Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
San Antonio, TX
Wednesday, February 21, 2024, 1:00 – 3:00 PM CST

Co-Chair:	**Partow Kebriaei, MD; M.D. Anderson Cancer Center, Houston, TX; Telephone: 713- 792-8750; E-mail: pkebriae@mdanderson.org**
Co-Chair:	**Christopher Hourigan, MD, DPhil; National Heart Blood and Lung Institute, Bethesda, MD; E-mail: hourigan@nih.gov**
Co-Chair:	**Nelli Bejanyan, MD; Moffitt Cancer Center, Minneapolis, MN; E-mail: nelli.bejanyan@moffitt.org**
Co-Chair:	**Filippo Milano, MD, PhD; Fred Hutch Cancer Center, Seattle, WA; E-mail: fmilano@fredhutch.org**
WCTL Program:	**Mariam Nawas, MD; The University of Chicago Medicine, Chicago, IL; E-mail: nawasm@bsd.uchicago.edu**
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Statistician:	**Wentong Liu, CIBMTR Statistical Center, Milwaukee, WI; E-mail: dylanliu@mcw.edu**

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1. Introduction

. Minutes from 2023 meeting (Attachment 1)
. Acknowledgement of outgoing co-chairs:
Partow Kebriaei; MD Anderson Cancer Center
Christopher Hourigan; National Heart Blood and Lung Institute
Thank you for all your contributions!
. Introduction of incoming co-chair:
Veronika Bachanova; University of Minnesota Blood and Marrow Transplant Program - Adults **Filippo Milano;** Fred Hutch Cancer Center – Transitioning from the Graft Sources Working Committee
d. Introduction of WCTL program participant:
Mariam Nawas; The University of Chicago Medicine

2. Accrual summary (Attachment 2)

3. Presentations, Published or Submitted papers

. **LK21-02b** Abid MB, Meryl NE, Zhang MJ, Chen K, Bredeson C, Allan D, Sabloff M, Marks DI, Litzow M, Hourigan CS, Kebriaei P, Saber W. Younger matched unrelated donors confer decreased relapse risk compared to older sibling donors in older patients with B-cell acute lymphoblastic leukemia undergoing allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2023 Oct 1; 29(10):611-618. doi: 10.1016/j.jtct.2023.07.015. Epub 2023 Jul 21. PMC10592336.***

b. **LK19-01** Murthy HS, Zhang MJ, Chen K, Ahmed S, Deotare U, Ganguly S, Kansagra A, Michelis FV, Nishihori T, Patnaik M, Abid MB, Aljurf M, Arai Y, Bacher U, Badar T, Badawy SM, Ballen K, Battiwalla M, Beitinjaneh A, Bejanyan N, Bhatt VR, Brown VI, Martino R, Cahn JY, Castillo P, Cerny J, Chhabra S, Copelan E, Daly A, Dholaria B, Diaz Perez MA, Freytes CO, Grunwald MR, Hashmi S, Hildebrandt GC, Jamy O, Joseph J, Kanakry CG, Khera N, Krem MM, Kuwatsuka Y, Lazarus HM, Lekakis LJ, Liu H, Modi D, Munshi PN, Mussetti A, Palmisiano N, Patel SS, Rizzieri DA, Seo S, Shah MV, Sharma A, Sohl M, Solomon SR, Ulrickson M, Ustun C, van der Poel M, Verdonck LF, Wagner JL, Wang T, Wirk B, Zeidan A, Litzow M, Kebriaei P, Hourigan CS, Weisdorf DJ, Saber W, Kharfan-Dabaja MA. Allogeneic hematopoietic cell transplantation for blastic plasmacytoid dendritic cell neoplasm: a CIBMTR analysis. ***Blood Adv. 2023 Nov 28;7(22):7007-7016. doi: 10.1182/bloodadvances.2023011308. PMID: 37792849; PMCID: PMC10690553.***

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 Gomez/A Dias/J Yared) **Protocol Development/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) **Manuscript Preparation.**
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) **Manuscript Preparation.**
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.**
g. **LK23-01** The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities (A Law/ T Moya)) **Protocol Development.**
h. **LK23-02** Prognostic impact of cytogenetic and molecular risk classification in AML after hematopoietic stem cell transplant in adolescents and young adults (H Lust/ S Chaudhury) **Protocol Development.**
i. **LK23-03** Impact of donor source in second allogeneic hematopoietic cell transplant in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020) (A Lucas/ A Scaradavou) - Transferred from Graft Sources Working Committee. **Protocol Development.**

