Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Orlando, FL
Wednesday, February 15, 2023, 1:00 p.m. – 3:00 p.m. (EST)

Co-Chair:	**Partow Kebriaei, MD; M.D. Anderson Cancer Center, Houston, TX; Telephone: 713- 792-8750; E-mail: pkebriae@mdanderson.org**
Co-Chair:	**Mark R. Litzow, MD; Mayo Clinic, Rochester, MN; Telephone: 206-667-4961; E-mail: litzow.mark@mayo.edu**
Co-Chair:	**Christopher Hourigan, MD, DPhil; National Heart Blood and Lung Institute; E-mail: hourigan@nih.gov**
Scientific Director:	**Kristin Page, MD, CIBMTR Statistical Center, Milwaukee, WI; E-mail: kpage@mcw.edu**
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Statistician:	**TBD**

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1. Introduction

a. Minutes from April 2022 meeting (Attachment 1)
b. Introduction of incoming co-chair: Nelli Bejanyan, MD

2. Accrual summary (Attachment 2)

3. Presentations, Published or Submitted papers

a. **LK19-03** Boyiadzis M, Zhang MJ, Chen K, Abdel-Azim H, Abid MB, Aljurf M, Bacher U, Badar T, Badawy SM, Battiwalla M, Bejanyan N, Bhatt VR, Brown VI, Castillo P, Cerny J, Copelan EA, Craddock C, Dholaria B, Perez MAD, Ebens CL, Gale RP, Ganguly S, Gowda L, Grunwald MR, Hashmi S, Hildebrandt GC, Iqbal M, Jamy O, Kharfan-Dabaja MA, Khera N, Lazarus HM, Lin R, Modi D, Nathan S, Nishihori T, Patel SS, Pawarode A, Sharma A, Solh M, Wagner JL, Wang T, Williams KM, Winestone LE, Wirk B, Hourigan CS, Litzow M, Kebriaei P, de Lima M, Page K, Weisdorf DJ. Impact of pre-transplant induction and consolidation cycles on AML allogeneic transplant outcomes: A CIBMTR analysis in 3113 AML patients. ***Leukemia. 2022 Oct 30. doi: 10.1038/s41375-022-01738-3.***
b. **LK19-01** Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm (H Murthy/M Kharfan-Dabaja). ***Submitted.***
c. **LK19-02** Krem MM, Zhang MJ, Chen K, Hildebrandt GC, Maziarz RT, Hourigan CS, Kebriaei P, Litzow MR, Weisdorf DJ, Page K, Saber W. Ph-Positive ALL Patients Who Are Treated with Tyrosine Kinase Inhibitors Have SimilarPost-Transplant Survival As Ph-Negative Patients. ***Poster presentation, Tandem 2023.***

4. Studies in progress (Attachment 3)

a. **LK19-02** Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era (M Krem/R Maziarz) **Manuscript Preparation.**
b. **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) **Data File Preparation.**
c. **LK20-02** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia (P Liu/L Cunningham) **Sample Typing.**
d. **LK20-03** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (H Murthy/M Iqbal/M Kharfan-Dabaja) **Data File Preparation.**
e. **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) **Analysis.**
f. **LK22-01** Impact of pre-allogeneic hematopoietic cell transplantation therapy in acute myeloid leukemia and myelodysplastic syndrome on post-transplant outcomes (N Ali) **Protocol Development.**

5. Future/proposed studies

a. **PROP 2210-04** Prognostic Significance of Measurable Residual Disease for Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplant in Second Complete Remission and Beyond (O Pasvolsky/ P Kebriaei) (Attachment 4)
b. **PROP 2210-10/2210-270** Development of prognostic 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/ B Gyurkocza/ F Michelis) (Attachment 5)
c. **PROP 2210-25** Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation (S Iyer/ Y Chen) (Attachment 6)
d. **PROP 2210-55** Comparative effectiveness study of novel agent consolidation versus allogeneic transplantation for AML in patients ≥ 75 years of age (A Artz/ P Koller) (Attachment 7)
e. **PROP 2210-148/2210-164** Real-world evidence for brexucabtagene autoleucel in the treatment of relapsed/refractory B cell ALL in adults and analysis of factors associated with outcomes (S Manjappa/ E Bezerra/ J Gauthier/ P Kebriaei) (Attachment 8)
f. **PROP 2210-179** The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities (A Law/ T Moya) (Attachment 9)
g. **PROP 2210-191/2210-193** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms (L Williams/ S Mirza/ L Gowda/ C Lai) (Attachment 10)
h. **PROP 2210-218** Prognostic Impact of Cytogenetic and Molecular Risk Classification in AML after Hematopoietic Stem Cell Transplant in Adolescents, and Young Adults (H Lust/ S Chaudhury) (Attachment 11)
i. **PROP 2210-232** Outcomes of allogeneic hematopoietic cell transplantation for relapsed acute myeloid leukemia based on minimal residual disease status: CIBMTR analysis (G Murthy/ W Saber) (Attachment 12)
j. **PROP 2210-297** Outcomes of allogeneic transplant using higher vs. lower dose melphalan (140 mg/m2 vs. 100 mg/m2) reduced-intensity conditioning for elderly patients with acute myeloid leukemia (H Alkhateeb/ C Shultz) (Attachment 13)
k. **PROP 2210-26** Equal access and outcome for transplantation in AML: a 21st-century goal (N El Jurdi/ D Weisdorf) (Attachment 14)

Proposed studies; not accepted for consideration at this time

k. **PROP 2209-06** Effect of Major Residual Disease on Hematopoietic Stem Cell Transplantation: Transplant Outcomes in Patients with Primary Induction Failure
l. **PROP 2209-08** Effects of Cytogenetic Features in TP53 mutated Myeloid Malignancies Post-Allogeneic Transplant
m. **PROP 2209-19** Donor Lymphocyte Infusion versus Second Transplant for Relapsed MDS/AML After Allogeneic Transplant
n. **PROP 2210-13** Chimeric Antigen Receptor (CAR) T-cell Therapy or Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in Measurable Residual Disease – Negative Complete Remission
o. **PROP 2210-14** Maintenance Therapy for Patients with FLT3 Mutated Acute Myeloid Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation
p. **PROP 2210-21** Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Philadelphia -Like Acute Lymphoblastic Leukemia
q. **PROP 2210-31** Does Augmenting Total Body Irradiation with a Cranial or Craniospinal Boost before Stem Cell Transplantation Protect Against Post-Transplant Central Nervous System Relapse in Patients with Acute Lymphoblastic Leukemia?
r. **PROP 2210-32** CD19+CAR-T therapy vs allogeneic HCT for poor-risk B-cell ALL with post-induction MRD positivity
s. **PROP 2210-48** Clinical outcomes in acute leukemia patients with co-existing diagnosis of human immunodeficiency virus (HIV) after allogeneic hematopoietic cell transplantation (Allo-HCT)
t. **PROP 2210-52** Peri-transplant use of novel FLT3 inhibitors for allogeneic stem cell transplant in Flt3 mutated acute myeloid leukaemia- CIBMTR study
u. **PROP 2210-55** Comparative effectiveness study of novel agent consolidation versus allogeneic transplantation for AML in patients ≥ 75 years of age
v. **PROP 2210-68** Low-intensity or chemotherapy-free regimens versus high-intensity regimens prior to allo-HCT for adults with newly diagnosed Ph+ ALL
w. **PROP 2210-81** Outcomes of allogeneic hematopoietic cell transplantation in older patients with acute myeloid leukemia treated with hypomethylating agent and venetoclax
x. **PROP 2210-96** Evaluation of outcomes of Donor lymphocyte Infusions with Hypomethylating agents in prophylaxis or treatment of relapse post Allogeneic Hematopoietic Cell Transplants in Acute Myeloid Leukemia and Myelodysplastic Syndromes
y. **PROP 2210-105** Comparing overall survival and progression free survival of CAR-T alone, allogenic hematopoietic stem cell transplant alone, and CAR-T before allogenic hematopoietic stem cell transplant in patients with relapsed/refractory B-cell leukemia: a retrospective analysis
z. **PROP 2210-126** Machine learning prediction of acute myeloid leukemia (AML) relapse after allogeneic hematopoietic cell transplantation
aa. **PROP 2210-135** Real-world experience of post-allogeneic hematopoietic cell transplantation maintenance in acute myeloid leukemia and transplant outcomes
ab. **PROP 2210-136** Validation of European Leukemia Net Genetic Risk Stratification 2022 for Acute Myeloid Leukemia Patients receiving Allogeneic Hematopoietic Cell Transplantation
ac. **PROP 2210-142** Outcomes of patients with AML/MDS undergoing reduced intensity allogeneic transplantation with clofarabine- versus fludarabine-based regimens
ad. **PROP 2210-146** Impact of minimal residual disease on outcomes of allogeneic hematopoietic cell transplantation for Philadelphia chromosome negative B-cell acute lymphoblastic leukemia.
ae. **PROP 2210-161** Comparison of Post-Transplant Cyclophosphamide -based with conventional GVHD Prophylaxis for TP53 mutated Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients undergoing Allogeneic Hematopoietic Cell Transplant

af. **PROP 2210-176** Comparison of outcomes of allogeneic stem cell transplantation in age matched patients with acute myeloid leukemia and myelodysplastic syndrome after induction with Azacitidine and Venetoclax versus Intensive Chemotherapy
ag. **PROP 2210-185** Allogeneic Stem Cell Transplant (Allo-SCT) Outcomes Based on Intensity of Induction therapy in Adult Patients with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)
ah. **PROP 2210-187** Outcomes of allogeneic hematopoietic stem cell transplantation (allo-SCT) for adult T cell leukemia-lymphoma (ATLL)
ai. **PROP 2210-195** Incidence and Outcomes of Mixed Phenotype Leukemia Patients Receiving Stem Cell Transplantation
aj. **PROP 2210-212** Comparison of transplant outcomes associated with commonly used reduced-intensity conditioning regimens in patients undergoing haploidentical stem cell transplant in acute leukemia
ak. **PROP 2210-215** Clinical Outcomes of Adults with Undergoing Allogeneic Stem Cell Transplant for secondary Acute Lymphoblastic Leukemia
al. **PROP 2210-230** KMT2A rearranged B- cell acute lymphoblastic leukemia post CD19 CAR-T cell therapy – impact of age and allogeneic stem cell transplantation on outcomes
am. **PROP 2210-231** Outcomes of single antigen-mismatched unrelated 7/8 allogeneic stem cell transplantation using posttransplant cyclophosphamide in patients with acute myeloid leukemia and myelodysplastic syndrome with TP 53 mutation versus 8/8 matched unrelated donors
an. **PROP 2210-246** Moving Transplant Conditioning Intensity Definitions into the Future: CIBMTR Validation of the Transplant Conditioning Intensity (TCI) Classification System in Patients with Acute Leukemia and MDS
ao. **PROP 2210-247** Donor lymphocyte infusion vs. second allogeneic hematopoietic cell transplantation for relapse after transplantation for AML/ MDS- a CIBMTR analysis
ap. **PROP 2210-248** Outcomes of patients with B-Cell Acute Lymphoblastic Leukemia (B-ALL) undergoing Allogeneic stem cell transplant (Allo-SCT) receiving novel immunotherapy agents based on measurable residual disease (MRD) and conditioning intensity
aq. **PROP 2210-250** Comparison of transplant outcomes associated with venetoclax-based therapy versus intensive induction therapies in patients with AML undergoing allogeneic stem cell transplant
ar. **PROP 2210-263** Inherited myeloid malignancy and donor cell leukemia
as. **PROP 2210-265** Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Acute Myeloid Leukemia with a Pure Hyperdiploid Karyotype
at. **PROP 2210-279** Defining the Landscape of Allogeneic Stem Cell Transplant in Relapsed Refractory Acute Lymphoblastic Leukemia
au. **PROP 2210-289** Role of Post Remission Consolidation Therapy Prior to Haploidentical Transplantation for Patients with Acute Myeloid Leukemia in First Complete Remission

6. Other business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Salt Lake City, UT
Monday, April 25, 2022, 6:30 AM - 8:15 AM MDT

Co-Chair:	**Partow Kebriaei, MD; M.D. Anderson Cancer Center, Houston, TX; Telephone: 713- 792-8750; E-mail: pkebriae@mdanderson.org**
Co-Chair:	**Mark R. Litzow, MD; Mayo Clinic, Rochester, MN; Telephone: 206-667-4961; E-mail: litzow.mark@mayo.edu**
Co-Chair:	**Christopher Hourigan, MD, Dphil; National Heart Blood and Lung Institute; E-mail: hourigan@nih.gov**
Scientific Director:	**Kristin Page, MD, CIBMTR Statistical Center, Milwaukee, WI; E-mail: kpage@mcw.edu**
Statistical Director:	**Mei-Jie Zhang, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8375; E-mail: meijie@mcw.edu**
Statistician:	**Karen Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0834; E-mail: kachen@mcw.edu**

1. Introduction

Dr. Partow Kebriaei called the meeting to order and introduced the current LKWC leadership members. Dr. Christopher Hourigan discussed the goals, expectations, and limitations of the LKWC and criteria that must be met to be considered for authorship on a manuscript. Details on publicly available datasets on the CIBMTR website were discussed. Dr. Hourigan explained the proposal scoring process and guidelines.

2. Accrual summary

The accrual summary was not presented due to time constraints but was made available to attendees as an attachment.

3. Presentations, published or submitted papers

Details regarding presentations and publications were not presented due to time constraints but were made available to attendees as an attachment.

4. Studies in progress

Details regarding the studies in progress were not presented due to time constraints but were made available to attendees as an attachment.

5. Future/proposed studies

Drs. Kebriaei and Hourigan led this session.

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)

Dr. Sunil Iyer presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes between patients with mutations in IDH1 or IDH2 and patients with wild type IDH1 and IDH2. A total of 2058 patients aged 18 years or older underwent allo-HCT for AML in 2013-2020 and had IDH1 and IDH2 molecular testing completed. In this cohort, 150 had mutated IDH1, 273 had mutated IDH2, 42 had both mutated IDH1 and IDH2, and 1593 had wild type IDH1 and IDH2.

Attendees questioned how patients who received maintenance therapy or those who only test positive for mutation at diagnosis and not after treatment will be handled. A comment was received noting the higher frequency of MRD positivity in the groups with IDH mutations.

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)

Dr. Naveed Ali presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes between AML and MDS patients who received low intensity induction therapies with those who received high intensity induction therapies. A total of 2592 patients aged 18 years or older underwent first allo-HCT for AML in first complete remission in the years 2015-2020, with 2352 receiving high intensity induction and 240 receiving low intensity induction. A total of 246 patients aged 18 years or older underwent first allo-HCT for MDS in complete remission in the years 2015-2020, with 55 receiving high intensity induction and 191 receiving low intensity induction.

A question was raised about how patients who received both low and high intensity induction will be handled. It was suggested to include post-transplant maintenance treatment and TP53 mutation status in the analysis and to consider grouping patients based on characteristics other than induction intensity, as treatment choice is influenced by disease related factors.

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)

Dr. Moneeza Walji presented the proposal. The main objective of the proposed study is to evaluate the influence of pre-transplant factors on post-transplant outcomes of acute leukemia patients and to develop separate risk scores for patients transplanted in complete remission and patients transplanted with relapsed or refractory disease. A total of 5614 patients aged 18 years or older received first allo-HCT for acute leukemia in 2009-2019, with 4606 in complete remission and 1008 with relapsed/refractory disease prior to transplant.

A question was raised about whether MRD positive patients will be grouped with CR patients.

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)

Dr. Yang Liang presented the proposal. The main objective of the proposed study is to perform mutational genetic analysis on pre-transplant blood samples from patients who received HCT for T-cell ALL and to evaluate the impact of these mutations on the incidence of relapse. A total of 1269 patients who underwent first allo-HCT for T-cell ALL in 2000-2020 were identified as having blood samples available through the NMDP biorepository.

Attendee comments included concerns about whether the sample quality will be sufficient for RNA-seq and the possible overlap between this study and existing work done on mutation classifiers for T-cell ALL. Questions were raised about the correlation between mutation topography during diagnosis and immediately before transplant and if early T-cell precursor ALL will be analyzed separately.

