalities, and other molecular/cytogenetic changes, that were not present in either the recipient or donor original bone marrow analysis.

In sum, our project seeks to describe the contributing factors and treatment outcomes for patients with MDS/AML after ASCT, with special focus on describing the molecular and cytogenetic changes in MDS/AML relapse after ASCT and characterizing the clonal evolution pre- and post-ASCT at time of relapse. Outcomes for patients with relapse post-ASCT were last reported through 2010 [11]. Now in the modern era, treatment advances and molecular analysis technologies have transformed care for AML/MDS patients. The CIBMTR database includes 702 patients with relapse after ASCT since 2017, with nearly half reported with molecular and/or cytogenetic information at time of relapse.

Patient Eligibility Population:

Inclusion: AML or MDS undergoing first ASCT in CR1 or CR2 between 2011 - 2021, comparator arm before 2010

Exclusion: AML beyond CR2 undergoing ASCT or in whom essential data is missing

Data Requirements:

- CIBMTR report forms will be used for data analysis. Supplemental data if made available will also be used. Study period Jan 2011 to Dec 2021.
- **Pre-Transplant**: Time from diagnosis to transplant, number of lines and types of induction/consolidation therapy used before ASCT, HCTCI comorbidity index, disease status pre-transplant.
- **Post-transplant:** Time to relapse, Maintenance post-transplant (Y/N), DLI-Y/N, Number of lines of therapy for relapse and types (chemo vs targeted agents). If available drugs used, second transplant-Y/N, Date of last follow up for survival, chimerism.
- **Donor:** HLA matching level (matched vs mismatched- related/unrelated), Donor-recipient CMV/ABO matching status
- **Recipient:** KPS, HCTCI, race, age, CMV, disease type/risk group, all baseline data
- **Graft:** peripheral blood or bone marrow with no ex-vivo T cell depletion.
- **Therapy:** Conditioning regimens (Intensity- MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-ASCT therapy to prevent relapse(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials)
- **Disease related:** Best response pre-transplant,. Rates of grade 3 or 4 aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death.
- **Molecular data:** cytogenetics, FISH, PCR, NGS testing at diagnosis, pre-transplant, and at relapse when available

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Table 1. Characteristics of patients receiving first allo-HCT for AML in CR1/CR2 or MDS in 2011-2020 and relapsed post-HCT, CRF track

Characteristic	AML N (%)	MDS N (%)
No. of patients	2184	2155
No. of centers	202	165
Age at HCT, years		
Median (range)	55 (0-77)	65 (1-81)
<10	163 (7)	27 (1)
10-17	90 (4)	17 (1)
18-29	174 (8)	25 (1)
30-39	192 (9)	40 (2)
40-49	260 (12)	91 (4)
50-59	508 (23)	370 (17)
60-69	657 (30)	1207 (56)
≥70	140 (6)	378 (18)
Recipient sex		
Male	1198 (55)	1386 (64)
Female	986 (45)	769 (36)
Karnofsky score		
<90	818 (37)	986 (46)
≥90	1349 (62)	1149 (53)
Missing	17 (1)	20 (1)
HCT-CI		
0	501 (23)	301 (14)
1	357 (16)	256 (12)
2	295 (14)	266 (12)
3+	954 (44)	1262 (59)
Missing	77 (4)	70 (3)
Disease status		
AML - CR1	1717 (79)	0 (0)
AML - CR2	467 (21)	0 (0)
MDS - early	0 (0)	472 (22)
MDS - advanced	0 (0)	1307 (61)
MDS - other	0 (0)	376 (17)
MRD at time of HCT		
Negative	1211 (55)	0 (0)
Positive	831 (38)	0 (0)
Disease not acute leukemia	0 (0)	2155 (100)
Missing	142 (7)	0 (0)
Donor type		

Characteristic	AML N (%)	MDS N (%)
HLA-identical sibling	485 (22)	583 (27)
Other related	437 (20)	299 (14)
Well-matched unrelated (8/8)	645 (30)	964 (45)
Partially-matched unrelated (7/8)	115 (5)	137 (6)
Mis-matched unrelated (<= 6/8)	13 (1)	7 (<1)
Multi-donor	6 (<1)	14 (1)
Unrelated (matching TBD)	59 (3)	28 (1)
Cord blood	424 (19)	123 (6)
Graft type		
Bone marrow	434 (20)	270 (13)
Peripheral blood	1326 (61)	1762 (82)
Cord blood	424 (19)	123 (6)
Conditioning regimen intensity		
MAC	974 (45)	584 (27)
RIC	648 (30)	1088 (50)
NMA	450 (21)	370 (17)
TBD	44 (2)	37 (2)
Missing	68 (3)	76 (4)
GVHD prophylaxis		
Ex-vivo T-cell depletion	17 (1)	7 (<1)
CD34 selection	81 (4)	53 (2)
Post-CY + other(s)	449 (21)	345 (16)
Post-CY alone	7 (<1)	1 (<1)
TAC + MMF +- other(s) (except post-CY)	252 (12)	386 (18)
TAC + MTX +- other(s) (except MMF, post-CY)	709 (32)	813 (38)
TAC + other(s) (except MMF, MTX, post-CY)	97 (4)	151 (7)
TAC alone	44 (2)	42 (2)
CSA + MMF +- other(s) (except post-CY)	256 (12)	189 (9)
CSA + MTX +- other(s) (except MMF, post-CY)	141 (6)	48 (2)
CSA + other(s) (except MMF, MTX, post-CY)	19 (1)	4 (<1)
CSA alone	11 (1)	6 (<1)
Other(s)	32 (1)	32 (1)
Missing	69 (3)	78 (4)
Year of HCT		
2011	128 (6)	127 (6)
2012	142 (7)	162 (8)
2013	261 (12)	294 (14)
2014	354 (16)	288 (13)
2015	324 (15)	293 (14)
2016	284 (13)	307 (14)