5. Future/proposed studies

a. **PROP 2309-02/2310-18/2310-50** Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Therapy Related Acute Lymphoblastic Leukemia (N Chokr/ R Vasudevan Nampoothiri/ H Murthy/ M Kharfan Dabaja) (Attachment 4a, 4b and 4c)
b. **PROP 2309-21/2310-25** Optimal Donor Selection for older adults undergoing Allo SCT for MDS or AML in the era of PTCY (N Chokr/ A Arteaga/ M Sorror/ N Khaire/ A Law) (Attachment 5a and 5b)
c. **PROP 2310-31/2310-33/2310-111/2310-206/2310-266** Real-world experience (RWE) of adult patients receiving CD19-CAR-T cell therapy for B cell Acute Lymphoblastic Leukemia (B-ALL) (K Wudhikarn/ M Perales/ M Abid/ F Cervoni-Curet/ A Mirza/ L Gowda/ N Bejanyan) (Attachment 6a, 6b, 6c, 6d, and 6e)
d. **PROP 2310-42** Safety and efficacy of CAR-T cell therapy in relapsed/refractory acute lymphoblastic leukemia with central nervous system involvement (L Gonzalez Mosquera/ S Farhan) (Attachment 7)
e. **PROP 2310-87/2310-89/2310-116/2310-127/2310-190** Sequencing of chimeric antigen receptor T-cell therapy and allogeneic transplantation in adult patients with B-cell acute lymphoblastic leukemia (D Eng/ H Sibai/ R Mohty/ M Kharfan-Dabaja/ J Wang/ L Metheny/ J Fein/ A Gomez-Arteaga) (Attachment 8)
f. **PROP 2310-93** Comparison of FluFTBI and other myeloablative conditioning regimens for haploidentical and mismatched unrelated hematopoietic cell transplant with post-transplant cyclophosphamide in patients with acute leukemia (S Arslan/ M Al Malki) (Attachment 9)
g. **PROP 2310-97/2310-186** Transplant Outcomes Based on Intensity of Induction in Adult Patients with Ph+ ALL (A Ali/ A Chergui/ A Pelcovits) (Attachment 10a and 10b)
h. **PROP 2310-122/2310-187/2310-199** Impact of prior novel therapies on post-transplant outcomes in B-ALL (A Sayyed/ I Pasic/ A Chergui/ J Reagan/ M Connor/ N Frey) (Attachment 11a, 11b and 11c)
i. **PROP 2310-146** The role of HLA class II mismatched HCT in patients with high-risk acute leukemia (R Mehta/ A Ruggeri) (Attachment 12)

Proposed studies; not accepted for consideration at this time

j. **PROP 2310-04** Impact of depth of response in outcomes on patient with ALL in remission undergoing allogeneic stem cell transplantation. *Dropped – overlap with current study/publication.*
k. **PROP 2310-10** Outcomes of allogeneic hematopoietic cell transplantation in relapsed/ refractory acute myeloid leukemia with active disease. *Dropped – low scientific impact.*
l. **PROP 2310-15** Donor and Conditioning Choice for Patients with a High Comorbidity Age Index Score without a Matched Sibling Donor. *Dropped – low scientific impact.*
m. **PROP 2310-17** Outcomes and Predictors of outcomes after allogeneic hematopoietic stem cell transplantation in adult patients with therapy-related hematological malignancies developing after multiple myeloma. *Dropped – low scientific impact.*
n. **PROP 2310-34** Predictive factors of response to subsequent salvage treatments for post-transplant relapse in patients with myeloid neoplasm who relapsed following allogeneic hematopoietic cell transplant. *Dropped – small sample size.*
o. **PROP 2310-39** Stability of FLT3 mutation at relapse post allogenic transplant in FLT3 ITD mutation positive AML in the era of FLT3 inhibitors and its impact on prognosis. *Dropped – low scientific impact.*
p. **PROP 2310-40** Optimization of Graft-versus-Acute Myeloid Leukemia Effect for Human Leukocyte Antigen-Matched Hematopoietic Stem Cell Transplantation in Patients Receiving Post-Transplant Cyclophosphamide. *Dropped – small sample size.*
q. **PROP 2310-82** Impact of Hypomethylating agents Consolidation post Allogeneic Hematopoietic cell Transplantation among AML and MDS patients. *Dropped – low scientific impact.*