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)

Dr. Anmol Baranwal presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes of AML patients who received haploidentical HCT with fludarabine, melphalan and TBI (Flu/Mel/TBI) to those of patients who received fludarabine, cyclophosphamide and TBI (Flu/Cy/TBI) conditioning. A total of 1423 patients aged 18 years or older underwent first allo-HCT from a haploidentical donor for AML in 2008-2020, with 208 receiving 208 Flu/Mel/TBI and 1423 receiving Flu/Cy/TBI.

Several suggestions were made including adding Flu/Mel/Thio as a third group, stratifying the study population by melphalan dose, and adding TBI dose as an analysis variable. A concern was raised regarding the increase in post-transplant cyclophosphamide use in the last few years and whether this would bias the results.

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)

Dr. Guru Murthy presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes for relapsed AML patients based on MRD status. A total of 1842 patients aged 18 years or older underwent first allo-HCT for AML in second or greater complete remission in 2008-2019, with 1186 testing MRD negative, 473 testing MRD positive, and 183 with unknown status prior to HCT.

Attendees suggested including data on the MRD testing methods used and adding time from diagnosis to achieving CR2 and time between CR2 and transplant as variables in the analysis.

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)

Dr. Lacey Williams presented the proposal. The main objective of the proposed study is to evaluate outcomes for AML and MDS patients after allo-HCT in the modern era and characterize molecular and cytogenetic mutations in relapsed patients. 2184 patients received first allo-HCT for AML and 2155 patients received first allo-HCT for MDS in 2011-2020 who relapsed after transplant.

A question was asked about the availability of post-transplant maintenance therapy date and dosing data. A comment was made that there may be multiple mechanisms aside from clonal evolution that lead to relapse.

h. **PROP 2110-298:** Impact of Pre-Transplant Extramedullary Disease on Allogeneic Transplant Outcomes in Acute Lymphoblastic Leukemia (ALL) (R Ramlal)

Dr. Reshma Ramlal presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes between ALL patients with and without extramedullary disease (EMD) prior to transplant. A total of 2312 patients aged 18 years or older underwent first allo-HCT for ALL in 2008-2018, including 387 with extramedullary disease and 1925 without extramedullary disease before transplant.

Attendees asked questions about availability of treatment data for EMD and documentation of remission status for patient with non-CNS EMD. It was suggested to analyze patients with CNS and non-CNS EMD separately.

i. **PROP 2110-323:** Allogeneic transplant for Relapsed Refractory ALL in Modern Era (L Gowda/A Zeidan)

Dr. Lohith Gowda presented the proposal. The main objective of the proposed study is to compare post-transplant outcomes of relapsed or refractory B-cell ALL patients who received novel therapies with those who received conventional chemotherapy. A total of 1040 patients underwent first allo-HCT for relapsed or refractory B-cell ALL in 2011-2020, with 289 receiving novel therapies and 751 receiving standard therapies.

Comments were received on appropriately accounting for a patient who received multiple therapies and limitations in available data on treatments used before transplant.

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)

Dr. Sayeef Mirza presented the proposal. The main objective of the proposed study is to evaluate the impact of the number of consolidation cycles on post-transplant outcomes of AML patients transplanted in first complete remission. A total of 468 patients underwent first allo-HCT from a haploidentical donor for AML in first complete remission in 2013-2018, with 193 receiving no consolidation and 275 receiving one or more cycles of consolidation prior to transplant.

Attendees suggested including time from diagnosis to transplant for patients who did not receive consolidation therapy and MRD status in the analysis. A comment was made that donor availability may be a confounding factor since more cycles of consolidation may be given to patients with difficulty finding donors.

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

After the proposals were presented, meeting participants had the opportunity to rate each proposal via the Tandem mobile app. Based on the voting results, current scientific merit, available number of relevant cases, and the impact of the study on the field, the following study will move forward in the committee's research portfolio for the upcoming year:

- **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

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm	Manuscript Preparation	1
LK19-02: Evolving significance of Philadelphia chromosome status on acute lymphoblastic leukemia prognosis in the TKI era	Manuscript Preparation	1
LK19-03: Outcomes of allogeneic transplants in acute myeloid leukemia patients who achieved first complete remission after two or more cycles of induction chemotherapy	Submitted	1
LK20-01: Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation	Data File Preparation	2
LK20-02: Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia	Data File Preparation	3
LK20-03: Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia	Protocol Development	2
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	Analysis	1
LK22-01: Intensive induction chemotherapy vs. hypomethylating agent therapy for older AML patients undergoing allogeneic hematopoietic cell transplantation	Protocol Pending	2

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 2022

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Number of patients	12360	4870
Number of centers	282	249
Age at transplant, years		
Median (range)	52 (0-88)	30 (0-79)
<10	811 (7)	867 (18)
10-17	777 (6)	772 (16)
18-29	992 (8)	826 (17)
30-39	1178 (10)	641 (13)
40-49	1796 (15)	671 (14)
50-59	2824 (23)	602 (12)
60-69	3192 (26)	449 (9)
>=70	790 (6)	42 (1)
Recipient sex		
Male	6659 (54)	2866 (59)
Female	5701 (46)	2004 (41)
HCT-CI		
0	3201 (26)	1772 (36)
1	1814 (15)	744 (15)
2	1604 (13)	607 (12)
3+	5068 (41)	1480 (30)
Missing	673 (5)	267 (5)
Disease status at time of HCT		
PIF	1458 (12)	129 (3)
CR1	7485 (61)	2773 (57)
CR2	2317 (19)	1422 (29)
>=CR3	170 (1)	328 (7)
Relapse	928 (8)	215 (4)
Missing	2 (<1)	3 (<1)
Time from diagnosis to HCT		
Median (range)	5 (0-352)	8 (1-499)
<6 months	6900 (56)	1647 (34)
6 - 12 months	2807 (23)	1323 (27)
>12 months	2650 (21)	1891 (39)

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Missing	3 (<1)	9 (<1)
Conditioning regimen intensity		
Myeloablative	7117 (58)	3746 (77)
Reduced intensity	2937 (24)	542 (11)
Non-myeloablative	1407 (11)	338 (7)
Missing	899 (7)	244 (5)
Graft type		
Bone marrow	2014 (16)	1037 (21)
Peripheral blood	8083 (65)	2469 (51)
Umbilical cord blood	2241 (18)	1347 (28)
Missing	22 (<1)	17 (<1)
Type of donor		
HLA-identical sibling	2607 (21)	969 (20)
Identical twin	36 (<1)	25 (1)
Other relative	1988 (16)	859 (18)
Unrelated	5478 (44)	1669 (34)
Cord blood	2241 (18)	1347 (28)
Missing	10 (<1)	1 (<1)
Year of HCT		
2008-2009	2544 (21)	931 (19)
2010-2011	1418 (11)	486 (10)
2012-2013	1471 (12)	560 (11)
2014-2015	2425 (20)	960 (20)
2016-2017	1939 (16)	833 (17)
2018-2019	1415 (11)	728 (15)
2020-2022	1148 (9)	372 (8)
Median follow-up of survivors (range), months	71 (1-172)	63 (1-175)

[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 2022

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)
2020-2022	0 (0)	0 (0)
Median follow-up of survivors (range), months	89 (2-171)	79 (25-96)

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

CIBMTR®
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

LK19-02: 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.

The manuscript is currently in progress. The plan is to finalize the manuscript and submit for publication by July 2023.

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.

Data file preparation is currently in progress. The plan is to finalize the data file and complete the analysis by July 2023.

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 2023.

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.

Data file preparation is currently in progress. The plan is to finalize the data file and begin analysis by July 2023.

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.

Analysis is currently in progress. The plan is to finalize the analysis and have a draft manuscript prepared by July 2023.

LK22-01: Impact of pre-allogeneic hematopoietic cell transplantation therapy in acute myeloid leukemia and myelodysplastic syndrome on post-transplant outcomes (Ali N)
The purpose of this study is to:

(1) Compare clinical outcomes of patients with AML and MDS undergoing alloHCT in first complete remission and receiving low intensity vs. high intensity induction therapies.
(2) Compare clinical outcomes of patients with MDS with <5% BM blasts or MDS-EB1 with 5-9% BM blasts undergoing Allo-HCT with low intensity/HMA vs. no pre-HCT therapy.

Protocol development is currently in progress. The plan is to finalize the protocol and study population by July 2023.

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

Prognostic Significance of Measurable Residual Disease for Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplant in Second Complete Remission and Beyond

Q2. Key Words

acute lymphoblastic leukemia; measurable residual disease; allogeneic; hematopoietic stem cell transplant.

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Oren Pasvolsky, MD
Email address:	opasvolsky@mdanderson.org
Institution name:	The University of Texas M.D. Anderson Cancer Center
Academic rank:	Assistant 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):	Partow Kebriaei, MD
Email address:	pkebriae@mdanderson.org
Institution name:	The University of Texas M.D. Anderson Cancer Center
Academic rank:	Professor

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Oren Pasvolsky

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.

Dr. Kebriaei is a collaborator on 2 cell therapy proposals: CT20-04 and CT20-03.

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:

What is the predictive impact of pre-transplant measurable residual disease (MRD) for patients with acute lymphoblastic leukemia (ALL) receiving allogeneic hematopoietic stem cell transplant (alloHCT) in second complete remission (CR2) or beyond?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that pre-transplant MRD status is predictive of outcomes for patients with ALL receiving alloHCT in CR2. The predictive yield might be reduced in patients transplanted in CR3 or beyond, due to early progression.

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

Suggested word limit of 200 words:

Aims:

• To compare outcomes of patients with ALL receiving their first alloHCT in CR2 or beyond, between those with pre-transplant MRD negative and MRD positive disease status.

• To examine whether the prognostic yield of pre-transplant MRD is similar for patients receiving alloHCT at CR2 or at a later CR.

Outcomes:

• Primary outcome will be progression free survival (PFS).

• Secondary outcomes will include overall survival (OS), progression rate, non-relapse mortality (NRM).

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.

Data from this proposed study will shed light on the predictive value of MRD in patients with ALL undergoing alloHCT at CR2 or beyond. In recent years novel therapeutic options have become available for patients with relapsed/refractory (R/R) ALL, including blinatumomab [1], inotuzumab ozogamicin [2] and anti-CD19 CAR T cells [3], capable of inducing deep molecular responses. Results of this study will enable more informative decisions whether maximizing efforts to reach MRD negativity are beneficial at later remissions, before proceeding with alloHCT.

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 a growing number of patients with ALL, alloHCT is deferred at CR1, with hope that adequate response to salvage treatment and subsequent transplantation would be possible at a later remission, if necessary. However, in reality, achieving and maintaining a second complete remission with subsequent consolidation with transplant is challenging [4]. Still, for patients who do achieve a second CR after relapse, alloSCT offers a chance at cure [5].

MRD status has proven to be a strong predictor of outcomes in ALL patients, both early after induction chemotherapy [5], as well as later during the consolidation phase [6]. For patients with ALL, MRD positivity prior to transplant at CR1 has been shown to correlate with post-transplant relapse rates and overall survival [7, 8].

It is unclear whether pre-transplant MRD assessment is also prognostic in the setting of alloHCT beyond CR1. A small single center report showed similar 3-year OS and event free survival (EFS) for patients who underwent alloHCT in MRD negative CR1 (n=50) compared to MRD negative CR2 (n=20) [9]. A Japanese registry study of 1625 patients with Philadelphia positive ALL evaluated the prognostic effect of MRD status prior to alloHCT both at CR1 and CR2 [10]. Among the 102 patients transplanted in CR2, MRD positivity prior to transplant was associated with inferior 4-year overall and leukemia free survival, compared to patients with negative MRD (51% and 49% vs. 38% and 29%, respectively). Amongst patients who underwent alloHCT in CR2, 38% (n=39) received an umbilical cord blood (UCB) graft and none received a haploidentical graft. Approximately half of patients in the CR2 group received MAC conditioning regimens, mostly TBI-based and graft versus host disease (GVHD) prophylaxis was mostly tacrolimus- or cysclosporin A-based.

We recently conducted a single center retrospective analysis at MD Anderson Cancer Center, that showed that pre-transplant MRD positivity is predictive of disease relapse in patients undergoing alloHCT for ALL in CR2 or beyond. Our data suggests that the survival advantage associated with MRD negativity was perhaps limited to patients undergoing alloHCT in CR2, yet the small number of patients hindered definitive conclusions [11]. Therefore, the prognostic significance of MRD status prior to alloHCT for Philadelphia positive and negative ALL in CR2 and beyond requires further clarification with a large dataset of patients.

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
• Pediatric and adult patients (all ages)
• Underwent first alloHCT due to ALL at CR2 or beyond
• Available MRD status data prior to transplant
• Transplanted from 01/01/2000 to 12/01/2021
Exclusion criteria
• Missing MRD data prior to transplant
• Previous alloHCT

Q21. Does this study include pediatric patients?

- Yes

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

• Patient characteristics: age; sex; race; karnofsky performance status; HCT-CI score.
• Disease characteristics: 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; MRD status prior to transplant;
• Transplant characteristics: Conditioning regimen: MAC vs. RIC/NMA; Total body irradiation (TBI) versus non-TBI; Graft type: Graft source - bone marrow/peripheral blood/cord blood; Donor type – matched related/matched unrelated/haploidentical/mismatched unrelated/cord blood; GVHD prophylaxis.
• GVHD: Acute GVHD + grade; Chronic GvHD + grade.
• Follow up data: maintenance therapy after alloHCT (yes/no and type); relapse yes/no; date of relapse; sites of involvement at relapse; disease state at time of evaluation; dead/alive at time of evaluation; date of death; cause of death.

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. Kantarjian, H., et al., Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med, 2017. 376(9): p. 836-847.
2. Kantarjian, H.M., et al., Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med, 2016. 375(8): p. 740-53.
3. Shah, B.D., et al., KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet, 2021. 398(10299): p. 491-502.
4. Forman, S.J. and J.M. Rowe, The myth of the second remission of acute leukemia in the adult. Blood, 2013. 121(7): p. 1077-82.
5. Gokbuget, N., et al., Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood, 2012. 120(9): p. 1868-76.
6. Bruggemann, M., et al., Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood, 2006. 107(3): p. 1116-23.
7. Bassan, R., et al., Different molecular levels of post-induction minimal residual disease may predict hematopoietic stem cell transplantation outcome in adult Philadelphia-negative acute lymphoblastic leukemia. Blood Cancer J, 2014. 4: p. e225.
8. Pavlu, J., et al., Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. J Hematol Oncol, 2019. 12(1): p. 108.
9. Cassaday, R.D., et al., Evaluation of allogeneic transplantation in first or later minimal residual disease - negative remission following adult-inspired therapy for acute lymphoblastic leukemia. Leuk Lymphoma, 2016. 57(9): p. 2109-18.
10. Nishiwaki, S., et al., Measurable residual disease affects allogeneic hematopoietic cell transplantation in Ph+ ALL during both CR1 and CR2. Blood Adv, 2021. 5(2): p. 584-592.
11. Pasvolsky O, Saliba R, Ledesma C, Popat U.R, Alousi A, Olson A, Oran B, Hosing C, Bashir Q, Qazilbash M.H, Short N, Ravandi F, Champlin R, Shpall E.J, Kebriaei P, Prognostic Significance of Measurable Residual Disease for Patients with Acute Lymphoblastic Leukemia Undergoing Allogeneic Stem Cell Transplant in Second Complete Remission and Beyond. 2022: Submitted, American Society of Hematology 2022 Annual Meeting

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

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

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

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

Partow Kebriaei: Clinical trial support Alaunos; Consultancy: Jazz, Kite, Pfizer

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

Characteristics of patients receiving first allo-HCT for ALL in CR2+ in 2013-2019

Characteristic	Negative	Positive	Unknown MRD status
No. of patients	2256	830	324
No. of centers	256	211	133
Age at HCT			
Median (min-max)	19 (1-79)	24 (1-77)	21 (3-67)
<10	551 (24)	176 (21)	60 (19)
10-17	509 (23)	129 (16)	60 (19)
18-29	565 (25)	186 (22)	101 (31)
30-39	213 (9)	97 (12)	44 (14)
40-49	160 (7)	90 (11)	30 (9)
50-59	141 (6)	82 (10)	19 (6)
60-69	99 (4)	59 (7)	10 (3)
>=70	18 (1)	11 (1)	0 (0)
Reporting track			
TED	1648 (73)	584 (70)	273 (84)
CRF	608 (27)	246 (30)	51 (16)
Recipient sex			
Male	1400 (62)	493 (59)	211 (65)
Female	856 (38)	337 (41)	113 (35)
Karnofsky score			
<90	599 (27)	243 (29)	77 (24)
>=90	1617 (72)	576 (69)	239 (74)
Missing	40 (2)	11 (1)	8 (2)
HCT-CI			
0	939 (42)	315 (38)	170 (52)
1	364 (16)	122 (15)	43 (13)
2	282 (13)	90 (11)	23 (7)
3	309 (14)	121 (15)	34 (10)
4	172 (8)	94 (11)	27 (8)
5	80 (4)	37 (4)	6 (2)
6+	81 (4)	37 (4)	3 (1)
Missing	29 (1)	14 (2)	18 (6)
Disease status at time of HCT			
CR2	1875 (83)	691 (83)	264 (81)
>=CR3	381 (17)	139 (17)	60 (19)
Received prior CART			