Characteristic	AML N (%)	MDS N (%)
2017	242 (11)	290 (13)
2018	229 (10)	245 (11)
2019	164 (8)	133 (6)
2020	56 (3)	16 (1)
Median follow-up of survivors (range), months	53 (3-122)	55 (3-120)
Pre-HCT cytogenetic testing data available		
No	20 (1)	46 (2)
Yes	2164 (99)	2109 (98)
Pre-HCT molecular testing data available		
No	696 (32)	1446 (67)
Yes	1488 (68)	709 (33)
Post-relapse cytogenetic/molecular testing data available		
Yes	636 (29)	0 (0)
No	1548 (71)	0 (0)
N/A	0 (0)	2155 (100)
Received post-HCT maintenance therapy		
No	1656 (76)	0 (0)
Yes	516 (24)	0 (0)
N/A	12 (1)	2155 (100)

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

Impact of Pre-Transplant Extramedullary Disease on Allogeneic Transplant Outcomes in Acute Lymphoblastic Leukemia (ALL)

Q2. Key Words

Extramedullary disease, acute lymphoblastic leukemia, allogeneic transplantation

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Reshma Ramlal MD
Email address:	rra247@uky.edu
Institution name:	University of Kentucky
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?

- No

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)

- 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.

LK19-02 Evolving significance of Ph-positive status on ALL post-transplant in the TKI Era. - I am a sub-investigator in this study.

Q13. PROPOSED WORKING COMMITTEE:

- Acute Leukemia

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:

Partow Kebriaei MD - has reviewed the proposal and is a co-author on this proposal.

Q15. RESEARCH QUESTION:

Impact of Pre-Transplant Extramedullary Disease on Allogeneic Transplant Outcomes in Acute Lymphoblastic Leukemia (ALL)

Q16. RESEARCH HYPOTHESIS:

We hypothesize that acute lymphoblastic leukemia (ALL) with extramedullary disease (EMD) at any time prior to transplant would have a worse overall survival following allogeneic transplantation compared to ALL patients without EMD.

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

Suggested word limit of 200 words:

Primary Objective

• To compare post-transplant overall survival (OS) and leukemia free survival (LFS) of ALL patients with EMD versus without EMD undergoing allogeneic transplant (alloHSCT) in complete remission.

Secondary Objectives

• To describe and compare the cumulative incidence of relapse (extra-medullary versus medullary) and non-relapsed mortality (NRM) between the two cohort of (ALL with EMD versus without EMD)

• To determine whether the site of EMD (central nervous system (CNS), mediastinum, testes and other site) influenced OS, LFS and non-relapse mortality (NRM).

• To compare OS, LFS, NRM of patients with ALL with EMD treated with myeloablative versus non-myeloablative conditioning regimen.

• To compare OS, LFS of patients with ALL with EMD treated with total body irradiation (TBI)- based regimen versus non-TBI based conditioning regimen.

• To describe and compare the cumulative incidence of Grade II-IV acute graft versus host disease (GVHD) and chronic GVHD in ALL patients with EMD versus ALL patients without EMD

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.

There is a paucity of data regarding the impact of EMD in ALL on post-transplantation outcomes. Available studies have largely focused on the impact of CNS involvement and results from these studies have been conflicting and confounded by the small numbers of patients with EMD. The Center for Internal Blood and Marrow Transplant Research (CIBMTR) database offers a comprehensive dataset to identify factors that influence outcome of alloHSCT for ALL with EMD and would allow comparison of outcomes of patients with EMD prior to transplant to matched cohort of patients with ALL without EMD. The feasibility of this study using the CIBMTR database is evident by a similar study conducted by Goyal et al to answer the question of the impact of EMD in acute myeloid leukemia on post transplantation outcomes[1].

This study would help to determine whether patients with ALL with EMD are at higher risk of relapse and poorer overall survival and therefore shape future research questions addressing this unique patient population such as the role of post-transplantation maintenance therapy.

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.

Extramedullary disease (EMD) in ALL refers to involvement of organs or tissues with acute leukemia outside of the blood and bone marrow. It is estimated that 20% of patients with ALL will present with extramedullary disease involving the lymph nodes, spleen or liver[2,3] while 3-7% will have CNS involvement at presentation. The sites of EMD in ALL appears to influence treatment outcomes. In a Danish study by Jensen et al of 56 adult ALL patients with EMD with 71% involving lymphoid tissue and 23% involving non-lymphoid tissue (CNS, testes, skin, pleural cavities and gingiva), they found that the presence of lymphoid EMD was associated with higher complete remission rates and longer disease free survival (DFS) compared to patients with ALL without EMD. This is in contrast to EMD involving non lymphoid tissue which was associated with lower CR rates and shorter DFS[4].