r. **PROP 2310-86** Use of FLT-3 inhibition in the peri-transplant period and its effect on transplant-related outcomes in patients with FLT-3 ITD positive Acute Myeloid Leukemia in CR1 in the CIBMTR database. *Dropped – low scientific impact.*

s. **PROP 2310-98** Outcomes of allogeneic hematopoietic stem cell transplant in patients with Ph+ve Acute Myeloid Leukemia. *Dropped – low scientific impact.*

t. **PROP 2310-104** Timed sequential busulfan to overcome MRD positivity and decrease the risk of leukemia relapse. *Dropped – small sample size.*

u. **PROP 2310-105** Impact of salvage therapy on outcomes post allogeneic transplantation for patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Dropped – low scientific impact.*

v. **PROP 2310-114** Characteristics and Post-Transplant Outcomes of Patients with Core-Binding Factor Acute Myeloid Leukemia. *Dropped – low scientific impact.*

w. **PROP 2310-115** Validation of the Transplant Conditioning Intensity (TCI) Score for Allogeneic Hematopoietic Cell Transplantation (alloHCT) in Acute Myeloid Leukemia (AML) Patients Receiving GVHD Prophylaxis with Post-Transplantation Cyclophosphamide (PTCy). *Dropped – low scientific impact.*

x. **PROP 2310-117** Outcomes of T-Cell Depleted Stem Cell Transplantation in Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome. *Dropped – low scientific impact.*

y. **PROP 2310-118** Chimeric antigen receptor (CAR) T-cell therapy versus Donor Lymphocyte Infusions (DLI) following Allogeneic Hematopoietic Stem Cell Transplantation in Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma. *Dropped – small sample size.*

z. **PROP 2310-124** Choice of therapy for Patients with AML Relapsing after Allogeneic Transplant in the Modern Era. *Dropped – overlap with current study/publication.*

aa. **PROP 2310-132** Evaluating survival outcomes of allogeneic hematopoietic stem cell transplantation in patients with isolated myeloid sarcoma. *Dropped – low scientific impact.*

ab. **PROP 2310-154** Impact of Early/ Late donor chimerism on outcomes in Acute Myeloid Leukemia/Myelodysplastic syndrome after reduced-intensity conditioning hematopoietic cell transplantation with matched sibling or matched unrelated donor transplant. *Dropped – small sample size.*

ac. **PROP 2310-158** Development of prognostic pre-transplant risk score for patients undergoing allogeneic HCT for acute leukemia transplanted in complete remission. *Dropped – low scientific impact.*

ad. **PROP 2310-168** Donor Lymphocyte infusion vs. second allogeneic hematopoietic cell transplantation for relapse after transplantation for AML/MDS- A CIBMTR analysis. *Dropped – low scientific impact.*

ae. **PROP 2310-174** Comparing Overall Survival in Patients Undergoing Allogenic Transplant with Extramedullary AML in Comparison to those with Intramedullary AML. *Dropped – small sample size*.

af. **PROP 2310-176** Donor lymphocyte Infusions with Hypomethylating agents in prophylaxis or treatment of relapse post Allogeneic Hematopoeitic Cell Transplants in Acute Myeloid Leukemia and Myelodysplastic Syndromes. *Dropped – small sample size.*

ag. **PROP 2310-184** Haploidentical versus mismatched unrelated donor transplant with post-transplant cyclophosphamide in Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome. *Dropped – overlap with current study/publication.*

ah. **PROP 2310-196** A Comparison of Fludarabine with Total Body Irradiation versus Etoposide with Total Body Irradiation as conditioning regimens for patients undergoing Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in First or Second Complete remission. *Dropped – small sample size.*

ai. **PROP 2310-202** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms. *Dropped – supplemental data needed.*