Characteristic	Negative	Positive	Unknown MRD status
No	2185 (97)	824 (99)	323 (100)
Yes	71 (3)	6 (1)	1 (0)
Immunophenotype (ALL)			
T-cell	361 (16)	98 (12)	61 (19)
B-cell	1839 (82)	718 (87)	251 (77)
Unspecified	56 (2)	14 (2)	12 (4)
MRD detection method			
Cytogenetic testing only	157 (7)	10 (1)	0 (0)
Molecular marker testing only	38 (2)	53 (6)	0 (0)
Flow cytometry only	1055 (47)	145 (17)	0 (0)
Cytogenetic, molecular	86 (4)	69 (8)	0 (0)
Cytogenetic, flow cytometry	257 (11)	37 (4)	0 (0)
Molecular, flow cytometry	375 (17)	220 (27)	0 (0)
Cytogenetic, molecular, flow cytometry	264 (12)	292 (35)	0 (0)
Missing	24 (1)	4 (0)	324 (100)
Donor type			
HLA-identical sibling	585 (26)	216 (26)	111 (34)
Other related	420 (19)	145 (17)	53 (16)
Well-matched unrelated (8/8)	623 (28)	228 (27)	64 (20)
Partially-matched unrelated (7/8)	212 (9)	71 (9)	30 (9)
Mis-matched unrelated (<= 6/8)	12 (1)	1 (0)	1 (0)
Multi-donor	5 (0)	2 (0)	2 (1)
Unrelated (matching TBD)	96 (4)	40 (5)	38 (12)
Cord blood	303 (13)	127 (15)	25 (8)
Graft type			
Bone marrow	909 (40)	277 (33)	104 (32)
Peripheral blood	1044 (46)	426 (51)	195 (60)
Cord blood	303 (13)	127 (15)	25 (8)
Conditioning intensity			
MAC	1904 (84)	640 (77)	275 (85)
RIC	195 (9)	119 (14)	26 (8)
NMA	106 (5)	42 (5)	10 (3)
TBD	48 (2)	27 (3)	11 (3)
Missing	3 (0)	2 (0)	2 (1)
GVHD prophylaxis			
Ex-vivo T-cell depletion	60 (3)	10 (1)	8 (2)
CD34 selection	50 (2)	18 (2)	5 (2)

Characteristic	Negative	Positive	Unknown MRD status
Post-CY	399 (18)	160 (19)	47 (15)
TAC based	929 (41)	325 (39)	102 (31)
CSA based	763 (34)	300 (36)	153 (47)
Other	27 (1)	10 (1)	4 (1)
Missing	28 (1)	7 (1)	5 (2)
Year of HCT			
2013	253 (11)	90 (11)	94 (29)
2014	274 (12)	124 (15)	45 (14)
2015	286 (13)	151 (18)	34 (10)
2016	281 (12)	153 (18)	28 (9)
2017	362 (16)	126 (15)	47 (15)
2018	384 (17)	86 (10)	44 (14)
2019	416 (18)	100 (12)	32 (10)
Median follow-up of survivors (range), months	36 (0-99)	47 (0-97)	37 (0-99)

CIBMTR Study Proposal for ALWC:

Study Title:

Development of prognostic 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

Principal Investigator Information:

Igor Novitzky-Basso, MD PhD:	Assistant Professor/Clinician Investigator Princess Margaret Cancer Centre, Toronto, Canada igor.novitzkybasso@uhn.ca
Moneeza Walji, MD MPH:	Adult Bone Marrow Transplant Fellow, MSKCC waljim@mskcc.org
Boglarka Gyurkocza, MD:	Assistant Professor, MSKCC gyurkocb@mskcc.org
Fotios V. Michelis, MD PhD:	Assistant Professor/Clinician Investigator Princess Margaret Cancer Centre, Toronto, Canada Fotios.Michelis@uhn.ca

Research Question:

Various 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. However, 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), and do not reflect these recent developments 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 with 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, the 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 predictions, which is 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 have become outdated, and a more refined tool is warranted.

Scientific Justification:

The most common indication for allogeneic HCT is AML (1), with curative potential for high-risk patients (2). Moreover, selected patients with ALL also benefit from allogeneic HCT (3). 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. Thus, comorbidity evaluation is considered an integral component of pre-transplant workup and to determine non-relapse mortality (NRM) and overall survival (OS) risks (4).

Other pre-transplant risk scores in use include the Pretransplant Assessment of Mortality (PAM) Score (5), 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 (6). In contrast, the Disease Risk Index (DRI) developed by Armand and colleagues (7) 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 (8).

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 (9). 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 (10). CMV seropositivity has also been shown to be a predictor of improved overall survival for primary refractory AML patients undergoing unrelated donor transplants (11). With significant improvements in standard of care and updated therapies available to relapsed/refractory patients, we hypothesize that the Duval score is now outdated for this patient population.

Several pre-allogeneic transplant risk scores have been developed specifically for AML and ALL but are based on single center data with limited numbers of patients, and some 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 partly explain the significant discrepancies in studies that apply these scores to AML and ALL specifically. Further, disease diagnostics and monitoring have advanced significantly, with prospective randomized studies demonstrating the validity of measurable residual disease monitoring as a pre- and post-transplant relapse predictor(12, 13). 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 the 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.

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)(14)(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) (7)
- MRD positivity (flow) > 0.1%
- MRD positivity qPCR

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 (5)
- HCT-CI/age index (15)
- Modified EBMT score (16)

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.

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

Characteristic	CR	R/R
No. of patients	4608	1008
No. of centers	194	124
Age at HCT		
Median (min-max)	52 (18-80)	54 (18-82)
18-29	650 (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	2102 (46)	440 (44)
Disease status at time of HCT		
PIF	0 (0)	651 (65)
CR1	3614 (78)	0 (0)
CR2	931 (20)	0 (0)
>=CR3	63 (1)	0 (0)
Relapse	0 (0)	357 (35)
Karnofsky score		
<90	1733 (38)	529 (52)
>=90	2828 (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+	1971 (43)	522 (52)
Missing	179 (4)	45 (4)
MRD at time of HCT		
Negative	2919 (63)	0 (0)
Positive	1346 (29)	0 (0)
Disease status not in CR	0 (0)	999 (99)
Missing	343 (7)	9 (1)
Donor type		

Characteristic	CR	R/R
HLA-identical sibling	2027 (44)	371 (37)
Well-matched unrelated (8/8)	2581 (56)	637 (63)
Graft type		
Bone marrow	682 (15)	138 (14)
Peripheral blood	3926 (85)	870 (86)
Conditioning regimen intensity		
MAC	2877 (62)	666 (66)
RIC	1403 (30)	273 (27)
NMA	201 (4)	35 (3)
TBD	57 (1)	20 (2)
Missing	70 (2)	14 (1)
GVHD prophylaxis		
Post-CY	266 (6)	46 (5)
TAC based	3509 (76)	833 (83)
CSA based	729 (16)	108 (11)
Other	25 (1)	8 (1)
Missing	79 (2)	13 (1)
Year of HCT		
2009	570 (12)	178 (18)
2010	442 (10)	128 (13)
2011	243 (5)	45 (4)
2012	205 (4)	38 (4)
2013	464 (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	72 (3-158)	73 (3-153)

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 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. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Sunil G Iyer
Email address:	siyer087@med.miami.edu
Institution name:	University of Miami
Academic rank:	Fellow, PGY-6

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):	Yi-Bin Chen
Email address:	ychen6@partners.org
Institution name:	Massachusetts General Hospital
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:

Sunil G Iyer

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.

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

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

- No

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 (mutIDH1/2) acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplantation (HCT) versus AML patients with wild- type IDH1 and IDH2 (wtIDH1/2) undergoing HCT?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that there will be no difference in rates of DFS, OS, and relapse between mutIDH1/2 AML patients undergoing HCT versus wtIDH1/2AML patients undergoing HCT.

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

Suggested word limit of 200 words:

- Primary Objective. To identify differences in the following post-transplant outcomes between mutIDH1, mutIDH2 and wtIDH1/2patients:
o Overall survival (OS)
o Disease free survival (DFS)
o Cumulative incidence of relapse
- Secondary Objectives. To describe the following prognostic factors associated with post-transplant outcomes in patients with mutIDH1/2 AML
o CR1 vs. >CR2
o Pre-transplant measurable residual disease (MRD positive vs. negative)
o Conditioning intensity (reduced intensity/non-myeloablative vs. myeloablative)
o Mutation isoform (IDH1 vs. IDH2)
o Concurrent mutations (FLT3-ITD, NPM1, DNMT3A)

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.

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), with data regarding the use of enasidenib maintenance in this setting published this year;[10] 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 2021. 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 is an active area of investigation with new and evolving data reported since our prior submission. 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 mutIDH1/2 patients (relative to wtIDH1/2 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: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.

To our knowledge, only two peer-reviewed publications have described survival outcomes of IDH1/2-mutated (mutIDH1/2) AML patients following hematopoietic cell transplant (HCT). The first involved a small cohort of 23 patients.[11] 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.[12] 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 mutIDH1 patients and 58% for mutIDH2 patients. The two-year cumulative incidence of relapse was 31% and 25% for mutIDH1 and mutIDH2 patients, respectively. The study involved the largest cohort of mutIDH1/2 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 mutIDH1/2 AML patients.

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:
- Age ≥18 years with diagnosis of AML
- Underwent first allogeneic HCT between 2010 and 2021
- 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).[13

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 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 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:

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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 adult patients receiving first allo-HCT for AML in 2013-2020, CRF track

Characteristic	IDH1 only	IDH2 only	Both	WT	Unknown IDH1/IDH2
No. of patients	150	273	42	1593	3971
No. of centers	62	74	28	131	192
Age at HCT					
Median (min-max)	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)	424 (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)	1230 (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)	1809 (46)
Disease status at time of HCT					
PIF	18 (12)	35 (13)	7 (17)	214 (13)	489 (12)
CR1	97 (65)	198 (73)	28 (67)	1065 (67)	2459 (62)
CR2	26 (17)	30 (11)	7 (17)	210 (13)	721 (18)
>=CR3	2 (1)	2 (1)	0 (0)	7 (0)	45 (1)
Relapse	7 (5)	8 (3)	0 (0)	96 (6)	255 (6)
Missing	0 (0)	0 (0)	0 (0)	1 (0)	2 (0)
Karnofsky score					
<90	76 (51)	127 (47)	25 (60)	724 (45)	1617 (41)
>=90	73 (49)	142 (52)	17 (40)	841 (53)	2307 (58)
Missing	1 (1)	4 (1)	0 (0)	28 (2)	47 (1)
HCT-CI					
0	24 (16)	49 (18)	2 (5)	246 (15)	819 (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)	1891 (48)
Missing	1 (1)	3 (1)	0 (0)	32 (2)	131 (3)
FLT3-ITD mutation status (pre-HCT)					
Negative	114 (76)	192 (70)	31 (74)	1179 (74)	1685 (42)
Positive	28 (19)	71 (26)	8 (19)	346 (22)	670 (17)
Missing	8 (5)	10 (4)	3 (7)	68 (4)	1616 (41)
NPM1 mutation status (pre-HCT)					

Characteristic	IDH1 only	IDH2 only	Both	WT	Unknown IDH1/IDH2
Negative	93 (62)	179 (66)	21 (50)	1198 (75)	1365 (34)
Positive	50 (33)	86 (32)	19 (45)	341 (21)	664 (17)
Missing	7 (5)	8 (3)	2 (5)	54 (3)	1942 (49)
MRD at time of HCT					
Negative	47 (31)	90 (33)	12 (29)	696 (44)	1968 (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)	743 (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)
Other related	53 (35)	79 (29)	16 (38)	448 (28)	842 (21)
Well-matched unrelated (8/8)	38 (25)	77 (28)	10 (24)	453 (28)	1318 (33)
Partially-matched unrelated (7/8)	6 (4)	11 (4)	2 (5)	76 (5)	252 (6)
Mis-matched unrelated (<= 6/8)	0 (0)	1 (0)	4 (10)	12 (1)	16 (0)
Multi-donor	0 (0)	0 (0)	0 (0)	6 (0)	11 (0)
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)	550 (14)
Peripheral blood	101 (67)	193 (71)	28 (67)	1071 (67)	2888 (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)	1877 (47)
RIC	46 (31)	100 (37)	11 (26)	529 (33)	1324 (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)	0 (0)	13 (1)	31 (1)
CD34 selection	6 (4)	8 (3)	2 (5)	91 (6)	104 (3)
Post-CY	62 (41)	102 (37)	23 (55)	576 (36)	869 (22)
TAC based	59 (39)	127 (47)	13 (31)	747 (47)	2091 (53)
CSA based	15 (10)	25 (9)	1 (2)	129 (8)	747 (19)
Other	1 (1)	4 (1)	0 (0)	7 (0)	39 (1)
Missing	3 (2)	5 (1)	3 (7)	30 (2)	90 (2)
Year of HCT					
2013	2 (1)	5 (2)	1 (2)	49 (3)	798 (20)

Characteristic	IDH1 only	IDH2 only	Both	WT	Unknown IDH1/IDH2
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)	174 (4)
2020	18 (12)	29 (11)	5 (12)	159 (10)	44 (1)
Median follow-up of survivors (range), months	37 (11-97)	38 (3-97)	47 (17-73)	46 (3-97)	66 (0-113)

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

Comparative effectiveness study of novel agent consolidation versus allogeneic transplantation for AML in patients ≥ 75 years of age

Q2. Key Words

AML, allogeneic HCT, older adults, non-relapse mortality, survival

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Andrew Artz
Email address:	aartz@coh.org
Institution name:	City of Hope
Academic rank:	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):	Paul Koller
Email address:	pkoller@coh.org
Institution name:	City of Hope
Academic rank:	Assistant Professor

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:

Andrew Artz

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

N/A

LETTER OF COMMITMENT:

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

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

None

Q13. PROPOSED WORKING COMMITTEE:

- 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:

Kristin Paige responded to email sent to entire acute leukemia committee

Q15. RESEARCH QUESTION:

Does allogeneic transplantation benefit patients 75 years and older with AML in the era of novel agents?

Q16. RESEARCH HYPOTHESIS:

We hypothesize allogeneic HCT worsens short-term mortality but affords a longer-term survival benefit relative to novel AML therapy in patients 75 years and older

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

Suggested word limit of 200 words:

Primary: To compare survival of patients ≥ 75 years with AML in first remission receiving ongoing hypomethylating therapy with or without venetoclax to patients receiving allogeneic transplantation
Secondary:
Evaluate OS, relapse, leukemia-free survival, and TRM at landmark periods of 1, 2 year and 3 years by treatment modality
Evaluate differences in outcomes by genetic risk stratification
To benchmark outcomes for AML patients 75 years and older

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 for the first-time report on transplant outcomes in patients ≥ 75 years for which the field lacks prospective or comparative data. This study relevance is markedly amplified by novel agent treated non-transplant control: hypomethylating with or without venetoclax treated patients enrolled on a prospective trial. This may also be a new model for transplant observational studies to ensure appropriate controls to contextualize results.
As novel therapies emerge as mainstream for older and unfit patients, the number of patients eligible for transplant has expanded rapidly; but in parallel non-transplant consolidation and maintenance options have proliferated. The findings also partner exceptionally well with BMT CTN 1704 “CHARM” to develop a composite health assessment risk model for non-relapse mortality (NRM) among older adults employing geriatric assessments, comorbidity and biomarkers, which has completed accrual. (clinicaltrials.gov/ct2/show/NCT03992352)

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.

Age and Hematologic Malignancies. Hematologic malignancies are more common and often more fatal in older patients. [1] Table 1 summaries recent disease registry estimates for hematologic malignancies for ≥ 75 years and older with available data.