In the pediatric setting ALL with CNS disease at diagnosis has been associated with significantly decreased event free survival (EFS) rates. In adults, however, the studies evaluating the impact of CNS involvement at presentation of ALL has yielded conflicting results. The French LALA-94 study which included 48 patients with CNS disease showed a favorable outcome with a median DFS of 19.2 months and with 44% of patients alive at 3 years. [5] Several other series have failed to show a significant impact on outcomes of CNS involvement in patients with ALL receiving intensive treatment.[6,7] In contrast, in the largest series of adult ALL patients ever reported, Lazarus et al evaluated the outcomes of 77 patients with CNS disease at presentation of ALL treated as part of the MRC UKALL XII/ECOG E2993 trial (total number of patients treated 1508) and found that patient with CNS disease had an inferior 5 year overall survival of 29% versus 38% for those without CNS involvement (p=0.03)[8]. However, in patients undergoing a matched related donor (MRD) transplant in CR1 there was no statistically significant difference in 5-year OS in patients with CNS disease compared to those without CNS disease (44% versus 55%, p=0.3). This suggest that consolidative allogeneic transplant overcomes the negative impact of CNS involvement in ALL.

This is contrary to the finding of Aldoss et al, who in a retrospective single center study analyzed the outcomes of 87 patients with ALL and history of CNS involvement who later underwent allogeneic transplant and compared these post-transplant outcomes to patients with ALL without CNS disease. They found that patients with pre-transplant CNS involvement had a high risk of CNS relapse after transplantation (2 year CNS relapse: 9.6% versus 1.4%; p< 0.000 1), inferior EFS (hazard ratio[HR] 1.52; p=0.003) and worse OS (HR 1.55; p=0.003) compared with patients without pre-transplant CNS involvement (n=543)[9].

The results of these studies have been conflicting and confounded by small sample size. A large retrospective study is therefore necessary to address this question using a large transplantation database such as the CIBMTR.

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

• Adult patients ages 18-70 years in CR with B and T-cell acute lymphoblastic leukemia who underwent an allogeneic HCT between 2008 and 2018.

Exclusion Criteria

• Recipients of second or later allo-HSCT
• Patient not transplanted in CR
• Patient who did not consent to participation in CIBMTR research
• Patients with CML with lymphoid blast crisis

Q21. Does this study include pediatric patients?

- No

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

The disease biology, cytogenetic risk and prognosis of acute lymphoblastic leukemia is vastly different between the pediatric and adult population. The majority of pediatric patients with ALL are treated with chemotherapy only approaches based on pediatric protocols with allogeneic transplantation reserved for patients failing to attain a remission or in the setting or relapsed disease. This is in contrast to the adult population who has a higher incidence of poor risk cytogenetics and therefore are more likely to receive an allogeneic transplantation in CR1.

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.

VARIABLES TO BE DESCRIBED

Main Effect

• Presence of Extramedullary disease : Yes, No
• Site of Extramedullary disease – CNS, mediastinum, testes, other [Form 2011 R 4.0: Acute Lymphoblastic Leukemia (ALL) Pre-HSCT Data]
• Timing of extramedullary disease – at diagnosis, at relapse

Patient related

• Age at transplant : 18-29, 30-39, 40-49, 50-59, 60-70
• Sex: female versus male
• Race: Caucasian, African American, Asian vs. others
• Karnofsky performance status at transplantation ≥ 90 vs. < 90
• HCT comorbidity index at transplantation 0 vs. 1-2 vs ≥ 3

Disease Related

• B-cell ALL [Ph+ versus Ph-] versus T-cell ALL
• WBC at diagnosis (<10, 10-100, >100x 10^9/l)
• Cytogenetics, FISH
• Disease status prior to transplant : CR1, CR2, >CR2

Treatment Related:

• CNS prophylaxis give : Yes, no
o Specific prophylaxis
Cranial irradiation
High dose methotrexate
Intrathecal therapy
Spinal irradiation
Other prophylaxis
• Treatment of extramedullary disease pre-transplant
o Radiation therapy : Yes versus No [site]
• Line of therapy
o Purpose [induction, consolidation, maintenance, treatment of disease relapse]
o Number of cycles

Transplant Related:

• Conditioning regimen: MAC vs. RIC/NMA [Total body irradiation [TBI] versus non-TBI]
• Graft type: Bone marrow versus peripheral blood stem cell vs. cord blood
• Donor type : HLA-identical sibling vs. matched unrelated donor versus mismatch unrelated donor vs. other unrelated versus cord
• GvHD prophylaxis : CNI based, versus sirolimus based
• Acute GvHD prior to day 100: none vs. Grade I-II vs Grade III-IV
• Presence of chronic GvHD: Yes, No
• CMV Status (+/+. +/-, -+, -/-)
• Gender mismatch – (M/M, M/F, F/M, F/F)

Post-Transplant :

• Was there planned post-transplantation therapy (maintenance, consolidation) : Yes, No
• Type of post-transplant therapy
o CNS irradiation
o Systemic therapy
o TKI
o Intrathecal therapy
o Donor cell infusion