aj. **PROP 2310-203** Prognostic significance of the AML European LeukemiaNet 2022 risk stratification for patients undergoing allogeneic stem cell transplantation with subgroup analysis based on age and race. *Dropped – overlap with current study/publication.*

ak. **PROP 2310-224** Outcome of patients with Acute Myeloid leukemia (AML) after allogeneic hematopoietic cell (HCT) transplantation using novel International Consensus Classification (ICC) classification 2022 for AML in comparison to patients with AML using WHO classification (2016). *Dropped – supplemental data needed.*

al. **PROP 2310-226** Chimeric antigen receptor T-cell therapy versus Donor Lymphocyte Infusions following Allogeneic Hematopoietic Stem Cell Transplantation in Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma. *Dropped – low scientific impact.*

am. **PROP 2310-227** Survival after relapse following first allogeneic transplant for patients with AML and MDS in the modern era. *Dropped – low scientific impact.*

an. **PROP 2310-229** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms. *Dropped – supplemental data needed.*

ao. **PROP 2310-247** The impact of obesity and body weight on outcomes in patients with lymphoid malignancies treated with CAR-T therapy. *Dropped – low scientific impact.*

ap. **PROP 2310-249** Characterizing differences in clinical outcomes of commercial CAR T-cell therapy for relapsed/refractory ALL and LBCL large B-cell lymphoma based on gender. *Dropped – low scientific impact.*

aq. **PROP 2310-268** Impact of mixed donor chimerism and donor lymphocyte infusions on future relapse in the post-transplant cyclophosphamide-based graft versus host disease (GVHD) prophylaxis setting. *Dropped – low scientific impact.*

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Orlando, FL
Wednesday, February 15, 2023, 1:00 – 3:00 PM

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:	**TDB**

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1. **Introduction**
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. Mark Litzow welcomed the first presenter.

   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)

   Dr. Pasvolsky presented the proposal on behalf of the group. The group hypothesize that pre-transplant MRD status is predictive of outcomes for patients with ALL receiving allo-HCT in CR2. The predictive yield might be reduced in patients transplanted in CR3 or beyond, due to early

progression. The study looks to compare outcomes of patients with ALL receiving their first allo-HCT in CR2 or beyond, between those with pretransplant MRD negative and MRD positive disease status. Also, looks to examine whether the prognostic yield of pre-transplant MRD is similar for patients receiving allo- HCT at CR2 or at a later CR. Lastly, it looks to describe outcomes for this population. We identified 3410 cases receiving first allo-HCT for ALL in CR2+ from 2013 to 2019 registered in the CIBMTR database.

The floor was opened for questions and comments from the audience. A member of the audience asked if this question has not been addressed previously. Another member made a comment on the age of the cohort and asked for generalizable is the MRD collection across all centers and CIBMTR data collection forms. A member asked about how to treat the different detection thresholds among the field. A question was raised on the use of novel agents and the main effect of the study. A member suggested to restrict to the most sensitive MRD detection threshold or do a subset analysis with this.

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)

Dr. Novitzky presented the proposal on behalf of the group. The group hypothesize that changes in standard of care, updated molecular and cytogenetic information, and novel pre- and posttransplant 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. The study looks to determine the Overall Survival, Leukemia Free Survival and other outcomes. Also, looks to identify significant covariates on post transplants outcomes on this groups. Lastly, to develop a specific risk score by disease status at transplant. We identified 5616 cases receiving first allo-HCT for AML or ALL from 2013 to 2019 registered in the CRF-level track.

The proposal was opened for questions and comments. A member of the audience asked on how the group will be going to select which variables will be incorporated into the risk score modeling. Another member asked if this score will be used to decide if a patient goes to transplant or not. A suggestion was made to look at the AUC and compare with other established scores and models. A member asked how ALL and AML cohort will be treated in the

score modelling since they are very different disease entities. Suggestion on create different models for each disease.

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)
Dr. Iyer presented the proposal concept. The group hypothesizes that there will be no difference in rates of DFS, OS, and relapse between mutated IDH1/2 AML patients undergoing HCT versus wtIDH1/2AML patients undergoing HCT. The primary objective is to identify differences in the following post-transplant outcomes between mutIDH1, mutIDH2 and wtIDH1/2patients. Also, looks to identify prognostic factors associated with post-transplant outcomes in patients with mutIDH1/2 AML. We identified 6029 cases receiving first allo-HCT for AML from 2013-2020 in the CRF track, of those 3971 cases had unknown IDH1/IDH2.