Table 1. Registry estimates of age at diagnosis

Disease	Proportion ≥ 75 years
AML (seer.cancer.gov)	33.8%
ALL (seer.cancer.gov)	6%
MDS [2]	55.9%
CMML [3]	≈50%

For AML, older age confers worse outcomes due to a variety of factors including adverse disease biology, undertreatment (which may include lack of HCT), and late diagnosis.

New treatment options.

The therapeutic landscape has been reshaped by novel treatment options for hematologic malignancy patients; a higher number of successfully treated AML patients may further promote alloHCT consideration. In a large randomized study of AML patients 60-75 years, CPX-351 bested standard induction therapy for secondary AML, with particularly favorable outcomes among those consolidating responses by alloHCT, particularly in those 70 years and older.[4] Non-cytotoxic novel agents have excited the field as even older and less fit patients may pursue successful induction therapy. In the Viale-A seminal study by DiNardo reported for newly diagnosed AML ≥ 75 years or unfit for standard therapy, impressive composite complete response rates of 66.4% for hypomethylating agent with the BCL-2 inhibitor, venetoclax, compared 28.3% with hypomethylating therapy alone.[5] In fact, 75% of patients were ≥ 75 years. Additional targeted options exist for AML harboring IDH1, IDH2 and FLT-3 mutations both for initial therapy and at relapse.[6] [7] [8] More patients historically excluded from remission induction therapy can now achieve first if not second remission.

Consolidating response

Long-term AML control is infrequent for patients in their eighth decade and even less for those ≥ 75 years. [9] Initial data from the VIALE-A cohort suggest quite promising remission duration after composite complete remission with median duration of 17.5 months and 13.4 months in the azacitidine-venetoclax versus azacitidine alone study arms. Additional data suggest some older AML patients in remission after one year of venetoclax therapy may have prolonged treatment free remission after treatment discontinuation. [10]

HCT in Older Age. As a procedure with considerable toxicity such as non-relapse mortality (NRM), alloHCT has generally been restricted to more fit and/or younger patients. Comparative studies of alloHCT to non-HCT approaches confirming a benefit in older adults with AML and MDS, capped the upper age at 75 years.[11-14] Older age constitutes the most significant barrier for referral for alloHCT.[15] In a survey, transplant physicians reported an upper age limit between 70 and 80 years for reduced intensity conditioning (RIC) alloHCT; only 17.7% described no upper age limit for RIC HCT.[16]

Registry studies uncovered the broadening application of alloHCT in patients in their eighth decade. Muffly's CIBMTR analysis among alloHCT patients at least 70 years of age for all diseases through 2013 found 1106 patients; however, only 115(10%) were 75-79 years and 8 (1) were ≥80 years. [17] In the EBMTR experience for AML among 713 patients with AML ≥ 70 years of age, Ringden reported a median age of 72(70-79) without further age breakdown.[18] In the most recent CIBMTR analysis of AML in CR, Maakaron analyzed 1321 patients from 2007 to 2017 age ≥ 60 years, thus prior to the venetoclax era. [19] Only 197 patients of these patients were ≥ 70 years; among those the median age was 72 years suggesting very few patients 75 years or older. For patients ≥ 70 years 1 year OS inferior, but no difference in long-term 3-5 year survival by age.

CIBMTR data reveal emerging use of alloHCT in historically age restricted patients. Specifically, for patients 76 years of age, 203 patients received first allografts in 2014 to 2019 compared to 34 in the 2008-2013 period (covered by the Muffly CIBMTR analysis)-a six fold increase and rising quickly. [20]

Non-relapse mortality is high in older adults. Although transplant morbidity and quality of life are critical patient centered outcomes, NRM has emerged as the most objective and reproducible tool for serious transplant toxicity and remains a barrier to widespread HCT application in older patients. In "real-world" HCT registry data of patients 70 years and older, 1 and 2 year NRM was estimated at 25% and 33% in the 2008-2013 period. In an EBMT series of MDS or secondary AML in patients ≥ 70 years, NRM at 1 year was 32%. [21] The EBMT experience of the same age group with AML undergoing alloHCT had a median age of 72(70-79) without further age breakdown; 2 year NRM was 34% [18] In CIBMTR of AML in CR1, the authors reported increased NRM of for those in their eight decade relative to patients in the seventh decade (HR=1.44, p =0.023). [19] Single institutional studies of matched donors or haploidentical donors described 2 year NRM of 17% and 27%, respectively. [22, 23]

Weakness. The largest limitations are differences in baseline factors and timing of capture (pre-chemotherapy for VIALE-A vs pre-HCT). Still, the essential items of genetic AML risk can be compared. A second limitation is presently the VIALE-A data can only be used in aggregate right now that preclude individual level analysis. Group data from time of CR remains the most important comparison and moreover individual level data may be available soon. The biases of referral for VIALE-A study or transplant can not be addressed by this study.

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 HCT:
• Adults ≥ 75 years at time of first allo-HCT between 2016-2021
• AML
• First remission at transplant
Exclusion criteria:
• Patients who did not consent to research
Inclusion criteria non-HCT patients
• Enrolled and treated on VIALE-A randomized study [24]
• Adults ≥ 75 years at time of enrollment
• Achieved composite complete remission
Exclusion criteria:
• Patients did not receive transplant in first remission

Q21. Does this study include pediatric patients?

- No

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

Target age is older 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: Treatment cohort- HCT vs novel agent consolidation
Patient-related:
• Sex: M, F
• Race: Caucasian, African-American, Asian, Pacific Islander, Native American, other
• Performance status
o HCT: Karnofsky score: <90, ≥90 *
o VIALE-A: ECOG 0 vs 1+
• HCT-CI: 0, 1-2, 3+ (Transplant only)
Disease-related:
• Disease for HCT
• Cytogenetics and molecular. Classification to be determined (consider adapted ELN) [25]
• MRD status
o HCT: positive, negative, unavailable
o VIALE-A. After cycle 1 and cycle 4 (when routinely collected)
Transplant-related:
• Conditioning regimen intensity: MAC RIC, NMA
• Conditioning regimen- flu-bu, flu-mel, flu-cy +/- TBI, flu-TBI, other
• Donor type: MRD, other related, MUD, mismatched unrelated, UCB
• Donor/recipient sex match: M/M, M/F, F/M, F/F
• Donor/recipient CMV status: +/+, +/-, -/+, -/-
• Graft type: BM, PB, UCB
• GVHD prophylaxis: PT-Cy, TAC-based, CSA-based, other
• In-vivo T-cell depletion with ATG or alemtuzumab: yes, no
• Year of transplant: 2008-2013, 2014-2020

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.

The data will not be linked but compared to the VIALE-A study. [5] CIBMTR has not data on non-transplant patients. We have a letter of support from Abbvie to provide the data (verbal Communication M. Werner from Abbvie). The data are necessary to compare outcomes in a similarly aged non-HCT cohorts receiving modern therapy for hypomethylating agent alone or hypomethylating agent plus venetoclax. We estimate 100- 150 patients will be eligible for comparison.

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)?

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

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

Consultant to Abbvie (AA)

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 aged >=75 receiving first allo-HCT for AML in CR1 in 2016-2021

Characteristic	TED	CRF
No. of patients	152	47
No. of centers	54	23
Age at HCT - median (range)	76 (75-81)	76 (75-82)
Recipient sex		
Male	106 (70)	35 (74)
Female	46 (30)	12 (26)
Karnofsky score		
<90	70 (46)	15 (32)
>=90	78 (51)	30 (64)
Missing	4 (3)	2 (4)
HCT-CI		
0	36 (24)	12 (26)
1	22 (14)	7 (15)
2	20 (13)	5 (11)
3+	73 (48)	23 (49)
Missing	1 (1)	0 (0)
MRD at time of HCT		
Negative	73 (48)	20 (43)
Positive	67 (44)	22 (47)
Missing	12 (8)	5 (11)
Donor type		
HLA-identical sibling	11 (7)	0 (0)
Other related	32 (21)	10 (21)
Well-matched unrelated (8/8)	86 (57)	29 (62)
Partially-matched unrelated (7/8)	15 (10)	4 (9)
Multi-donor	3 (2)	2 (4)
Unrelated (matching TBD)	5 (3)	0 (0)
Cord blood	0 (0)	2 (4)
Graft type		
Bone marrow	10 (7)	6 (13)
Peripheral blood	142 (93)	38 (81)
Cord blood	0 (0)	3 (6)
Conditioning intensity		
MAC	8 (5)	1 (2)
RIC	101 (66)	32 (68)
NMA	42 (28)	14 (30)

Characteristic	**TED**	**CRF**
Missing	1 (1)	0 (0)
GVHD prophylaxis		
CD34 selection	0 (0)	1 (2)
Post-CY	63 (41)	19 (40)
TAC based	72 (47)	24 (51)
CSA based	14 (9)	3 (6)
Other	3 (2)	0 (0)
Year of current transplant		
2016	16 (11)	4 (9)
2017	16 (11)	0 (0)
2018	28 (18)	6 (13)
2019	26 (17)	5 (11)
2020	32 (21)	16 (34)
2021	34 (22)	16 (34)
Median follow-up of survivors (range), months	24 (3-62)	12 (3-73)

COMBINED PROPOSAL- 2210-148 and 2210-164

Study Title:

Real-world evidence for brexucabtagene autoleucel in the treatment of relapsed/refractory B cell ALL in adults and analysis of factors associated with outcomes

Key Words:

"Real-world evidence", "Brexucabtagene autoleucel", "Adults", "Relapsed Refractory acute lymphoblastic leukemia", " Allogeneic HCT"

Principle Investigators:

1. Shivaprasad Manjappa
   Acting Assistant Professor
   Fred Hutchinson Cancer Center
   Email- smanjapp@fredhutch.org
   Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)- Yes
   Corresponding PI

2. Evandro Bezerra
   Assistant Professor
   The Ohio State University – The James Cancer Center
   Email- evandro.bezerra@osumc.edu
   Junior investigator status (defined as <40 years of age and/or ≤5 years from fellowship)- Yes

3. Jordan Gauthier
   Assistant Professor
   Fred Hutchinson Cancer Center
   Email- jgauthier@fredhutch.org

4. Partow Kebriaei
   Professor
   University of Texas MD Anderson Cancer Center
   Email- pkebriae@mdanderson.org

Research Question:

- Whether real-world experience with brexucabtagene autoleucel (Brexu-Cel) for acute lymphoblastic leukemia (ALL) matches the outcomes observed in the Zuma-3 trial
- Whether consolidative allogeneic hematopoietic cell transplant (allo-HCT) improves outcomes of ALL patients who are in remission after Brexu-cel
- How different are patient and disease characteristics of patients treated with Brexu-cel as the standard of care compared to the study population in the Zuma-3 study and how these might impact outcomes.

Research Hypothesis:

- Brexu-cel as SOC is associated with inferior outcomes when compared to the Zuma-3 pivotal study and consolidative allo-HCT can improve outcomes of patients who are in remission following Brexu-cel

Specific Objectives/Outcomes to be investigated

- Primary Aims:
    - Describe response rates, survival outcomes (OS, PFS) and non-relapse mortality (NRM) after Brexu-Cel as SOC and compare with published data from the Zuma-3 study
    - Describe survival outcomes and NRM of adult patients in CR after brexu-cel with and without consolidative allo-HCT

- Secondary Aims:
    - Describe the cumulative incidence of relapse (CIR) after Brexu-cel and the impact of consolidative allo-HCT on CIR
    - Identify factors impacting outcomes after Brexu-Cel

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

With the approval of Brexu-cel based on the excellent results from the Zuma-3 trial, its use as SOC for the treatment of relapsed/refractory ALL is bound to increase. This necessitates validation of real-world evidence not only as a regulatory requirement but also to ensure that the trial results hold in real-world experience, due to differences between the clinical trial and real-world population.

Further, while consolidation with an allo-HCT for those who achieve a second remission using salvage chemotherapy has been the standard of care in the treatment of relapsed ALL, its role following CAR-T cell therapy remains debated. Previous studies exploring this question have been only single-institution studies with limited numbers precluding robust multivariable modeling. A CIBMTR study allows us to validate the efficacy of brexu-cel and analyze factors that impact outcomes, including the role of post-CAR-T consolidation allo-HCT in a large patient population.

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

CD19 CAR-T cell therapy has demonstrated unprecedented efficacy in the treatment of relapsed refractory B-ALL leading to the FDA approval of tisagenlecleucel (tisa- cel) in 2017 for pediatric and young adults (≤ 25 years old) population and, more recently, approval of brexu-cel in 2021, for adult patients (≥ 18 years old). However, previous experiences have shown that there could be differences between real-world results compared to clinical trial data.[1-3] For example, the real-world evidence of brexu-cel in mantle cell lymphoma (MCL) revealed a higher rate of fatal events compared to the pivotal Zuma-2 trial, 15% vs. 3%, respectively.[2] This higher fatality rate seen with real-world results has been attributed to treating patients with higher risk disease, outside of clinical trial.

Hence, exploring real-world data is fundamental not only as a regulatory post-market requirement, but because there may exist profound differences between the real-world patients and pivotal clinical trials study population, as seen in the above example. Pasquini et al., using the CIBMTR data of 255 pediatric and young adult patients with B-ALL treated with tisa-cel in the real-world setting, demonstrated similar efficacy and toxicity to the pivotal clinical trial-ELIANA.[1] However, the external validation of the efficacy and safety of the use of brexu-cel as the standard of care is still needed.

This study will give us the opportunity not only to identify differences between the clinical trial and real-world patient populations but also the ability to analyze factors that may impact outcomes in a large study population with high statistical power. For instance, there was a non-statistical difference in response rates (60 vs. 80%) in patients previously treated Vs. not treated with blinatumomab (anti- CD19 bi-specific T-cell engager, BiTE, antibody), respectively.[4,5] Forty-five percent of patients in Zuma-3 had received blinatumomab prior to brexu-cel. However, as seen in the tisa-cel pivotal trial vs. real-world evidence, the use of blinatumomab may be significantly more prevalent in real-world practice, as, until October of 2021, CD19 CAR-T therapy was not available for most of these patients outside of a clinical trial.[1]

Moreover, despite the high rates of of MRD-negative CR achieved with brexu-cel in R/R B-ALL, remission remains short-lived and allo-HCT is frequently performed following remission. However, the role of consolidative allo-HCT remains undefined in this setting. Several single-institute studies have explored the role of consolidative allo-HCT in adults. Frey et al., in a single-arm, open-label study, reported improvement in EFS with consolidative allo-HCT but no statistically significant difference in OS.[6] In a phase 1 trial at Memorial Sloan Kettering Cancer Center, 53 patients received CD19-28z CAR-T cell infusion for relapsed B-cell ALL. Among the 32 patients with MRD-negative CR, no significant differences were noted in EFS and OS between those who underwent transplantation and those who did not.[7] However, Investigators from the Fred Hutchinson Cancer Center explored the role of consolidation allo-HCT after defined-composition CD19 CAR T-cell therapy in 45 out of 53 patients in MRD- negative CR and reported that 18% percent of those in CR proceeded to allo-HCT and in multivariable analyses consolidative allo-HCT remained associated with improved EFS.[5] In the Zuma-3 trial, 69% of patients who had achieved CR had relapsed by the data cut-off date and had a median RFS of 11.6 months. Ten (18%) patients underwent subsequent allo-HCT and sensitivity analysis showed no change in the duration of remission with a subsequent allo-HCT.[4] A recent update to the ZUMA-3 study, with a longer follow-up (median follow-up of 26.8 months), reported a relapse-free survival (RFS) of 11.6 months (2.7-20.5) when censored at subsequent allo- HCT vs. 11.7 months (2.8-20.5) when not censored.[8]

Taken together, previous studies have yielded mixed results regarding the impact of post-CAR-T allo-HCT among adults, and it is unclear if it results in the improvement of RFS and more importantly, OS. Evaluation of the role of allo-HCT in a larger study population would help better characterize the role of transplant and identify optimal therapeutic options (induction regimen, conditioning regimen, stem cell source, donor type) and how they might impact outcomes. This study could also potentially identify subgroups of patients who are likely or unlikely to benefit from a consolidative allo-HCT.