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:

1. Goyal SD, Zhang MJ, Wang H-L, Akpek G, et al. Allogeneic hematopoietic cell transplant for acute myeloid leukemia: no impact of pre-transplant extramedullary disease on outcome. Bone Marrow Transplant. 2015:50(8):1057-1062.
2. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 7, e577(2017).
3. Alvarnas JC, Brown PA, Aoun P et al. Acute lymphoid leukemia (version 2.2015). Natl Comprehens Cancer Netw 2015: 13:1240-1279.
4. Jensen M, Jensen PD, Ellegard J, Bastrup-Madsen P, Hokland P. Extramedullary manifestations among adult patients with acute lymphoblastic leukemia (ALL). Ugeskr Laeger. 1991; 153(16):1125-9.
5. Thomas X, Boiron JM, Huguet F, Dombert H et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol. 2004; 22: 4075-4086.
6. Fiere D, Lepage E, Sebban C, et al. Adult acute lymphoblastic leukemia: A mutlicentric randomized trial testing bone marrow transplantation as postremission therapy. J Clin Oncol. 1993; 11: 1990-2001.
7. Hoelzer D, Thiel E, Löffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood. 1998; 71:123-131
8. Lazarus HM, Richards SM, Chopra Raj, Litzow MR, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. Blood 2006; 108(20): 465-472.
9. Aldoss I, Malki MMA, Stiller T, et al. Implications and management of central nervous system involvement before allogeneic hematopoietic cell transplantation in acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2016; 22: 571-588.

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 ≥ 18 receiving first allo-HCT for ALL in 2008-2018, CRF track

Characteristic	EMD N (%)	No EMD N (%)
No. of patients	387	1925
No. of centers	112	183
Age at HCT, years		
Median (range)	37 (18-69)	42 (18-70)
18-29	134 (35)	533 (28)
30-39	80 (21)	362 (19)
40-49	87 (22)	422 (22)
50-59	56 (14)	380 (20)
60-69	30 (8)	228 (12)
Recipient sex		
Male	238 (61)	1088 (57)
Female	149 (39)	837 (43)
Karnofsky score		
<90	157 (41)	680 (35)
≥90	227 (59)	1227 (64)
Missing	3 (1)	18 (1)
HCT-CI		
0	100 (26)	544 (28)
1	59 (15)	307 (16)
2	59 (15)	310 (16)
3+	155 (40)	674 (35)
Missing	14 (4)	90 (5)
Immunophenotype		
T-cell	144 (37)	206 (11)
B-cell	231 (60)	1686 (88)
Unspecified	12 (3)	33 (2)
Disease status at time of HCT		
CR1	262 (68)	1399 (73)
CR2	107 (28)	443 (23)
≥CR3	18 (5)	83 (4)
MRD at time of HCT		
Negative	231 (60)	1125 (58)
Positive	125 (32)	676 (35)
Missing	31 (8)	124 (6)
Donor type		
HLA-identical sibling	100 (26)	505 (26)
Other related	49 (13)	287 (15)
Well-matched unrelated (8/8)	117 (30)	557 (29)
Partially-matched unrelated (7/8)	32 (8)	151 (8)
Mis-matched unrelated (<= 6/8)	1 (<1)	11 (1)
Multi-donor	0 (0)	6 (<1)
Unrelated (matching TBD)	4 (1)	15 (1)
Cord blood	84 (22)	393 (20)
Graft type		
Bone marrow	68 (18)	325 (17)
Peripheral blood	235 (61)	1207 (63)
Cord blood	84 (22)	393 (20)

Characteristic	EMD N (%)	No EMD N (%)
Conditioning regimen intensity		
MAC	314 (81)	1400 (73)
RIC	41 (11)	281 (15)
NMA	29 (7)	216 (11)
TBD	3 (1)	16 (1)
Missing	0 (0)	12 (1)
GVHD prophylaxis		
Ex-vivo T-cell depletion	9 (2)	17 (1)
CD34 selection	15 (4)	41 (2)
Post-CY + other(s)	48 (12)	273 (14)
Post-CY alone	3 (1)	14 (1)
TAC + MMF +- other(s) (except post-CY)	60 (16)	284 (15)
TAC + MTX +- other(s) (except MMF, post-CY)	130 (34)	650 (34)
TAC + other(s) (except MMF, MTX, post-CY)	24 (6)	116 (6)
TAC alone	5 (1)	35 (2)
CSA + MMF +- other(s) (except post-CY)	45 (12)	237 (12)
CSA + MTX +- other(s) (except MMF, post-CY)	35 (9)	182 (9)
CSA + other(s) (except MMF, MTX, post-CY)	0 (0)	11 (1)
CSA alone	4 (1)	15 (1)
Other(s)	5 (1)	23 (1)
Missing	4 (1)	27 (1)
Year of HCT		
2008	46 (12)	239 (12)
2009	34 (9)	158 (8)
2010	21 (5)	102 (5)
2011	20 (5)	115 (6)
2012	16 (4)	87 (5)
2013	32 (8)	166 (9)
2014	56 (14)	251 (13)
2015	49 (13)	220 (11)
2016	47 (12)	216 (11)
2017	38 (10)	176 (9)
2018	28 (7)	195 (10)
Median follow-up of survivors (range), months	60 (3-147)	60 (3-151)

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 transplant for Relapsed Refractory ALL in Modern Era

Q2. Key Words

Novel Therapies (Ino, Blina and Car-T) . Improved Remission, MRD negativity. Cure with allograft

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Lohith Gowda
Email address:	Lohith.gowda@yale.edu
Institution name:	Yale 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?