The floor was opened for questions and comments from the audience. A member of the audience asked if CIBTMR collects information on IDH1/IDH2. Another member recommended to look at the impact of Venetoclax on these patients. A member followed-up the previous question and asked on how reliable the reporting of drugs is used before transplant. A member of the audience referenced Dr. Hourigan study and asked if those panels could be used for this study. A concern was raised on a possible selection bias on the cohort that reported not tested.

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)

Dr. Koller presented the proposal concept. The study hypothesizes that allo-HCT worsens short term mortality but affords longer-survival benefit relative to novel AML therapy in patients 75 years or older. The study looks 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. Also looks to outcomes at landmark periods of 1, 2 year and 3 years by treatment modality. Lastly, looks to evaluate differences in outcomes by genetic risk stratification and benchmark outcomes for AML patients 75 years and older.
We identified 199 cases receiving first allo-HCT for AML in CR1 from 2016-2021 aged >=75 in the CIBMTR database.

The floor was opened for questions and comments from the audience. A member raised a concern on possible selection bias when comparing patients from VIALE vs. HCT, since the age distribution is different. A comment was made on adjusting at Age and comorbidity. Another concern was raised on possible lead-time bias when using CR1 cases and suggested using CR2 instead or do a landmark analysis to correct for the mandatory time needed to get a transplant. Another suggestion made was to investigate CR1 cases with an additional cycle of therapy or use time from diagnosis to HCT as a proxy.

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)

Dr. Manjappa presented the concept virtually on behalf of the group. The study hypothesizes that 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. The study looks to 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 and describe survival outcomes and NRM of adult patients in CR after Brexu-cel with and without consolidative allo-HCT. Also looks to identify factors impacting outcomes after Brexu-Cel. We identified 83 cases receiving Brexu-Cel for ALL in 2021-2022 registered in the CIBMTR database.

The floor was opened for questions and comments from the audience. A question of cases was raised on the availability of relapse/refractory cases were MRD+ in this cohort. How many cases underwent second transplant in the cohort and how the reason for the second transplant. Concern was raised regarding the small sample size. Concern between comparisons made in the real-word data against a clinical trial.

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)

Dr. Law presented the concept virtually to the audience. The study hypothesizes that allo-HCT does not modify outcomes in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with chromosome 3 abnormalities. The study aims to assess outcomes in patients diagnosed with AML and MDS with chromosome 3 abnormalities undergoing Allo-HCT and to identify factors contributing to adverse outcomes in AML and MDS with chromosome 3 abnormalities undergoing Allo-HCT. We identified 733 cases receiving first allo-HCT for AML/MDS with chromosome 3 abnormality from 2008-2019 with CRF level data, which 53% were diagnosed with AML.

The session was opened for questions from the audience. A question was raised on how this data compares to EBMT, can you learn anything on it and the benefit of transplant. Another member raised a concern on disease status at transplants CR vs non-CR. How many patients went to transplant in a leukemia-free state. Another question was raised on how to analysis co-

existing chromosomal abnormalities. Another question was asked on the availability on mutational data.

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)

Dr. Williams presented the concept on behalf of the group. The group hypothesize that post relapse survival for patients with MDS and AML undergoing first ASCT has improved substantially and anticipate that patients with relapsed AML/MDS after ASCT harbor unique molecular and cytogenet¬¬ic changes compared to their original disease. The study looks to Overall Survival (OS) for patients with MDS and AML relapse following first or second allogeneic stem cell transplant in the modern era and describe the molecular and cytogenetic mutational landscape in AML/MDS relapse after ASCT. Also looks to identify predictors of relapse post-ASCT based on pre-transplant characteristics, determine one-year progression free survival (PFS) post relapse, characterize dynamic changes in clonal evolution (molecular and cytogenetics) at time of disease relapse compared to their original disease. Lastly determine real-world practice patterns for use of maintenance (Y/N), and the impacts of maintenance on cumulative incidence of relapse after first ASCT (stratified by disease risk group, minimal residual disease MRD status, conditioning intensity) and develop predictive model for relapse after ASCT. We identified 2184 AML patients in CR1/CR2 and 2155 MDS cases receiving first allo-HCT from 2011-2020 with relapse post-HCT.