In conclusion, single or cooperative institutional data will unlikely be powered enough to generate meaningful data. However, CIBMTR has the largest registry of commercial cell therapy products. Therefore, we propose to use CIBMTR data to establish the brexu-cel real-world evidence data for both efficacy and toxicity, explore the role of consolidative allo-HCT and possibly identify factors associated with outcomes.

PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria

Inclusion criteria:
1. Patients Brexu-Cel for relapsed/refractory ALL
2. Age ≥ 18 years
3. CAR-T cell therapy between 2016 and 2022

Exclusion Criteria:
1. Prior CAR-T cell therapy with CAR-T products other than brexu-cel

PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.

Patient related variables

- Patient age at post-CAR-T HCT
- Patient gender
- Race: White vs. African American vs. Hispanics vs. others
- Recipient performance score (KPS 90-100 versus <90)
- Recipient HCT-CI (0-1 vs. ≥2)
- Time from CAR-T cell therapy to HCT

Disease related variables

- Cytogenetics including FISH (Fluorescent in situ hybridization)
- Presenting features (WBC, platelet count, Hemoglobin, CNS involvement at diagnosis)
- Use of tyrosine kinase inhibitor
- MRD testing results including multiparametric flow cytometry and PCR (Yes vs. NO)
- Disease status at the time of CAR-T cell therapy
- Time from relapse to CAR-T
- CNS involvement at relapse (yes vs. no)
- Induction treatment received including number of cycles
- Salvage chemotherapy received at relapse including number of cycles
- Use of Blinatumomab (yes vs no) and number of cycles
- Use of Inotuzumab (yes vs no) and number of cycles
- Number of prior lines of therapy
- Prior Allo-HCT (yes vs. no)
- If Yes to prior allo-HCT – Donor chimerism prior to CAR-T
- Acute GVHD (yes vs. no) prior to brexu-cel
- Chronic GVHD (yes vs. no) prior to brexu-cel

CAR-T therapy related variables

- Incidence of CRS (yes vs. no)
- Highest grade of CRS
- Incidence of ICANS (yes vs. no)
- Highest grade of ICANS
- Cumulative dose of steroids used
- Number of days of steroids used post-CAR-T
- Post-CAR-T disease status at day 30 (MRD-ve CR vs MRD +ve CR vs relapse/refractory)
- Evidence of antigen escape

Transplant related variables (post-CAR-T allo-HCT)

- Donor gender
- Donor age
- Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
- Remission status prior to post-CAR-T allo-HCT
- Conditioning intensity (myeloablative vs. reduced intensity/non-myeloablative)
- TBI-based conditioning (yes vs. no)
- Graft source (peripheral blood vs. marrow vs. umbilical cord)
- Transplant type (Matched related donor vs. Matched unrelated donor vs. Haploidentical vs Cord)
- GVHD prophylaxis regimen
- Use of ATG (yes /no)

Does this study include pediatric patients? No

If this study does not include pediatric patients, please provide justification:
Brexu-cel only approved for 18 year-older

PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: NO

SAMPLE REQUIREMENTS: No

NON-CIBMTR DATA SOURCE: No

REFERENCES:

1. Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. *Blood Adv*. Nov 10 2020;4(21):5414-5424. doi:10.1182/bloodadvances.2020003092
2. Iacoboni G, Rejeski K, Villacampa G, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. Jun 28 2022;6(12):3606-3610. doi:10.1182/bloodadvances.2021006922

3. Jacobson CA, Locke FL, Ma L, et al. Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States. *Transplant Cell Ther*. Sep 2022;28(9):581.e1-581.e8. doi:10.1016/j.jtct.2022.05.026
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5. Hay KA, Gauthier J, Hirayama AV, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. *Blood*. 04 11 2019;133(15):1652-1663. doi:10.1182/blood-2018-11-883710
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7. Park JH, Rivière I, Gonen M, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med*. 02 01 2018;378(5):449-459. doi:10.1056/NEJMoa1709919
8. Shah BD, Ghobadi A, Oluwole OO, et al. Two-year follow-up of KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (Pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) in ZUMA-3. *Journal of Clinical Oncology*. 2022;40(16_suppl):7010-7010. doi:10.1200/JCO.2022.40.16_suppl.7010

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Table 1. Characteristics of patients age >=18 receiving brexu-cel for ALL in 2021-2022

Characteristic	N (%)
No. of patients	83
No. of centers	45
Age at infusion, by category	
Median (min-max)	43 (20-79)
18-29	16 (19)
30-39	23 (28)
40-49	10 (12)
50-59	16 (19)
60-69	17 (20)
>=70	1 (1)
Sex	
Male	43 (52)
Female	40 (48)
Race	
White	58 (70)
Black or African American	6 (7)
Asian	6 (7)
American Indian or Alaska Native	1 (1)
Other	2 (2)
More than one race	6 (7)
Missing	4 (5)
Karnofsky score	
<90	58 (70)
>=90	20 (24)
Missing	5 (6)
Disease status prior to CT	
PIF	16 (19)
CR2	11 (13)
>=CR3	12 (14)
Relapse	44 (53)
Year of CT	
2021	11 (13)
2022	72 (87)

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

The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities

Q2. Key Words

acute myeloid leukemia, chromosome 3

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Arjun Datt Law
Email address:	Arjun.Law@uhn.ca
Institution name:	Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre
Academic rank:	Assistant Professor

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Tommy Alfaro Moya, MD
Email address:	tommy.alfaromoya@uhn.ca
Institution name:	Hans Messner Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre
Academic rank:	Clinical Fellow

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?

- Yes

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

N/A

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:

What is the outcome of patients diagnosed with acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities.

Q16. RESEARCH HYPOTHESIS:

Allogeneic stem cell transplantation does not modify outcomes in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with chromosome 3 abnormalities.

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

Suggested word limit of 200 words:

1. To assess outcomes in patients diagnosed with AML and MDS with chromosome 3 abnormalities undergoing allogeneic stem cell transplantation (Allo-SCT)
2. To identify factors contributing to adverse outcomes in AML and MDS with chromosome 3 abnormalities undergoing Allo-SCT

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.

1. This study will assist in framing recommendations regarding Allo-SCT in patients with AML or MDS with chromosome 3 abnormalities.
2. If Allo-SCT does not change the poor prognosis of these high risk patients, efforts to improve patient management would be directed towards other potential therapies and/or clinical trials.
3. The identification of factors that affect outcomes in this patient group would guide future management strategies.
4. This study would potentially generate further research investigating the role of driver mutations detected by next generation sequencing in combination with chromosome 3 abnormalities.

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.

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) with chromosome 3 abnormalities are associated with adverse outcomes (1-5). AML with Inv(3)(q21q26.2)/t(3;3)(q21;q26.2) is considered a distinct entity associated with poor prognosis (6, 7). Other chromosome 3 abnormalities in AML have been also shown to portend adverse outcomes (2, 3, 5). Abnormalities involving chromosome 3 are considered a poor risk cytogenetic abnormality for patients with MDS in the revised international prognostic score (IPPS-R) (8).

Eligible patients with AML and MDS with these cytogenetic abnormalities are offered allogeneic stem cell transplantation (Allo-SCT). The benefit of Allo-SCT in this setting is controversial. A few studies have indicated improvement in patient outcomes (9-11) whilst other studies suggest no advantage over conventional chemotherapy (3-5, 12). It is essential to evaluate outcomes in this high risk group to determine appropriate therapeutic management strategies.

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.

1. All patients >17 years old with AML or MDS with any chromosome 3 abnormality on diagnosis, determined by conventional karyotyping, who have received Allo-SCT, will be included in the analyses
2. All patients with the following concomitant cytogenetic abnormalities: t(8;21); inv 16, t(15;17) will be excluded.

Q21. Does this study include pediatric patients?

- No

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

Chromosome 3 abnormalities are extremely rare in children

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

Data on the following will be retrieved: age, sex, diagnosis (de novo AML or MDS/secondary AML/treatment related AML or MDS), date of diagnosis, cytogenetics, molecular studies, prior treatment received before transplant, number of prior HSCT (auto and/or allo HSCT), disease status at time of transplant, KPS at time of transplant, date of transplant, number of lines of chemotherapy prior to transplant, date of transplant, donor (related, unrelated, haploidentical, cord), HLA match, donor sex, donor and recipient CMV status, product type of stem cells (bone marrow, peripheral blood, single cord, double cord), conditioning regimen, GVHD prophylaxis, time to neutrophil and platelet engraftment, aGVHD grade and cGVHD grade, date of diagnosis of aGVHD and cGVHD, date of relapse and date and cause of death.

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/Comı

none required

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

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

none required

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

none required

Q26. REFERENCES:

1. Alfayez M, Assi RE, Kantarjian HM, Jabbour E, Ravandi F, Dinardo CD, et al. Characteristics and outcomes of myelodysplastic syndrome (MDS) with chromosome (chr)3q abnormalities. Journal of Clinical Oncology. 2018;36(15_suppl):7069-.
2. Lugthart S, Groschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL, et al. Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol. 2010;28(24):3890-8.
3. Raya JM, Martin-Santos T, Luno E, Sanzo C, Perez-Sirvent ML, Such E, et al. Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2): Clinical and biological features and comparison with other acute myeloid leukemias with cytogenetic aberrations involving long arm of chromosome 3. Hematology. 2015;20(8):435-41.
4. Rogers HJ, Vardiman JW, Anastasi J, Raca G, Savage NM, Cherry AM, et al. Complex or monosomal karyotype and not blast percentage is associated with poor survival in acute myeloid leukemia and myelodysplastic syndrome patients with inv(3)(q21q26.2)/t(3;3)(q21;q26.2): a Bone Marrow Pathology Group study. Haematologica. 2014;99(5):821-9.
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11. Sun J, Konoplev SN, Wang X, Cui W, Chen SS, Medeiros LJ, et al. De novo acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2): a clinicopathologic and cytogenetic study of an entity recently added to the WHO classification. Mod Pathol. 2011;24(3):384-9.
12. Reiter E, Greinix H, Rabitch W, Keil F, Schwarzinger I, Jaeger U, et al. Low curative potential of bone marrow transplantation for highly aggressive acute myelogenous leukemia with inv (3)(q21q26) or homologous translocation t(3;)(q21;26). Annals of Hematology 2000(79):374-7.

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

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

- 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 AML/MDS with chromosome 3 abnormality in 2008-2019, CRF track

Characteristic	N (%)
No. of patients	777
No. of centers	127
Age at HCT	
Median (min-max)	60 (19-88)
18-29	58 (7)
30-39	54 (7)
40-49	92 (12)
50-59	188 (24)
60-69	299 (38)
>=70	86 (11)
Recipient sex	
Male	419 (54)
Female	358 (46)
Karnofsky score	
<90	368 (47)
>=90	396 (51)
Missing	13 (2)
HCT-CI	
0	144 (19)
1	101 (13)
2	98 (13)
3	126 (16)
4	99 (13)
5	73 (9)
6+	120 (15)
Missing	16 (2)
Primary disease for HCT	
AML	415 (53)
MDS	362 (47)
Donor type	
HLA-identical sibling	183 (24)
Other related	112 (14)
Well-matched unrelated (8/8)	336 (43)
Partially-matched unrelated (7/8)	66 (8)
Mis-matched unrelated (<= 6/8)	7 (1)

Characteristic	**N (%)**
Multi-donor	3 (0)
Unrelated (matching TBD)	2 (0)
Cord blood	68 (9)
Graft type	
Bone marrow	116 (15)
Peripheral blood	593 (76)
Cord blood	68 (9)
GVHD prophylaxis	
Ex-vivo T-cell depletion	3 (0)
CD34 selection	14 (2)
Post-CY	130 (17)
TAC based	499 (64)
CSA based	118 (15)
Other	6 (1)
Missing	7 (1)
Year of HCT	
2008	58 (7)
2009	46 (6)
2010	37 (5)
2011	24 (3)
2012	20 (3)
2013	52 (7)
2014	107 (14)
2015	98 (13)
2016	115 (15)
2017	106 (14)
2018	71 (9)
2019	43 (6)
Median follow-up of survivors (range), months	60 (3-153)

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

Prognostic Impact of Cytogenetic and Molecular Risk Classification in AML after Hematopoietic Stem Cell Transplant in Adolescents, and Young Adults

Q2. Key Words

AYA, AML, leukemia, cytogenetics, molecular, risk stratification

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hannah Lust, MD
Email address:	hlust@luriechildrens.org
Institution name:	Ann & Robert H. Lurie Children's Hospital of Chicago
Academic rank:	fellow

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):	Sonali Chaudhury, MD
Email address:	schaudhury@luriechildrens.org
Institution name:	Ann & Robert H. Lurie Children's Hospital of Chicago
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?

N/A

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

Hannah Lust

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- 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:

What is the prognostic impact of established cytogenetic and molecular risk classifications in acute myeloid leukemia (AML) after hematopoietic stem cell transplant (HSCT) in the adolescent/young adult (AYA) population?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that while the cytogenetic landscape of AML in AYA patients differs from that of exclusively pediatric or older adult populations, the recently published European LeukemiaNet 2022 (ELN2022) risk stratification guidelines will predict survival and relapse risk in AYA patients receiving HSCT. Further, we hypothesize that analysis of molecular mutations that may be unique to AYA patients with AML will enhance the prognostic impact of the ELN2022 guidelines.

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

Suggested word limit of 200 words:

Specific aim 1. We aim to describe the prognostic significance of ELN2022 cytogenetic risk stratification in AYA patients with AML receiving HSCT in CR1 or CR2. We aim to determine if this system of risk stratification remains reliable in the AYA population. Within the AYA population, we also plan to do analyses of age-stratified subgroups to examine younger vs older AYAs.
Specific aim 2. In determining the prognostic impact of ELN2022 guidelines in this patient population, we also aim to describe the frequency of reported cytogenetic changes in AYA patients with AML, particularly less common karyotypic changes and concurrent reported molecular changes in this patient population.
Specific aim 3. By collecting data on reported race/ethnicity we also aim to clarify if these prognostic tools are equally significant in non-white AYA patient populations, given reported survival disparities in non-white patients with AML.
Primary outcomes to be investigated include overall survival (OS) and leukemia-free survival (LFS). Secondary outcomes include non-relapse mortality (NRM), early death rate, and relapse rate. OS will be defined by absence of death from any cause. LFS will be defined as survival in CR following HSCT. Early death rate will be defined as death within 30 days of stem cell infusion. NRM will be defined as death due to any cause other than disease relapse. All outcomes will be measured from time of stem cell infusion.

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.

AYA patients with AML who receive HSCT have decreased overall survival and event-free survival when compared to pediatric populations (1,2). While some portion of this survival discrepancy appears to be related to increased non-relapse mortality in AYA patients compared to pediatric patients, relapsed disease remains the most significant cause of treatment failure and mortality after HSCT in AML overall (3). Survival in any age population after relapsed AML remains dismal (3,4). Furthermore, Black AYA patients with AML have been shown to have decreased overall survival in the setting of both cytogenetically normal and abnormal AML compared to white AYA patients (5). Several potential causes have been proposed for lower survival rates in AYA patients in the setting of AML and other malignancies, including increased rate of comorbidities compared to pediatric patients, issues with medication compliance, and differences in treatment approach between pediatric and adult institutions (6). It is likely that disease biology also plays a role.
Improving survival in AML in AYA patients will require close examination of cytogenetic and molecular risk stratification tools that are currently in use, particularly as we learn more about the impact of mutations detected with NGS, to ensure that they are appropriately applicable to this unique patient population. Efforts to improve survival in AYA patients with AML will necessitate both increased inclusion of AYA patients in clinical trials and design of clinical trials specifically tailored towards AYA patient populations. Additionally, accurate risk stratification of AML is critical as use of post-HSCT maintenance therapy becomes more commonplace. Validation of AML risk stratification in AYA patients will be particularly useful in clinical trials examining both upfront targeted treatment protocols as well as post-HSCT therapies. Refining our ability to appropriately risk-stratify AYA patients with AML receiving HSCT will ensure that we are applying appropriate upfront treatment recommendations for HSCT, post-HSCT disease monitoring guidelines, and implementation of post-HSCT therapy to maintain lasting disease remission. Ensuring that these prognostic guidelines are equally applicable to non-white patients, who historically experience worse outcomes in the setting of AML therapy, may help improve survival in these patient populations as well.

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.

Survival discrepancies exist in AYA patients with AML who receive HSCT as demonstrated in multiple retrospective studies comparing outcomes in AYA patients to those of pediatric patients (1,2). These differences are further highlighted among Black AYA patients with AML (5). Combined age and race-related survival disparities highlight a need to perform dedicated analysis of the AYA population with AML receiving HSCT to determine specific contributors to decreased survival compared to pediatric populations.