- No

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Amer Zeidan
Email address:	Amer.zeidan@yale.edu
Institution name:	Yale cancer center
Academic rank:	Associate 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:

Lohith.gowda@yale.edu

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

- Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project

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.

A few projects I serve as co-PI

Q13. PROPOSED WORKING COMMITTEE:

- Acute Leukemia

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

- No

Q15. RESEARCH QUESTION:

Has recent FDA approved therapies to manage relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) favorably impacted allogeneic stem cell transplant (ASCT) utilization and its efficacy?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that with the advent of inotuzumab(Ino), Blinatumamab (blina) and chimeric antigen receptor -T (CAR-T) cells (here forward collectively referred as novel therapies) to treat R/R-ALL, clinical outcomes for patients opting to proceed with ASCT has improved in modern era.

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

Suggested word limit of 200 words:

Specific aims: Measure best response pre-transplant and post- transplant and develop predictive model for efficacy and toxicity with the use of novel therapies compared to chemotherapy based salvaged regimens in management of R/R ALL, in patients undergoing ASCT.
Primary Aim: Determine post ASCT progression free survival (PFS) for patients with R/R ALL receiving novel therapies pre-transplant and compare it those receiving conventional chemotherapy.
Secondary Aims: 1) Identify trends in the number of ASCT performed for R/R ALL since the approval of novel agents compared to chemotherapy era.
2) Determine Overall Survival (OS) post ASCT in recipients of pre-ASCT novel agents and compare it with those that had received chemotherapy.
3) Determine prognostic value of detectable measurable residual disease (MRD) post novel therapy for r/r ALL patients undergoing subsequent ASCT.
4) Determine cumulative incidence of infections, relapse, GVHD and non-relapse mortality (NRM) for the above 2 groups
5) Identify predictors of post ASCT relapse and stratify PFS and OS outcomes based on different novel therapies used to treat them

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.

While remission rates with different upfront induction therapies have been relatively high for decades, industry sponsored, and some cooperative group trials have largely focused on eradicating upfront MRD to see if that translates to survival advantage to prolong CR1. FDA approval of newer therapies in r/r setting has been a breakthrough for the field of ALL. Whether this advancement has led to more patients accessing transplant or not in real world is not known. Further, if the quality of remissions achieved with the novel agents used for salvage is high, whether it results in superior post ASCT PFS and OS is subject to investigation. Arguably, majority of these novel agents are not curative, for whom ASCT retains curative promise. Data from this study evaluating r/r ALL outcomes may offer compelling evidence to position ASCT (CR1 and CR2) in a strategic position moving forward while we work to reduce toxicities and NRM associated with it. It also offers unique opportunity to study the prognostic role of MRD in r/r setting in the context of ASCT and in better understanding of progress made in management of post ASCT relapse with the application of newer agents.

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.

In management of acute lymphoblastic leukemias (ALL), despite high initial remission rate (up to 80%-90%), relapses are frequent. A few decades ago LALA-87, LALA-94 and MRC-ECOG trials had shown the utility of transplanting in first complete remission (CR1) for several risk groups. For those with relapse/refractory disease outcomes were generally poor, with second remission rate of 18%-44%
achieved with salvage chemotherapy. Unfortunately, these remissions were not long lasting with a medial overall survival of about 2-6 months. However, if the patient had a suitable donor availability and achieved second CR (CR2), the 5-year OS was 33% in LALA study1. This was confirmed again in the MRC/ECOG 2993 study where the 5 year OS was 23%, 16% and 4% for patients receiving matched sibling, matched unrelated donor alloHCT and chemotherapy respectively2,3. A MD Anderson study reported 1- and 2-year OS of 17% and 10% respectively for those who relapse after ASCT despite getting different salvage options including a second ASCT4. Collectively, these results allude to the point that prolonging CR1(irrespective of the consolidation) is our best approach to cure ALL as outcomes for r/r ALL were generally dismal.
Recent arrival of CD 19 and CD 22 targeting antibody and antibody drug conjugates have modified the landscape of r/r ALL management as has been expertly reviewed before5. Briefly, in the Tower trial, remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard of care (SOC) group, both with respect to CR (34% vs. 16%, P<0.001) and with respect to CR with full, partial, or incomplete hematologic recovery (Cri- 44% vs. 25%, P<0.001). Median OS was 7.7 m vs 4.0 months in favor of blinatumomab. Grade 3 or higher adverse events were 87% and 92% in blina and SOC arms respectively. (28249141). Similarly, for Inotuzumab, CR rates were higher (80.7% vs 29.4%) with an improved median survival (7.7 m vs 6.7 m) compared to SOC (27292104). Seventeen patients in Inotuzumab arm had grade 5 adverse events. On a positive note the depth of remissions obtained with these novel drugs (MRD negative blina- 76% in Tower and 78.4% in Ino trial) is quite significant for patients that reach CR. In the pivotal Blina and Ino registration trials mentioned above many patients did not get to transplant or rather there was only a small representation of ASCT 6. Jabbour et al reporting from TOWER study disputes the benefit of ASCT after Blina exposure for those that achieve CR7. In contrast, investigators from city of hope make a compelling case to pursue ASCT after blina exposure to prolong remissions8. Despite high CR rates, veno-occlusive disease (VOD) toxicity concerns with inotuzumab is omnipresent, but certain adjustments are recommended to minimize this event9. With the approval of CD-19 CAR-T, initially, for those < 25 years (ELIANA) and more recently for adults (Zuma-3), we now have a viable cellular approach to be used as salvage therapy for r/r ALL. Like CD19 and CD 22 targeting drugs, MRD negativity rates are higher with CAR-T (97% in ZUMA-3) for those that regain remission. Further, 100% of patients > 65 years of age with R/R ALL reached CR in ZUMA-3, a feat that has been difficult to achieve in this vulnerable population. Unfortunately, 95% of patients in Zuma- 3 and 88% in ELINA trial had ^{3} grade 3 advers events. While there was initial optimism that post CAR-T ASCT consolidation may not be necessary, few recent long term studies have highlighted its need for prolonging remissions in both kids and adults (33764809) (33851211). Collectively, these studies have offered increased avenue for r/r ALL patients to pursue ASCT in modern era, while there are many unanswered questions that can possibly only be explained by reviewing real world data.