The floor was opened for questions. A concern was raised on the difference in relapse definitions among centers. A comment was made on the hominization of relapse definition globally. A comment made on the important of characterizing relapse. A concern was raised on how relapse is capture at the CIBMTR. A comment was made on the molecular landscape and the use of maintenance therapy. A comment was made on the availability of chimerism data.

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)

Dr. Lust presented the concept. The study hypothesizes 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. We identified 1173 cases aged 15-39 receiving a MAC conditioned first allo-HCT for AML and 237 RIC/NMA allo-HCT having CRF-level from data 2008-2019.

The floor was opened for questions. A question was made on the availability of Molecular data and the differences among the AYA group. Another concern was made on the wide age range for AYA. A comment was made to use a dataset that also include patients that did not get a transplant. A concern was raised that this study cohort is mostly Young adults and numbers for adolescents will be too small for comparisons.

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)

Dr. Murthy presented the concept. The group hypothesizes that 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. The study looks to compare the major clinical outcomes of allo-HCT for relapsed AML based on the MRD status. We identified 4734 MRD negative cases and 2088 MRD positive cases receiving first allo-HCT in CR2 from 2008-2019 with CRF-level information.

The floor was opened for questions and comments from the floor. A member raised a concern on the variability on MRD definitions, different cut-offs and measurements. Another member commented on the difference between of MRD among the CR1 and CR2 patients. Another member asked if in the time period proposed if there enough information on molecular data to assess MRD.

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)
Dr. Shultz presented the concept. The group hypothesizes that 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. The study aims to evaluate 3-years relapse-free survival and overall survival and other major clinical outcomes. We identified 546 cases from age >=60 receiving first allo-HCT for AML with FM100 or FM140 in 2008- 2019, CRF track.

The floor was open for questions and comments from the audience. A comment was made on analyzing the benefit of the higher melphalan dose. Any confounding factors when selecting melphalan dose. Another member commented on possible center effect among the treatment goals. The presenter proposed a match-propensity score to overcome differences confounding factors and possibly center effect.

K. **PROP 2210-26** Equal access and outcome for transplantation in AML: a 21st-century goal (N El Jurdi/ D Weisdorf) (Attachment 14)

Dr. El Jurdi presented the concept virtually while Dr. Weisdorf answered questions in-person to the audience. The group hypothesizes that access to therapy, availability of an array of suitable donors plus clinical and social comorbidities confounds outcomes for minority populations beyond the limits of their intrinsic disease biology. Social and economic factors compromise their potential for a best possible outcome. The study will 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 identified 8,004 adult patients receiving first allo-HCT for AML in 2008-2019 in the United States in CIBMTR-CRF track.

The floor was open for comments and questions from the audience. A member of the audience commented on would it be possible to match this analysis. A concern was raised on the use of self-reported data. The presenter proposes to use HLA-definitions for Race/ethnicity. A concern was raised on overlap with other CIBMTR studies looking into socioeconomic predictors and components. Another member asked if education level will be accounted in the model. Another member asked if they would analyze distance to transplant center. A member raised a concern on overlap with a recent publication from the Health Services Working Committee.

Proposed studies; not accepted for consideration at this time.

A. **PROP 2209-06** Effect of Major Residual Disease on Hematopoietic Stem Cell Transplantation: Transplant Outcomes in Patients with Primary Induction Failure
B. **PROP 2209-08** Effects of Cytogenetic Features in TP53 mutated Myeloid Malignancies Post-Allogeneic Transplant
C. **PROP 2209-19** Donor Lymphocyte Infusion versus Second Transplant for Relapsed MDS/AML After Allogeneic Transplant
D. **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
E. **PROP 2210-14** Maintenance Therapy for Patients with FLT3 Mutated Acute Myeloid Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation
F. **PROP 2210-21** Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Philadelphia -Like Acute Lymphoblastic Leukemia
G. **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?
H. **PROP 2210-32** CD19+CAR-T therapy vs allogeneic HCT for poor-risk B-cell ALL with post-induction MRD positivity
I. **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)
J. **PROP 2210-52** Peri-transplant use of novel FLT3 inhibitors for allogeneic stem cell transplant in Flt3 mutated acute myeloid leukaemia- CIBMTR study