Since the publication of ELN2017 guidelines (7), studies have examined the prognostic impact of the cytogenetic risk stratification in the setting of adults with AML receiving HSCT. Multiple recent studies have confirmed the significance of this risk classification system in predicting survival after HSCT. The cohorts in these studies have included patients aged 18 and older and importantly analyzed the impact of newer molecular risk factors, such as TP53 mutations, on survival. However, the median age ranges from 55-59 years old, and the published studies have not included sub-analysis of AYA patients (8–10). To our knowledge, the prognostic significance of AML cytogenetic and molecular risk stratification has not been analyzed specifically in the AYA population.

ELN2017 incorporated mutations in RUNX1, ASXL1, and TP53, reflecting the relevance of these three genes in predicting AML outcomes in adult patients, while ELN2022 goes further to incorporate multiple myelodysplasia-related pathogenic variants in genes including BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, AND ZRSR2 (11,12). Studies have confirmed the prognostic impact of several of these mutations, particularly the negative impact of TP53 mutations, in the setting of adults receiving HSCT.

Importantly, multiple studies have shown that the cytogenetic and molecular landscape of AML is quite different between pediatric and adult disease (13,14). From the TARGET initiative, a joint COG-NCI effort to characterize the molecular landscape of pediatric AML, we have learned that certain mutations are more common in pediatric AML, such as RAS, KIT, and specific FLT3 mutations. From COG trial AAML0531, which included patients up to 30 years old, additional retrospective NGS testing identified multiple high-risk mutations that, when applied retrospectively to the AAML0531 study population, significantly changed their risk stratification (Children's Oncology Group AAML1831 Study Protocol). However, this information was not applied to an age-stratified population, so the specific effect on AYA patients is unclear. Studies have also demonstrated that the frequency and location of mutations in certain genes differ between children and adults with AML, including CBL, GATA2, WT1, and MYC14. Given these age-related differences, we cannot assume that the cytogenetic and molecular landscape of AML in AYA patients is the same as that in either pediatric or adult populations, and thus cannot assume without close examination the same impact on prognosis in this patient population. It is worth examining the impact of these mutations, in combination with ELN2022 guidelines, now identifiable through NGS testing, on the AYA AML population.

Furthermore, earlier studies have demonstrated that prior cytogenetic risk guidelines ultimately had significantly different prognostic impact in specific age groups. For example, the intermediate risk I and II groups defined in ELN2010 guidelines were ultimately indistinguishable in older adults in terms of predicting survival (15). The possibility remains that similarly age-related discrepancies exist, and thus AYA-specific investigation is warranted.

Given recent data suggesting inferior survival in Black AYA patients with AML, even in the setting of cytogenetically normal AML (5), it will be equally important to perform a comparative sub-analysis of the prognostic impact of cytogenetic criteria in non-white patient populations receiving HSCT for AML.

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

N/A

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

Inclusion criteria: patients ages 15-39 years old receiving first stem cell transplant for AML in CR1 or CR2 between 2010 and 2022. Stem cell source may include peripheral blood stem cells, bone marrow, or cord blood from matched related, matched unrelated, or haploidentical donors. Both myeloablative and reduced intensity conditioning regimens will be included.

Exclusion criteria: patients receiving second or greater stem cell transplant, patients for whom cytogenetics data prior to transplant is not available, and patients with APL.

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.

- Demographics - sex, ethnicity, race, age
- pre-HSCT preparative regimen (myeloablative, nonmyeloablative, reduced intensity conditioning definitions based on CIBMTR criteria)
- Diagnosis of therapy-related AML
- Documented antecedent hematologic disorder or predisposing condition
- Disease status at time of HSCT
- Best response to HSCT, MRD by flow cytometry
- Disease Assessment following HSCT
- AML classification
- Cytogenetic abnormalities identified at diagnosis or relapse via karyotyping or FISH
- Molecular markers identified by NGS at diagnosis or relapse
- Evidence of extra-medullary disease at diagnosis or relapse
- Donor type, degree of mismatch if applicable
- Product type
- Survival status at date of last contact
- Date of death
- Primary cause of death

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. Pochon C, Detrait M, Dalle JH, et al. Improved outcome in children compared to adolescents and young adults after allogeneic hematopoietic stem cell transplant for acute myeloid leukemia: a retrospective study from the Francophone Society of Bone Marrow Transplantation and Cell Therapy (SFGM-TC). J Cancer Res Clin Oncol. 2022;148(8):2083-2097. doi:10.1007/s00432-021-03761-w
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5. Larkin K, Nicolet D, Kelly BJ, et al. High early death rates, treatment resistance, and short survival of Black adolescents and young adults with AML. Blood Adv. 2022;6(19). doi:10.1182/bloodadvances.2022007544
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13. Marceau-Renaut A, Duployez N, Ducourneau B, et al. Molecular Profiling Defines Distinct Prognostic Subgroups in Childhood AML: A Report from the French ELAM02 Study Group. HemaSphere. 2018;2(1). doi:10.1097/HS9.0000000000000031
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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 aged 15-39 years receiving first allo-HCT for AML in 2008-2019, CRF track

Characteristic	MAC	RIC/NMA
No. of patients	1173	237
No. of centers	183	88
Age at HCT		
Median (min-max)	28 (15-39)	29 (15-39)
10-17	137 (12)	13 (5)
18-29	558 (48)	115 (49)
30-39	478 (41)	109 (46)
Recipient sex		
Male	613 (52)	117 (49)
Female	560 (48)	120 (51)
Karnofsky score		
<90	291 (25)	64 (27)
>=90	865 (74)	170 (72)
Missing	17 (1)	3 (1)
HCT-CI		
0	463 (39)	79 (33)
1	159 (14)	39 (16)
2	172 (15)	25 (11)
3	173 (15)	39 (16)
4	101 (9)	27 (11)
5	43 (4)	14 (6)
6+	42 (4)	9 (4)
Missing	20 (2)	5 (2)
Disease status at time of HCT		
CR1	847 (72)	164 (69)
CR2	326 (28)	73 (31)
Clinical onset of AML		
De-novo	1071 (91)	212 (89)
Transformed from MDS/MPS	50 (4)	14 (6)
Therapy linked	52 (4)	11 (5)
MRD at time of HCT		
Negative	817 (70)	144 (61)
Positive	258 (22)	67 (28)
Missing	98 (8)	26 (11)
Donor type		

Characteristic	MAC	RIC/NMA
HLA-identical sibling	310 (26)	38 (16)
Other related	165 (14)	72 (30)
Well-matched unrelated (8/8)	433 (37)	46 (19)
Cord blood	265 (23)	81 (34)
Graft type		
Bone marrow	246 (21)	52 (22)
Peripheral blood	662 (56)	104 (44)
Cord blood	265 (23)	81 (34)
Conditioning intensity		
MAC	1173 (100)	0 (0)
RIC	0 (0)	152 (64)
NMA	0 (0)	85 (36)
GVHD prophylaxis		
Ex-vivo T-cell depletion	12 (1)	1 (0)
CD34 selection	31 (3)	18 (8)
Post-CY	156 (13)	73 (31)
TAC based	619 (53)	97 (41)
CSA based	347 (30)	43 (18)
Other	3 (0)	5 (2)
Missing	5 (0)	0 (0)
Year of HCT		
2008	124 (11)	15 (6)
2009	145 (12)	11 (5)
2010	137 (12)	8 (3)
2011	63 (5)	8 (3)
2012	51 (4)	7 (3)
2013	105 (9)	25 (11)
2014	122 (10)	29 (12)
2015	93 (8)	33 (14)
2016	91 (8)	31 (13)
2017	80 (7)	28 (12)
2018	83 (7)	22 (9)
2019	79 (7)	20 (8)
Median follow-up of survivors (range), months	63 (3-152)	51 (3-149)

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

Prognostic Impact of Cytogenetic and Molecular Risk Classification in AML after Hematopoietic Stem Cell Transplant in Adolescents, and Young Adults

Q2. Key Words

AYA, AML, leukemia, cytogenetics, molecular, risk stratification

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Hannah Lust, MD
Email address:	hlust@luriechildrens.org
Institution name:	Ann & Robert H. Lurie Children's Hospital of Chicago
Academic rank:	fellow

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):	Sonali Chaudhury, MD
Email address:	schaudhury@luriechildrens.org
Institution name:	Ann & Robert H. Lurie Children's Hospital of Chicago
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?

N/A

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

Hannah Lust

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- 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:

What is the prognostic impact of established cytogenetic and molecular risk classifications in acute myeloid leukemia (AML) after hematopoietic stem cell transplant (HSCT) in the adolescent/young adult (AYA) population?

Q16. RESEARCH HYPOTHESIS:

We hypothesize that while the cytogenetic landscape of AML in AYA patients differs from that of exclusively pediatric or older adult populations, the recently published European LeukemiaNet 2022 (ELN2022) risk stratification guidelines will predict survival and relapse risk in AYA patients receiving HSCT. Further, we hypothesize that analysis of molecular mutations that may be unique to AYA patients with AML will enhance the prognostic impact of the ELN2022 guidelines.

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

Suggested word limit of 200 words:

Specific aim 1. We aim to describe the prognostic significance of ELN2022 cytogenetic risk stratification in AYA patients with AML receiving HSCT in CR1 or CR2. We aim to determine if this system of risk stratification remains reliable in the AYA population. Within the AYA population, we also plan to do analyses of age-stratified subgroups to examine younger vs older AYAs.
Specific aim 2. In determining the prognostic impact of ELN2022 guidelines in this patient population, we also aim to describe the frequency of reported cytogenetic changes in AYA patients with AML, particularly less common karyotypic changes and concurrent reported molecular changes in this patient population.
Specific aim 3. By collecting data on reported race/ethnicity we also aim to clarify if these prognostic tools are equally significant in non-white AYA patient populations, given reported survival disparities in non-white patients with AML.
Primary outcomes to be investigated include overall survival (OS) and leukemia-free survival (LFS). Secondary outcomes include non-relapse mortality (NRM), early death rate, and relapse rate. OS will be defined by absence of death from any cause. LFS will be defined as survival in CR following HSCT. Early death rate will be defined as death within 30 days of stem cell infusion. NRM will be defined as death due to any cause other than disease relapse. All outcomes will be measured from time of stem cell infusion.

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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.

Survival discrepancies exist in AYA patients with AML who receive HSCT as demonstrated in multiple retrospective studies comparing outcomes in AYA patients to those of pediatric patients (1,2). These differences are further highlighted among Black AYA patients with AML (5). Combined age and race-related survival disparities highlight a need to perform dedicated analysis of the AYA population with AML receiving HSCT to determine specific contributors to decreased survival compared to pediatric populations.

Since the publication of ELN2017 guidelines (7), studies have examined the prognostic impact of the cytogenetic risk stratification in the setting of adults with AML receiving HSCT. Multiple recent studies have confirmed the significance of this risk classification system in predicting survival after HSCT. The cohorts in these studies have included patients aged 18 and older and importantly analyzed the impact of newer molecular risk factors, such as TP53 mutations, on survival. However, the median age ranges from 55-59 years old, and the published studies have not included sub-analysis of AYA patients (8–10). To our knowledge, the prognostic significance of AML cytogenetic and molecular risk stratification has not been analyzed specifically in the AYA population.

ELN2017 incorporated mutations in RUNX1, ASXL1, and TP53, reflecting the relevance of these three genes in predicting AML outcomes in adult patients, while ELN2022 goes further to incorporate multiple myelodysplasia-related pathogenic variants in genes including BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, AND ZRSR2 (11,12). Studies have confirmed the prognostic impact of several of these mutations, particularly the negative impact of TP53 mutations, in the setting of adults receiving HSCT.

Importantly, multiple studies have shown that the cytogenetic and molecular landscape of AML is quite different between pediatric and adult disease (13,14). From the TARGET initiative, a joint COG-NCI effort to characterize the molecular landscape of pediatric AML, we have learned that certain mutations are more common in pediatric AML, such as RAS, KIT, and specific FLT3 mutations. From COG trial AAML0531, which included patients up to 30 years old, additional retrospective NGS testing identified multiple high-risk mutations that, when applied retrospectively to the AAML0531 study population, significantly changed their risk stratification (Children's Oncology Group AAML1831 Study Protocol). However, this information was not applied to an age-stratified population, so the specific effect on AYA patients is unclear. Studies have also demonstrated that the frequency and location of mutations in certain genes differ between children and adults with AML, including CBL, GATA2, WT1, and MYC14. Given these age-related differences, we cannot assume that the cytogenetic and molecular landscape of AML in AYA patients is the same as that in either pediatric or adult populations, and thus cannot assume without close examination the same impact on prognosis in this patient population. It is worth examining the impact of these mutations, in combination with ELN2022 guidelines, now identifiable through NGS testing, on the AYA AML population.

Furthermore, earlier studies have demonstrated that prior cytogenetic risk guidelines ultimately had significantly different prognostic impact in specific age groups. For example, the intermediate risk I and II groups defined in ELN2010 guidelines were ultimately indistinguishable in older adults in terms of predicting survival (15). The possibility remains that similarly age-related discrepancies exist, and thus AYA-specific investigation is warranted.

Given recent data suggesting inferior survival in Black AYA patients with AML, even in the setting of cytogenetically normal AML (5), it will be equally important to perform a comparative sub-analysis of the prognostic impact of cytogenetic criteria in non-white patient populations receiving HSCT for AML.

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

N/A

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

Inclusion criteria: patients ages 15-39 years old receiving first stem cell transplant for AML in CR1 or CR2 between 2010 and 2022. Stem cell source may include peripheral blood stem cells, bone marrow, or cord blood from matched related, matched unrelated, or haploidentical donors. Both myeloablative and reduced intensity conditioning regimens will be included.

Exclusion criteria: patients receiving second or greater stem cell transplant, patients for whom cytogenetics data prior to transplant is not available, and patients with APL.

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.