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.

Patients with r/r B-ALL patients undergoing first allografting between 2011- 2021 recieveing novel agents (ino, blina and CAR-T) an for conventional chemotherapy as a bridge an din management of post allo-transplant relapse

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.

Pre-Transplant: Time from diagnosis to transplant, number of lines of induction/consolidation therapy used before alloSCT, HCTCI comorbidity index, disease status pre-transplant. Washout period from ino/blina pre-transplant.
Post transplant: Time to relapse, Maintenance post-transplant (Y/N), DLI-Y/N, Number of lines of therapy. If available drugs used, second transplant-Y/N, Date of last follow up for survival, VOD,
Disease specific- Best response, MRD (FLOW, FISH, cytogenetics, sequencing based) data, if molecular data available we will use it.
Donor: HLA matching level (matched vs mismatched- related/unrelated), Donor-recipient CMV/ABO matching status
Recipient: KPS, HCTCI, race, age, CMV, disease type/risk group at time of transplant and CAR_T
Graft: peripheral blood or bone marrow with no ex-vivo T cell depletion.
Therapy: Conditioning regimens (Intensity- MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-alloSCT therapy to prevent relapse(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials)
Disease related: Best response pre-transplant. Rates of grade ¾ aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death.
CAR-T data. Timing of CAR-T use pre and post ASCT, best response to CAR-T, median duration of remission, Time to relapse

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

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.**

No

Q26. **REFERENCES:**

PMID: 28249141PMID: 27292104,PMID: 34097852

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 allo-HCT for relapsed/refractory B-cell ALL in 2011-2020, CRF track

Characteristic	Novel N (%)	Standard N (%)
No. of patients	289	751
No. of centers	105	164
Age at HCT, years		
Median (range)	29 (0-75)	18 (1-76)
<10	50 (17)	216 (29)
10-17	29 (10)	153 (20)
18-29	71 (25)	154 (21)
30-39	37 (13)	68 (9)
40-49	39 (13)	66 (9)
50-59	26 (9)	51 (7)
60-69	27 (9)	39 (5)
≥70	10 (3)	4 (1)
Recipient sex		
Male	161 (56)	443 (59)
Female	128 (44)	308 (41)
Karnofsky score		
<90	103 (36)	205 (27)
≥90	182 (63)	533 (71)
Missing	4 (1)	13 (2)
HCT-CI		
0	75 (26)	290 (39)
1	56 (19)	138 (18)
2	35 (12)	80 (11)
3+	120 (42)	207 (28)
Missing	3 (1)	36 (5)
Disease status at time of HCT		
PIF	8 (3)	58 (8)
CR2	194 (67)	535 (71)
≥CR3	67 (23)	108 (14)
Relapse	20 (7)	50 (7)
Donor type		
HLA-identical sibling	52 (18)	111 (15)
Other related	86 (30)	161 (21)
Well-matched unrelated (8/8)	60 (21)	143 (19)
Partially-matched unrelated (7/8)	15 (5)	56 (7)
Mis-matched unrelated (<= 6/8)	1 (<1)	2 (<1)
Multi-donor	2 (1)	0 (0)
Unrelated (matching TBD)	14 (5)	8 (1)
Cord blood	59 (20)	270 (36)
Graft type		
Bone marrow	81 (28)	212 (28)
Peripheral blood	149 (52)	269 (36)
Cord blood	59 (20)	270 (36)
Conditioning regimen intensity		
MAC	192 (66)	635 (85)
RIC	51 (18)	70 (9)
NMA	31 (11)	34 (5)