K. **PROP 2210-55** Comparative effectiveness study of novel agent consolidation versus allogeneic transplantation for AML in patients ≥ 75 years of age
L. **PROP 2210-68** Low-intensity or chemotherapy-free regimens versus high-intensity regimens prior to allo-HCT for adults with newly diagnosed Ph+ ALL
M. **PROP 2210-81** Outcomes of allogeneic hematopoietic cell transplantation in older patients with acute myeloid leukemia treated with hypomethylating agent and venetoclax
N. **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
O. **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
P. **PROP 2210-126** Machine learning prediction of acute myeloid leukemia (AML) relapse after allogeneic hematopoietic cell transplantation
Q. **PROP 2210-135** Real-world experience of post-allogeneic hematopoietic cell transplantation maintenance in acute myeloid leukemia and transplant outcomes
R. **PROP 2210-136** Validation of European Leukemia Net Genetic Risk Stratification 2022 for Acute Myeloid Leukemia Patients receiving Allogeneic Hematopoietic Cell Transplantation
S. **PROP 2210-142** Outcomes of patients with AML/MDS undergoing reduced intensity allogeneic transplantation with clofarabine- versus fludarabine-based regimens
T. **PROP 2210-146** Impact of minimal residual disease on outcomes of allogeneic hematopoietic cell transplantation for Philadelphia chromosome negative B-cell acute lymphoblastic leukemia.
U. **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
V. **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
W. **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)
X. **PROP 2210-187** Outcomes of allogeneic hematopoietic stem cell transplantation (allo-SCT) for adult T cell leukemia-lymphoma (ATLL)
Y. **PROP 2210-195** Incidence and Outcomes of Mixed Phenotype Leukemia Patients Receiving Stem Cell Transplantation
Z. **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
AA. **PROP 2210-215** Clinical Outcomes of Adults with Undergoing Allogeneic Stem Cell Transplant for secondary Acute Lymphoblastic Leukemia
BB. **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

CC. **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

DD. **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

EE. **PROP 2210-247** Donor lymphocyte infusion vs. second allogeneic hematopoietic cell transplantation for relapse after transplantation for AML/ MDS- a CIBMTR analysis

FF. **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

GG. **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

HH. **PROP 2210-263** Inherited myeloid malignancy and donor cell leukemia

II. **PROP 2210-265** Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Acute Myeloid Leukemia with a Pure Hyperdiploid Karyotype

JJ. **PROP 2210-279** Defining the Landscape of Allogeneic Stem Cell Transplant in Relapsed Refractory Acute Lymphoblastic Leukemia

KK. **PROP 2210-289** Role of Post Remission Consolidation Therapy Prior to Haploidentical Transplantation for Patients with Acute Myeloid Leukemia in First Complete Remission

Proposed studies; not accepted for consideration after Tandem meeting evaluations

LL. **PROP 2210-26** Equal access and outcome for transplantation in AML: a 21st-century goal

MM. **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

NN. **PROP 2210-297** 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)

OO. **PROP 2210-191; 2210-193** Impact of Clonal Evolution in Post-Transplantation Relapsed Myeloid Neoplasms

PP. **PROP 2210-2210; 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

QQ. **PROP 2210-232** Outcomes of allogeneic hematopoietic cell transplantation for relapsed acute myeloid leukemia based on minimal residual disease status: CIBMTR analysis

RR. **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

SS. **PROP 2210-25** Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation

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:

A. **PROP 2210-179** The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities.
B. **PROP 2210-218** Prognostic impact of cytogenetic and molecular risk classification in AML after hematopoietic stem cell transplant in adolescents and young adults.