- Demographics - sex, ethnicity, race, age
- pre-HSCT preparative regimen (myeloablative, nonmyeloablative, reduced intensity conditioning definitions based on CIBMTR criteria)
- Diagnosis of therapy-related AML
- Documented antecedent hematologic disorder or predisposing condition
- Disease status at time of HSCT
- Best response to HSCT, MRD by flow cytometry
- Disease Assessment following HSCT
- AML classification
- Cytogenetic abnormalities identified at diagnosis or relapse via karyotyping or FISH
- Molecular markers identified by NGS at diagnosis or relapse
- Evidence of extra-medullary disease at diagnosis or relapse
- Donor type, degree of mismatch if applicable
- Product type
- Survival status at date of last contact
- Date of death
- Primary cause of death

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. Pochon C, Detrait M, Dalle JH, et al. Improved outcome in children compared to adolescents and young adults after allogeneic hematopoietic stem cell transplant for acute myeloid leukemia: a retrospective study from the Francophone Society of Bone Marrow Transplantation and Cell Therapy (SFGM-TC). J Cancer Res Clin Oncol. 2022;148(8):2083-2097. doi:10.1007/s00432-021-03761-w
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13. Marceau-Renaut A, Duployez N, Ducourneau B, et al. Molecular Profiling Defines Distinct Prognostic Subgroups in Childhood AML: A Report from the French ELAM02 Study Group. HemaSphere. 2018;2(1). doi:10.1097/HS9.0000000000000031
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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 aged 15-39 years receiving first allo-HCT for AML in 2008-2019, CRF track

Characteristic	MAC	RIC/NMA
No. of patients	1173	237
No. of centers	183	88
Age at HCT		
Median (min-max)	28 (15-39)	29 (15-39)
10-17	137 (12)	13 (5)
18-29	558 (48)	115 (49)
30-39	478 (41)	109 (46)
Recipient sex		
Male	613 (52)	117 (49)
Female	560 (48)	120 (51)
Karnofsky score		
<90	291 (25)	64 (27)
>=90	865 (74)	170 (72)
Missing	17 (1)	3 (1)
HCT-CI		
0	463 (39)	79 (33)
1	159 (14)	39 (16)
2	172 (15)	25 (11)
3	173 (15)	39 (16)
4	101 (9)	27 (11)
5	43 (4)	14 (6)
6+	42 (4)	9 (4)
Missing	20 (2)	5 (2)
Disease status at time of HCT		
CR1	847 (72)	164 (69)
CR2	326 (28)	73 (31)
Clinical onset of AML		
De-novo	1071 (91)	212 (89)
Transformed from MDS/MPS	50 (4)	14 (6)
Therapy linked	52 (4)	11 (5)
MRD at time of HCT		
Negative	817 (70)	144 (61)
Positive	258 (22)	67 (28)
Missing	98 (8)	26 (11)
Donor type		

Characteristic	MAC	RIC/NMA
HLA-identical sibling	310 (26)	38 (16)
Other related	165 (14)	72 (30)
Well-matched unrelated (8/8)	433 (37)	46 (19)
Cord blood	265 (23)	81 (34)
Graft type		
Bone marrow	246 (21)	52 (22)
Peripheral blood	662 (56)	104 (44)
Cord blood	265 (23)	81 (34)
Conditioning intensity		
MAC	1173 (100)	0 (0)
RIC	0 (0)	152 (64)
NMA	0 (0)	85 (36)
GVHD prophylaxis		
Ex-vivo T-cell depletion	12 (1)	1 (0)
CD34 selection	31 (3)	18 (8)
Post-CY	156 (13)	73 (31)
TAC based	619 (53)	97 (41)
CSA based	347 (30)	43 (18)
Other	3 (0)	5 (2)
Missing	5 (0)	0 (0)
Year of HCT		
2008	124 (11)	15 (6)
2009	145 (12)	11 (5)
2010	137 (12)	8 (3)
2011	63 (5)	8 (3)
2012	51 (4)	7 (3)
2013	105 (9)	25 (11)
2014	122 (10)	29 (12)
2015	93 (8)	33 (14)
2016	91 (8)	31 (13)
2017	80 (7)	28 (12)
2018	83 (7)	22 (9)
2019	79 (7)	20 (8)
Median follow-up of survivors (range), months	63 (3-152)	51 (3-149)

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

Acute myeloid leukemia, Relapse, Minimal residual disease, allogeneic

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Guru Subramanian Guru Murthy
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
Email address:	wasber@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:

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- 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, Kristin Page (email)

Q15. RESEARCH QUESTION:

Primary question:
Would measurable residual disease (MRD) status be able to predict the outcomes of allogenetc hematopoietic cell transplantation (allo-HCT) for relapsed acute myeloid leukemia
Secondary question (if time and resources permit):
Would the outcomes of relapsed AML patients (≥CR2) who are MRD negative prior to allo-HCT be comparable to those who undergo allo-HCT in first complete remission (CR1)

Q16. RESEARCH HYPOTHESIS:

We postulate that MRD status would significantly affect the outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) for patients with relapsed acute myeloid leukemia (AML) [second complete remission (CR) or beyond] and positive minimal residual disease would be associated with higher relapse and worse 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 AML based on the MRD status:

- Overall survival (OS) (Primary)
- Disease free survival (DFS) (Primary)
- 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.

The current literature highlights the role for MRD status mainly in CR1 for AML patients undergoing allo-HCT. Hence, the role of MRD status in the setting of second complete remission (CR2) or beyond still remains unclear, even though there are several patients who undergo allo-HCT in CR2 or beyond. 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.

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 CR2 or beyond 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.

For primary analysis:

Adults aged ≥18 with relapsed AML who underwent allo-HCT (CR2 or beyond) between the period 2008 to 2022 and reported to CIBMTR will be included. Patients whose MRD status is unknown would be excluded.

For exploratory analysis (if time/resources permits): Comparing allo-HCT outcomes in CR1 vs ≥CR2 based on MRD status

Adults aged ≥18 with AML who underwent allo-HCT in CR1 between the period 2008 to 2022 and reported to CIBMTR will be included. Patients whose MRD status is unknown 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 management and transplant practice between pediatric vs adult AML, focusing on adult AML was considered.

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 prior to/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 relapsed AML who underwent allo-HCT in CR2 or beyond and meet the above-mentioned study criteria. MRD status prior to (or at) transplant would be the main effect and comparisons would be done between MRD positive vs. MRD negative patients. The primary outcome will be OS and DFS. 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, DFS 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 analysis: aiming to compare allo-HCT outcomes in CR1 vs ≥CR2 based on MRD status
Given the variability in clinical practice regarding the timing in which allo-HCT is performed in adult AML (CR1 vs. ≥CR2) and the favorable prognostic impact of MRD negative status prior to allo-HCT, we are interested in comparing the outcomes of allo-HCT in CR1 vs ≥CR2 based on MRD status, if time and resources permit. The dataset being used in the ongoing study with acute leukemia working group analyzing the role of MRD in CR1 could be used for this analysis without additional effort from statistician's standpoint. This would provide important information about the value of aiming for MRD negativity based on the disease status 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:

1. Thol F, Schlenk RF, Heuser M, et al. How I treat refractory and early relapsed acute myeloid leukemia. Blood. 2015;126(3):319–327.
2. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol. 2005;23(9): 1969–1978.
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4. Short NJ, Zhou S, Fu C, et al. Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA Oncol. 2020;6(12):1890–1899.
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11. Musthaq MU, Harrington AM, Guru Murthy GS et al. Prognostic Significance of Minimal/Measurable Residual Disease in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed/Refractory Acute Myeloid Leukemia. Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR 2021; Volume: 27, Issue: 3

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 AML in CR2+ in 2008-2019, CRF track

Characteristic	MRD neg	MRD pos
No. of patients	4734	2088
No. of centers	207	173
Age at HCT		
Median (min-max)	53 (18-81)	56 (18-78)
18-29	603 (13)	194 (9)
30-39	586 (12)	193 (9)
40-49	842 (18)	321 (15)
50-59	1285 (27)	582 (28)
60-69	1187 (25)	652 (31)
>=70	231 (5)	146 (7)
Recipient sex		
Male	2477 (52)	1110 (53)
Female	2257 (48)	978 (47)
Karnofsky score		
<90	1653 (35)	833 (40)
>=90	3006 (63)	1232 (59)
Missing	75 (2)	23 (1)
HCT-CI		
0	1136 (24)	427 (20)
1	683 (14)	330 (16)
2	661 (14)	327 (16)
3+	1991 (42)	921 (44)
Missing	263 (6)	83 (4)
Clinical onset of AML		
De-novo	3783 (80)	1612 (77)
Transformed from MDS/MPS	629 (13)	348 (17)
Therapy linked	322 (7)	128 (6)
Disease status at time of HCT		
CR1	3547 (75)	1615 (77)
CR2	1103 (23)	441 (21)
>=CR3	84 (2)	32 (2)
Donor type		
HLA-identical sibling	1163 (25)	458 (22)
Other related	680 (14)	375 (18)
Well-matched unrelated (8/8)	1630 (34)	659 (32)
Partially-matched unrelated (7/8)	356 (8)	163 (8)
Mis-matched unrelated (<= 6/8)	25 (1)	18 (1)
Multi-donor	10 (0)	5 (0)
Unrelated (matching TBD)	63 (1)	54 (3)
Cord blood	807 (17)	356 (17)
Graft type		
Bone marrow	684 (14)	317 (15)
Peripheral blood	3243 (69)	1415 (68)
Cord blood	807 (17)	356 (17)
Conditioning regimen intensity		
MAC	2638 (56)	1013 (49)
RIC	1227 (26)	681 (33)
NMA	749 (16)	311 (15)

Characteristic	MRD neg	MRD pos
TBD	65 (1)	39 (2)
Missing	55 (1)	44 (2)
Year of HCT		
2008	588 (12)	146 (7)
2009	578 (12)	92 (4)
2010	452 (10)	88 (4)
2011	223 (5)	42 (2)
2012	220 (5)	53 (3)
2013	437 (9)	161 (8)
2014	493 (10)	304 (15)
2015	463 (10)	306 (15)
2016	385 (8)	316 (15)
2017	316 (7)	237 (11)
2018	314 (7)	177 (8)
2019	265 (6)	166 (8)
Median follow-up of survivors (range), months	73 (3-171)	61 (3-168)

Characteristics of patients receiving first allo-HCT for AML in CR1 and CR2+ in 2008-2019, CRF track

Characteristic	CR1	CR2	>=CR3
No. of patients	5162	1544	116
No. of centers	208	173	57
Age at HCT			
Median (min-max)	55 (18-81)	50 (18-78)	43 (18-76)
18-29	544 (11)	224 (15)	29 (25)
30-39	528 (10)	229 (15)	22 (19)
40-49	824 (16)	314 (20)	25 (22)
50-59	1443 (28)	403 (26)	21 (18)
60-69	1504 (29)	318 (21)	17 (15)
>=70	319 (6)	56 (4)	2 (2)
Recipient sex			
Male	2736 (53)	789 (51)	62 (53)
Female	2426 (47)	755 (49)	54 (47)
Karnofsky score			
<90	1912 (37)	546 (35)	28 (24)
>=90	3180 (62)	973 (63)	85 (73)
Missing	70 (1)	25 (2)	3 (3)
HCT-CI			
0	1177 (23)	357 (23)	29 (25)
1	774 (15)	225 (15)	14 (12)
2	750 (15)	217 (14)	21 (18)
3+	2216 (43)	649 (42)	47 (41)
Missing	245 (5)	96 (6)	5 (4)
Clinical onset of AML			
De-novo	3896 (75)	1387 (90)	112 (97)
Transformed from MDS/MPS	877 (17)	98 (6)	2 (2)
Therapy linked	389 (8)	59 (4)	2 (2)
MRD			
MRD neg	3547 (69)	1103 (71)	84 (72)

Characteristic	CR1	CR2	>=CR3
MRD pos	1615 (31)	441 (29)	32 (28)
Donor type			
HLA-identical sibling	1308 (25)	302 (20)	11 (9)
Other related	790 (15)	253 (16)	12 (10)
Well-matched unrelated (8/8)	1775 (34)	483 (31)	31 (27)
Partially-matched unrelated (7/8)	361 (7)	141 (9)	17 (15)
Mis-matched unrelated (<= 6/8)	32 (1)	10 (1)	1 (1)
Multi-donor	12 (0)	3 (0)	0 (0)
Unrelated (matching TBD)	97 (2)	19 (1)	1 (1)
Cord blood	787 (15)	333 (22)	43 (37)
Graft type			
Bone marrow	781 (15)	211 (14)	9 (8)
Peripheral blood	3594 (70)	1000 (65)	64 (55)
Cord blood	787 (15)	333 (22)	43 (37)
Conditioning regimen intensity			
MAC	2675 (52)	906 (59)	70 (60)
RIC	1522 (29)	365 (24)	21 (18)
NMA	800 (15)	236 (15)	24 (21)
TBD	84 (2)	20 (1)	0 (0)
Missing	81 (2)	17 (1)	1 (1)
Year of HCT			
2008	514 (10)	197 (13)	23 (20)
2009	452 (9)	203 (13)	15 (13)
2010	397 (8)	127 (8)	16 (14)
2011	204 (4)	54 (3)	7 (6)
2012	187 (4)	80 (5)	6 (5)
2013	460 (9)	129 (8)	9 (8)
2014	603 (12)	188 (12)	6 (5)
2015	590 (11)	170 (11)	9 (8)
2016	559 (11)	132 (9)	10 (9)
2017	448 (9)	98 (6)	7 (6)
2018	383 (7)	103 (7)	5 (4)
2019	365 (7)	63 (4)	3 (3)
Median follow-up of survivors (range), months	71 (3-171)	72 (3-169)	96 (3-150)

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 transplant using higher vs. lower dose melphalan (140 mg/m2 vs. 100 mg/m2) reduced-intensity conditioning (RIC) for elderly patients with acute myeloid leukemia (AML).

Q2. Key Words

acute myeloid leukemia, reduced intensity conditioning, allogeneic hematopoietic cell transplantation

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

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

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Carl Shultz, DO
Email address:	shultz.carl@mayo.edu
Institution name:	Mayo Clinic
Academic rank:	Blood and Marrow Transplant Fellow

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:

Carl Shultz, DO

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

N/A

LETTER OF COMMITMENT:

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

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

n/a

Q13. PROPOSED WORKING COMMITTEE:

- 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:

Is there a RIC regimen of choice for elderly patients with AML receiving allogeneic hematopoietic cell transplantation?

Q16. RESEARCH HYPOTHESIS:

In elderly (age ≥ 60 years) patients with AML undergoing RIC transplant, the lower dose (100 mg/m2) melphalan with fludarabine (FM100) is as beneficial as the higher dose melphalan (140 mg/m2) with fludarabine (FM140) while reducing the toxicity profile.

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

Suggested word limit of 200 words:

Primary study end-points:
1. 3-year relapse-free survival (RFS) and overall survival (OS).

Secondary study end-points:
1. Nonrelapse mortality (NRM) 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

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.

By investigating whether a RIC regimen of FM with a reduced dose of melphalan is associated with a decreased incidence of toxicity without an increase in disease relapse in elderly patients with AML, we will be able to determine the optimal treatment for this vulnerable population.

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.

Acute myeloid leukemia (AML) remains a challenging disease of the elderly with a median age of diagnosis greater than 60 years old. Hematopoietic stem cell transplantation remains a potential curative treatment for patients. Advanced age, multiple comorbidities, and heterogenous disease biology are challenges that face the transplant physician. The advent of reduced-intensity conditioning (RIC) has significantly expanded the accessibility to transplant, allowing previously ineligible patients to undergo transplant safely (Ciurea, Rodrigues et al. 2009). While the utility of RIC transplant is undeniable, the optimal conditioning regimen remains undetermined and largely a matter of institutional preference for elderly patients with AML. The most widely used RIC regimens are fludarabine in conjunction with melphalan (FM) or busulfan (FB). In a retrospective analysis, our group showed that the use of FB was associated with a significantly higher relapse rate than FM140, though 2-year nonrelapse mortality (NRM) and overall survival (OS) were similar (Damlaj, Alkhateeb et al. 2016).

FM140 regimen has been increasingly used for HLA-matched transplants. There is encouraging evidence supporting the use of FM100 in elderly patients. In a single institution retrospective analysis of elderly patients with high-risk MDS/AML undergoing RIC transplant with matched related- (MRD) or matched unrelated (MUD) donors, there was no significant difference in survival and risk of relapse between the patients treated with lower (FM100) or higher (FM140 or FM180) doses of melphalan. However, the patients treated with FM100 were older and mostly in the first complete remission (CR1) compared to the FM140/FM180 patients who were younger and were less likely be in CR (Oran, Giralt et al. 2007). A more recent single institution retrospective analysis of elderly patients with AML compared four conditioning regimens: FM100, FM140, FB20000 (AUC >5000 daily x 4 days), and FB16000 (AUC 4000 daily x 4 days). Using a propensity score analysis, the FM100 group had better 5-year PFS despite the preferential use of the treatment in patients unable to tolerate more intense conditioning (Ciurea, Kongtim et al. 2020).

While encouraging, these findings have not been recapitulated in a larger, more diverse cohort of elderly patients with AML. 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: patients diagnosed with AML at age 60 or older undergoing first allogeneic HSCT between July 2007 and January 2022.

Q21. Does this study include pediatric patients?

- No

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

Study aim is to assess elderly patients (>60 years old)

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:
Age at diagnosis (<70 vs. ≥70 years)
Sex: Female vs. male
Age at the time of transplantation
Karnofsky performance score (< 70 vs. ≥ 70)
Hematopoietic stem cell transplant comorbidity index (HCT-CI)
Disease related variables at diagnosis and pre-transplant treatment
Date of diagnosis of AML
De novo or secondary AML
Complete blood count (hemoglobin, absolute neutrophil count, and platelet) at diagnosis
Cytogenetics at diagnosis (G-banding and FISH)
Bone marrow blast count
Molecular studies
Risk category for AML at diagnosis
Systemic therapy given prior to allogeneic stem cell transplant
Best response to the systemic therapy prior to allogeneic stem cell transplant
Disease related variables prior to transplant (before initiation of conditioning regimen)
Complete blood count (hemoglobin, absolute neutrophil count, and platelet) at the time of transplant
Blast count in the peripheral blood
Blast count in the bone marrow
Cytogenetic test results from the bone marrow (G-banding and FISH)
Disease status at stem cell transplantation
Pre-transplant serum creatinine
Pre-transplant AST and bilirubin
Pre-transplant serum ferritin
Pre-transplant fungal infection
Transplant related variables:
Donor type – HLA-matched sibling, HLA-matched unrelated, Haploidentical, and umbilical cord
Conditioning regimen – for this study we will compare two RIC: FM140 and FM100
Graft source – bone marrow (BM) vs. peripheral blood stem cell (PBSC)
Graft manipulation, if any
Donor and recipient CMV serologic status
GVHD prophylaxis – cyclosporine-based, calcineurin inhibitor-based, methotrexate, post-transplant cyclophosphamide, Alemtuzumab (yes vs. no) and ATG (yes vs. no)
Study variables post-transplant:
Time to neutrophil recovery
Time to platelet recovery
Chimerism studies
Acute GVHD – grade 0-I vs. grade II-IV
Chronic GVHD – yes vs. no

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:

Brammer, J. E., I. Khouri, S. Gaballa, P. Anderlini, C. Tomuleasa, S. Ahmed, C. Ledesma, C. Hosing, R. E. Champlin and S. O. Ciurea (2016). "Outcomes of Haploidentical Stem Cell Transplantation for Lymphoma with Melphalan-Based Conditioning." Biology of Blood and Marrow Transplantation 22(3): 493-498.