Characteristic	Novel N (%)	Standard N (%)
TBD	4 (1)	10 (1)
Missing	11 (4)	2 (<1)
GVHD prophylaxis		
Ex-vivo T-cell depletion	12 (4)	16 (2)
CD34 selection	8 (3)	21 (3)
Post-CY + other(s)	80 (28)	130 (17)
Post-CY alone	4 (1)	5 (1)
TAC + MMF +- other(s) (except post-CY)	39 (13)	116 (15)
TAC + MTX +- other(s) (except MMF, post-CY)	65 (22)	172 (23)
TAC + other(s) (except MMF, MTX, post-CY)	4 (1)	16 (2)
TAC alone	3 (1)	9 (1)
CSA + MMF +- other(s) (except post-CY)	32 (11)	144 (19)
CSA + MTX +- other(s) (except MMF, post-CY)	19 (7)	85 (11)
CSA + other(s) (except MMF, MTX, post-CY)	2 (1)	16 (2)
CSA alone	2 (1)	11 (1)
Other(s)	0 (0)	4 (1)
Missing	19 (7)	6 (1)
Year of HCT		
2011	0 (0)	69 (9)
2012	1 (<1)	73 (10)
2013	5 (2)	101 (13)
2014	7 (2)	114 (15)
2015	13 (4)	129 (17)
2016	28 (10)	98 (13)
2017	40 (14)	69 (9)
2018	87 (30)	47 (6)
2019	78 (27)	43 (6)
2020	30 (10)	8 (1)
Median follow-up of survivors (range), months	24 (3-100)	50 (1-120)

Role of Post Remission Consolidation Therapy Prior to Haploidentical Transplantation for Patients with Acute Myeloid Leukemia in First Complete Remission

PRINCIPAL INVESTIGATOR Provide the following information for each investigator:Principal Investigator #1:

First and last name, degree(s): Lohith Gowda
Email address: Lohith.gowda@yale.edu
Institution name: Yale Cancer Center
Academic rank: Assistant Professor

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

Do you identify as an underrepresented/minority?
No

Principal Investigator #2 (If applicable):

First and last name, degree(s): Abu-Sayeef Mirza
Email address: abu-sayeef.mirza@yale.edu
Institution name: Yale Cancer Center
Academic rank: Fellow, Hematology and Oncology

To evaluate the prognostic significance of consolidation therapy for patients with AML in first complete remission (CR1) undergoing first haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-ASCT). As an extension of this we will investigate the number of cycles of consolidation and or delaying transplant after CR would confer disease control advantage with minimal toxicity (i.e. graft versus host disease-GVHD, infections etc;) for both peripheral blood- PB and bone marrow- BM graft separately.

Decreasing post-transplant relapse and non-relapse mortality (NRM) is an area of unmet need for patients with AML undergoing ASCT. The benefit of consolidation chemotherapy for intermediate and adverse risk AML groups prior to HCT is not well defined in prospective studies, especially since the advent of modern HAPLO-HCT. Advances in Haplo-HCT has now expanded donor pool (more than 95% of patients have a choice) and it is relatively easy to prepare the donor early in anticipation for transplant. Repeat chemotherapy prior to transplant while holds promise to deepen response after CR1 and prolong post-allo remissions, runs the risk of making people more fragile, alter microbiome, worsen infectious complications, which collectively could enhance NRM. Arguably, coming into transplant with less hits may make it easier to consider post-transplant pre-emptive maintenance drugs to decrease relapse, opening novel avenues to address unmet need of allo-HCT. It is very unlikely we will ever have a randomized prospective trial to address the question of either

the need for consolidation chemo or the number of cycles needed in modern era with haplo-transplants. CIBMTR being the largest database for consolidation therapy can give unprecedented insights into this important question. Identifying predictors who may or may not benefit from consolidation significantly impacts future practice on how best to address relapse and NRM post ASCT. Some of the ongoing pharmaceutical trials when choosing consolidation still refer to HLA matched graft as the best donor option and data from this will atleast ensure haplo donors are not neglected.

Between 1950- 2000 the need for intensive chemotherapy was widely investigated with 1 or more rounds of 7+3 (cytarabine/daunorubicin) or equivalent induction backbone to get patients with AML into CR1. After that based on the efficacy of HIDAC in favorable risk AML as effective post remission therapy (PRT), multiple groups explored either short bursts of continued high intensity or longer duration of low intensity chemo or hypomethylating agents-based combinations. Unfortunately, for a large portion of intermediate risk and high-risk AML subgroups, chemo consolidation alone was not sufficient to prolong remissions. Toxicities were also substantial with this approach over extended follow up. In such patients the need for reconstituting healthy donor hematopoiesis in the recipient and then exerting immuno-modulatory properties from donor origin T cells to reduce relapse risk, subsequently found favorable space in clinical practice. This technology which we now call ASCT was first tested in late 1950's and since then has made significant progress. However, cytoreduction prior to transplant is a key maneuver with events upstream having a decisive role on post-transplant outcomes.

Amongst many major advances in the field of ASCT, our ability to chose haplo-donors without significant concerns of GVHD or rejection was made possible with the application of post-transplant cyclophosphamide (PTCY) around 2008. As a testament to this important milestone a recent meta-analysis favorably compares haplo-HCT outcomes with other donor choices, that were traditionally favored.