Ciurea, S. O., M. Rodrigues, S. Giralt and M. de Lima "Aging, Acute Myelogenous Leukemia, and Allogeneic Transplantation: Do They Belong in the Same Sentence?" Clinical Lymphoma and Myeloma 9(4): 289-297.

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Zhou Z, Nath R, Cerny J, Wang HL, Zhang MJ, Abdel-Azim H, Agrawal V, Ahmed G, Al-Homsi AS, Aljurf M, Alkhateeb HB, Assal A, Bacher U, Bajel A, Bashir Q, Battiwalla M, Bhatt VR, Byrne M, Cahn JY, Cairo M, Choe H, Copelan E, Cutler C, Damlaj MB, DeFilipp Z, De Lima M, Diaz MA, Farhadfar N, Foran J, Freytes CO, Gerds AT, Gergis U, Grunwald MR, Gul Z, Hamadani M, Hashmi S, Hertzberg M, Hildebrandt GC, Hossain N, Inamoto Y, Isola L, Jain T, Kamble RT, Khan MW, Kharfan-Dabaja MA, Kebriaei P, Kekre N, Khera N, Lazarus HM, Liesveld JL, Litzow M, Liu H, Marks DI, Martino R, Mathews V, Mishra A, Murthy HS, Nagler A, Nakamura R, Nathan S, Nishihori T, Olin R, Olsson RF, Palmisiano N, Patel SS, Patnaik MM, Pawarode A, Perales MA, Politikos I, Popat U, Rizzieri D, Sandmaier BM, Savani BN, Seo S, Shah NN, Uy GL, Valcárcel D, Verdonck LF, Waller EK, Wang Y, Weisdorf D, Wirk B, Wong E, Yared JA, Saber W. "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.

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

Characteristics of patients age >=60 receiving first allo-HCT for AML with FM100 or FM140 in 2008-2019, CRF track

Characteristic	FM100	FM140
No. of patients	129	417
No. of centers	42	70
Age at HCT - no. (%)		
Median (min-max)	67.0 (60.2-78.4)	66.0 (60.0-78.2)
60-69	101 (78.3)	342 (82.0)
>=70	28 (21.7)	75 (18.0)
Recipient sex - no. (%)		
Male	69 (53.5)	247 (59.2)
Female	60 (46.5)	170 (40.8)
Karnofsky score - no. (%)		
<90	62 (48.1)	215 (51.6)
>=90	63 (48.8)	197 (47.2)
Not reported	4 (3.1)	5 (1.2)
HCT-CI - no. (%)		
0	10 (7.8)	84 (20.1)
1	29 (22.5)	61 (14.6)
2	19 (14.7)	42 (10.1)
3	28 (21.7)	80 (19.2)
4	10 (7.8)	57 (13.7)
5	11 (8.5)	31 (7.4)
6+	20 (15.5)	55 (13.2)
Missing	2 (1.6)	7 (1.7)
Clinical onset of AML - no. (%)		
De-novo	89 (69.0)	246 (59.0)
Transformed from MDS/MPS	32 (24.8)	135 (32.4)
Therapy linked	8 (6.2)	36 (8.6)
Disease status at time of HCT - no. (%)		
PIF	26 (20.2)	85 (20.4)
CR1	78 (60.5)	258 (61.9)
CR2	8 (6.2)	49 (11.8)
>=CR3	0 (0.0)	2 (0.5)
Relapse	16 (12.4)	23 (5.5)
Missing	1 (0.8)	0 (0.0)
Donor type - no. (%)		
HLA-identical sibling	26 (20.2)	98 (23.5)
Twin	0 (0.0)	2 (0.5)

Characteristic	FM100	FM140
Other related	12 (9.3)	15 (3.6)
Well-matched unrelated (8/8)	68 (52.7)	215 (51.6)
Partially-matched unrelated (7/8)	4 (3.1)	41 (9.8)
Mis-matched unrelated (<= 6/8)	0 (0.0)	3 (0.7)
Multi-donor	2 (1.6)	1 (0.2)
Unrelated (matching TBD)	1 (0.8)	0 (0.0)
Cord blood	16 (12.4)	42 (10.1)
Graft type - no. (%)		
Bone marrow	9 (7.0)	39 (9.4)
Peripheral blood	104 (80.6)	336 (80.6)
Cord blood	16 (12.4)	42 (10.1)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	0 (0.0)	2 (0.5)
CD34 selection	3 (2.3)	22 (5.3)
Post-CY	21 (16.3)	37 (8.9)
TAC based	78 (60.5)	296 (71.0)
CSA based	26 (20.2)	51 (12.2)
Other	1 (0.8)	5 (1.2)
Not reported	0 (0.0)	4 (1.0)
Year of HCT - no. (%)		
2008	6 (4.7)	29 (7.0)
2009	6 (4.7)	19 (4.6)
2010	1 (0.8)	1 (0.2)
2011	5 (3.9)	5 (1.2)
2012	5 (3.9)	10 (2.4)
2013	12 (9.3)	43 (10.3)
2014	17 (13.2)	65 (15.6)
2015	17 (13.2)	74 (17.7)
2016	16 (12.4)	67 (16.1)
2017	17 (13.2)	37 (8.9)
2018	15 (11.6)	34 (8.2)
2019	12 (9.3)	33 (7.9)

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

Equal access and outcome for transplantation in AML: a 21st-century goal

Q2. Key Words

AML, transplantation, access, structural racism

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Najla El Jurdi
Email address:	neljurdi@umn.edu
Institution name:	University of Minnesota
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?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Daniel Weisdorf
Email address:	weisd001@umn.edu
Institution name:	University of Minnesota
Academic rank:	Professor Of Medicine

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

Najla El Jurdi

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/pages/index.aspx#submission*

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

Daniel Weisdorf: past Scientific Director for Acute Leukemia committee

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:

Drs.: Kirsten page, Mark Litzow, Partow Kebriaei, Christopher Hourigan

Q15. RESEARCH QUESTION:

We propose to analyze outcomes of allogeneic transplantation for AML as differentially influenced within HLA-based ancestry classification (1) and in self-reported racial and ethnic/ancestry subgroups. We will also examine their interaction with AML biology, patients' pathophysiologic and sociologic comorbidities and their access to a donor for allogeneic transplantation.

Q16. RESEARCH HYPOTHESIS:

We hypothesize that access to therapy, availability of an array of suitable donors plus clinical and social comorbidities confound outcomes for minority populations beyond the limits of their intrinsic disease biology. Social and economic factors compromise their potential for a best possible outcome. Using data from the CIBMTR supplemented with patient residence ZIP Code (9 digit) and/or home address census tract along with available comorbidity data, we will categorize outcomes of allogeneic transplantation for all adult (>18 years) AML patients treated with allogeneic HCT between 2010 and 2021 using data reported to the CIBMTR.

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

Suggested word limit of 200 words:

Primary outcome: Overall survival

Secondary outcomes: treatment related mortality; relapse; acute GVHD, chronic GVHD and leukemia-free survival.

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.

Understanding the influence of structural racism, social and physiologic comorbidities and poverty as they influence both access to HCT and outcomes of HCT may highlight approaches to mitigate these inequalities. Data-driven understanding of barriers to curative therapy may impact social approaches to ensure equitable treatments and improve outcomes for more patients.

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

The outcomes of AML are determined by its biology with molecular and cytogenetic phenotype, the patients' age and associated comorbidities plus access to the best potentially curative therapy.

The other important comorbidities associated with racial, ethnic and economic subgroups may modify access to therapy, its delivery and strikingly, influence its outcome. Structural racism refers to the systematic disadvantage experienced by certain groups of people. Abraham et al among others have reported that the barrier of structural racism, as assessed by census tract variables, are a major influence on AML outcome and survival influenced by race, ethnicity and socioeconomic status (2–14). However, the influence of structural racism on disease specific transplant outcomes has not been well studied. The CIBMTR database would provide a unique and valuable opportunity to investigate this particularly pertinent question.

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 >18 years
AML
Disease status (CR1, CR2+, not in CR)
Including t-AML and preceding MDS/MPN
Any donor type and HLA match
Any conditioning intensity (MAC, RIC/NMA)
Any GVHD prophylaxis

Q21. Does this study include pediatric patients?

- No

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

Social and economic variables are much more difficult to assess in pediatric patients as their comorbidities and economic status are not well accessed with available data.

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/DataCollectionForms/Pages/index.aspx Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

We will assess clinical and demographic factors including:

- Age
- Gender
- Comorbidities identified by those enumerated in the HCT-CI
- BMI
- Leukemia phenotype defined by cytogenetics and molecular groupings, summarized as the CIBMTR modified ELN criteria
- t-AML yes/no
- Preceding MDS/MPN yes/no
- Disease status (CR1, CR2+, not in CR)

• Detectable MRD pre HCT (by flow, molecular or cytogenetic techniques) for those in CR.
• Donor type, graft source and HLA match
• Conditioning intensity (MAC, RIC/NMA)
• GVHD prophylaxis
Multivariate modeling using Cox and competing hazard estimates as appropriate will be used for estimating outcomes including patient (age, gender, comorbidities), disease (status, MRD and mELN grouping), transplant (donor, HLA match, conditioning intensity) plus
• Self-reported social demographics of White, non-Hispanic Black, Hispanic, Asian/Pacific Islander or other. Additionally, we propose conducting the same analysis after confirming and defining genetic ancestry using the model validated by V Damotte, M. Maiers et al (1) employing patients' HLA-haplotype data available.
• Payor type
• Zip code (9 digit) and/or census tract data will be included in all modeling as the primary covariate of interest with measures of income and racial/ethnic homogeneity reflected in the census tract demographics.

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/Committees/wc/LateEffects/Pages/default.aspx
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.aspx
None

Q25. NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required, i.e., neither database contains all the data required to answer the study question.
Zip code (9 digit) and census tract data:
In a preliminary feasibility study, we used a cohort of AML patients in first CR who underwent their first HCT between 2013-2019 (n=11,411). The CIBMTR has addresses (at time of HCT) for all patients

who had an unrelated donor HCT facilitated through the NMDP. It is recognized that some home address data might be confounded if reported as temporary housing near a transplant center.
For related donor HCTs, the CIBMTR has addresses for anyone that had an unrelated donor search initiated. Using an honest broker receiving addresses from a transplant center and then extracting 9 digit ZIP code and census tract data we would likely find relevant data for most patients (n=9475 of the sampled 11,411). Additional queries to HCT centers to report patients' home address to an honest broker for lookup and report of the missing ZIP and census tract data may reduce the amount of missing data.
Beginning with ZIP Code and as available, individual subject US census tract localization, we will include characterization of the census tract by percent minority population, economic status and payor type (private, Medicare, Medicaid) as primary covariates.
We propose conducting a multilevel analysis of disparities to determine the differential contribution of neighborhood measures of structural racism on self-reported racial/ethnic differences in survival, including 5 composite variables:
1. Structural racism (census tract disadvantage, affluence, and segregation)
2. Tumor biology (European Leukemia Network risk, secondary leukemia and remission status)
3. Health care access (insurance/payor and clinical trial enrollment)
4. Comorbidities (identified by those enumerated in the HCT-CI)
5. Treatment patterns (induction intensity and transplant utilization/access, conditioning intensity, graft and donor source)

Q26. REFERENCES:

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2. Abraham IE, Rauscher GH, Patel AA, Pearse WB, Rajakumar P, Burkart M, et al. Structural racism is a mediator of disparities in acute myeloid leukemia outcomes. Blood [Internet]. 2022 Apr 7 [cited 2022 May 16];139(14):2212–26. Available from: https://pubmed.ncbi.nlm.nih.gov/35061876/
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12. Bhatnagar B, Kohlschmidt J, Mrózek K, Zhao Q, Fisher JL, Nicolet D, et al. Poor Survival and Differential Impact of Genetic Features of Black Patients with Acute Myeloid Leukemia. Cancer Discov [Internet]. 2021 [cited 2022 May 12];11:626–63. Available from: http://aacrjournals.org/cancerdiscovery/article-pdf/11/3/626/1837521/626.pdf
13. Zeidan AM, Podoltsev NA, Wang X, Zhang C, Bewersdorf JP, Shallis RM, et al. Patterns of care and clinical outcomes with cytarabine-anthracycline induction chemotherapy for AML patients in the United States. 2020 [cited 2022 May 12]; Available from: http://ashpublications.org/bloodadvances/article-pdf/4/8/1615/1725453/advancesadv2020001728.pdf
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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 adult patients receiving first allo-HCT for AML in 2008-2019 in the United States, CRF track

Characteristic	N (%)
No. of patients	8004
No. of centers	164
Age at HCT	
Median (min-max)	55 (18-88)
18-29	853 (11)
30-39	897 (11)
40-49	1349 (17)
50-59	2168 (27)
60-69	2256 (28)
>=70	481 (6)
Recipient sex	
Male	4244 (53)
Female	3760 (47)
Race	
White	6490 (81)
Black or African American	717 (9)
Asian	471 (6)
Native Hawaiian or other Pacific Islander	23 (0)
American Indian or Alaska Native	42 (1)
More than one race	55 (1)
Missing	206 (3)
Ethnicity	
Hispanic or Latino	642 (8)
Non Hispanic or non-Latino	7203 (90)
Non-resident of the U.S.	43 (1)
Missing	116 (1)
ZIP code available	
No	98 (1)
Yes	7906 (99)
Karnofsky score	
<90	3346 (42)
>=90	4528 (57)
Missing	130 (2)
HCT-CI	
0	1816 (23)

Characteristic	N (%)
1	1201 (15)
2	1175 (15)
3	1455 (18)
4	931 (12)
5	598 (7)
6+	731 (9)
Missing	97 (1)
Clinical onset of AML	
De-novo	6037 (75)
Transformed from MDS/MPS	1462 (18)
Therapy linked	505 (6)
Disease status at time of HCT	
PIF	1073 (13)
CR1	4723 (59)
CR2	1446 (18)
>=CR3	103 (1)
Relapse	656 (8)
Missing	3 (0)
MRD at time of HCT	
Negative	4136 (52)
Positive	1745 (22)
Missing	391 (5)
N/A, Disease status not in CR	1732 (22)
Donor type	
HLA-identical sibling	1822 (23)
Other related	1204 (15)
Well-matched unrelated (8/8)	2922 (37)
Partially-matched unrelated (7/8)	652 (8)
Mis-matched unrelated (<= 6/8)	44 (1)
Multi-donor	7 (0)
Unrelated (matching TBD)	6 (0)
Cord blood	1347 (17)
Graft type	
Bone marrow	1145 (14)
Peripheral blood	5512 (69)
Cord blood	1347 (17)
Conditioning intensity	
MAC	4550 (57)

Characteristic	**N (%)**
RIC	2089 (26)
NMA	1104 (14)
TBD	197 (2)
Missing	64 (1)
GVHD prophylaxis	
Ex-vivo T-cell depletion	60 (1)
CD34 selection	217 (3)
Post-Cy	1329 (17)
Tac based	5071 (63)
CsA based	1190 (15)
Other	97 (1)
Missing	40 (0)
Year of HCT	
2008	935 (12)
2009	886 (11)
2010	721 (9)
2011	330 (4)
2012	282 (4)
2013	727 (9)
2014	871 (11)
2015	817 (10)
2016	788 (10)
2017	581 (7)
2018	571 (7)
2019	495 (6)
Median follow-up of survivors (range), months	66 (3-157)