Considering more than 95% of people with a diagnosis of AML will likely have a haplo donor identified at the time of diagnosis, it remains to be seen if it is useful to use consolidative therapies and delay transplant in modern era?. CALGB report that brought HIDAC as consolidation into mainstream was developed when haplo-HCT was not the favored graft source. Tallman et al leveraging CIBMTR dataset has shown chemo consolidation in CR1 for those undergoing HLA matched sibling ASCT did not confer any advantage. This observation needs further validation for haplo-cohorts with PTCY

Our understanding of factors beyond chemotherapy that influences immunology of transplant, and its post-transplant clinical course has grown substantially in modern era. With unbiased newer techniques (microbiome, metabolome, immune reconstitution studies) we are learning that repeat chemo associated injury can significantly alter the trajectory of

clinical outcomes both with induction and consolidation therapies. While this knowledge is of critical importance, majority of drug development action to date has been largely focused in relapsed setting or with induction therapies, with limited attention to consolidation. Collectively, the above data led to our hypothesis and study design.

We propose to include patients with AML in CR1 undergoing first Haplo-HCT between 2013- 2018. Both MAC and RIC/NMA are allowed. Peripheral blood and bone marrow grafts from 1st and 2nd degree donors will be included. Up to 2 rounds of chemotherapy to reach CR 1 is permitted. Radiation or chemo based transplant prep regimens will be included. PTCY based GVHD regimen will be considered as the sole method to decreasing adverse allo-immunity. Our primary aim will be to determine 1 year and 3year PFS based on consolidation variable (0 Vs 1 vs greater or equal to 2 rounds). Our secondary aims would be cumulative incidence of infection (D 30, 100, 180), rejection, relapse, cytokine release syndrome and NRM. OS at 1 and 3 years will also be evaluated. These outcomes will also be stratified based on age, HCTCI and graft source. We will work with CIBMTR statistician for finer details about the methodology and in developing predictive model.

Pre-Transplant: Time from diagnosis to transplant, time from CR to transplant, number of lines and types of induction/consolidation therapy used before ASCT, HCTCI comorbidity index, disease status pre-transplant. MRD- Y/N after induction and prior to all-HCT

Post-transplant: Time to relapse, Maintenance post-transplant (Y/N), DLI-Y/N, Number of lines of therapy for relapse and types (chemo vs targeted agents). If available drugs used, second transplant-Y/N, Date of last follow up for survival. Maintenance- Y/N, Rates of grade 3 or 4 aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death.

Donor: HLA matching level (5/10, 6/10, 7/10), Donor-recipient CMV/ABO matching status

Recipient: age at transplant, KPS, HCTCI, race, age, CMV, disease type/risk group

Graft: peripheral blood or bone marrow with no ex-vivo T cell depletion.

Therapy: Conditioning regimens (Intensity- MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-ASCT therapy to prevent relapse(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials)

Disease related: Best response pre-transplant,.

PMID: 10942365. PMID 31065565 PMID: 15572587

Table 1. Characteristics of patients receiving first allo-HCT for AML in CR1 in 2013-2018 with haploidentical donor, CRF track

Characteristic	No consolidation N (%)	≥ 1 cycles consolidation N (%)
No. of patients	193	275
No. of centers	77	89
Age at HCT, years		
Median (range)	56 (1-81)	53 (1-77)
<10	11 (6)	8 (3)
10-17	6 (3)	5 (2)
18-29	22 (11)	30 (11)
30-39	14 (7)	32 (12)
40-49	21 (11)	45 (16)
50-59	43 (22)	68 (25)
60-69	62 (32)	74 (27)
≥70	14 (7)	13 (5)
Recipient sex		
Male	98 (51)	157 (57)
Female	95 (49)	118 (43)
Karnofsky score		
<90	81 (42)	109 (40)
≥90	110 (57)	163 (59)
Missing	2 (1)	3 (1)
HCT-CI		
0	55 (28)	66 (24)
1	29 (15)	43 (16)
2	29 (15)	37 (13)
3+	74 (38)	120 (44)
Missing	6 (3)	9 (3)
Clinical onset of AML		
De-novo	147 (76)	233 (85)
Transformed from MDS/MPS	35 (18)	25 (9)
Therapy linked	11 (6)	17 (6)
MRD at time of HCT		
Negative	105 (54)	182 (66)
Positive	68 (35)	79 (29)
Missing	20 (10)	14 (5)
Total cycles of induction		
1	110 (57)	215 (78)
2	83 (43)	60 (22)

Characteristic	No consolidation N (%)	≥ 1 cycles consolidation N (%)
Total cycles of consolidation		
0	193 (100)	0 (0)
1	0 (0)	134 (49)
2	0 (0)	86 (31)
3+	0 (0)	55 (20)
Graft type		
Bone marrow	67 (35)	103 (37)
Peripheral blood	126 (65)	172 (63)
Conditioning regimen intensity		
MAC	82 (42)	127 (46)
RIC	22 (11)	42 (15)
NMA	85 (44)	104 (38)
TBD	4 (2)	2 (1)
Year of HCT		
2013	10 (5)	26 (9)
2014	20 (10)	34 (12)
2015	36 (19)	48 (17)
2016	35 (18)	59 (21)
2017	45 (23)	51 (19)
2018	47 (24)	57 (21)
Median follow-up of survivors (range), months	36 (3-99)	37 (3-78)