Working Committee Overview Plan for 2023-2024		
Study number and title	**Current status**	**Chairs priority**
LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm	Submitted	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	Published	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	2
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	2
LK22-01: Intensive induction chemotherapy vs. hypomethylating agent therapy for older AML patients undergoing allogeneic hematopoietic cell transplantation	Protocol Development	2
LK23-01: The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities.	Protocol Development	3
LK23-02: Prognostic impact of cytogenetic and molecular risk classification in AML after hematopoietic stem cell transplant in adolescents and young adults.	Protocol Development	3
LK23-03: Impact of donor source in second allogeneic hematopoietic cell transplant in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020)	Protocol Development	3

Accrual Summary for the Acute Leukemia Working Committee

Characteristics of recipients of first allogeneic transplants for AML and ALL reported to the CIBMTR between 2008 and 2023

Characteristic	AML	ALL
Number of patients	12683	5293
No. of centers	293	256
Age at HCT - no. (%)		
Median (min-max)	52.4 (0.3-87.8)	29.3 (0.3-78.6)
<10	846 (6.7)	912 (17.2)
10-17	625 (4.9)	723 (13.7)
18-29	1213 (9.6)	1071 (20.2)
30-39	1232 (9.7)	716 (13.5)
40-49	1822 (14.4)	721 (13.6)
50-59	2862 (22.6)	643 (12.1)
60-69	3262 (25.7)	463 (8.7)
>=70	821 (6.5)	44 (0.8)
Recipient sex - no. (%)		
Male	6822 (53.8)	3117 (58.9)
Female	5861 (46.2)	2176 (41.1)
HCT-CI - no. (%)		
0	3863 (30.5)	2201 (41.6)
1	1864 (14.7)	810 (15.3)
2	1628 (12.8)	668 (12.6)
3+	5064 (39.9)	1526 (28.8)
Missing	264 (2.1)	88 (1.7)
Disease status at time of HCT - no. (%)		
PIF	1495 (11.8)	140 (2.6)
CR1	7689 (60.6)	2980 (56.3)
CR2	2378 (18.7)	1576 (29.8)
>=CR3	178 (1.4)	361 (6.8)
Relapse	931 (7.3)	232 (4.4)
Not reported	12 (0.1)	4 (0.1)
Time from diagnosis to HCT - no. (%)		
Median (min-max)	52.4 (0.3-87.8)	29.3 (0.3-78.6)
<6 months	7124 (56.2)	1725 (32.6)
6-12months	2913 (23.0)	1503 (28.4)
>12 months	2646 (20.9)	2065 (39.0)
Conditioning regimen intensity - no. (%)		
Myeloablative	7322 (57.7)	4162 (78.6)

Characteristic	AML	ALL
Reduced intensity	1193 (9.4)	249 (4.7)
Non-myeloablative	2531 (20.0)	616 (11.6)
Missing	1637 (12.9)	266 (5.0)
Product type - no. (%)		
Bone marrow	1957 (15.4)	1090 (20.6)
Peripheral blood	8397 (66.2)	2744 (51.8)
Umbilical cord blood	2326 (18.3)	1458 (27.5)
Not reported	3 (0.0)	1 (0.0)
Type of donor - no. (%)		
HLA-identical sibling	2671 (21.1)	1081 (20.4)
Identical twin	36 (0.3)	25 (0.5)
Other relative	2155 (17.0)	947 (17.9)
Unrelated	5686 (44.8)	1840 (34.8)
Cord blood	2135 (16.8)	1400 (26.5)
Year of HCT - no. (%)		
2008-2009	2498 (19.7)	940 (17.8)
2010-2011	1466 (11.6)	509 (9.6)
2012-2013	1516 (12.0)	599 (11.3)
2014-2015	2379 (18.8)	995 (18.8)
2016-2017	1884 (14.9)	854 (16.1)
2018-2019	1426 (11.2)	753 (14.2)
2020-2021	876 (6.9)	323 (6.1)
2022-2023	638 (5.0)	320 (6.0)
Median follow-up of survivors (range), months - median (range)	71.8 (0.0-181.3)	65.2 (0.0-175.9)

Characteristics of recipients of first autologous transplants for AML and ALL reported to the CIBMTR between 2008 and 2023

Characteristic	AML	ALL
Number of patients	214	20
No. of centers	73	12
Age at HCT - no. (%)		
Median (min-max)	45.9 (1.8-80.2)	35.5 (21.7-65.5)
<10	6 (2.8)	0 (0.0)
10-17	4 (1.9)	0 (0.0)
18-29	30 (14.0)	6 (30.0)
30-39	37 (17.3)	6 (30.0)
40-49	42 (19.6)	4 (20.0)
50-59	49 (22.9)	2 (10.0)
60-69	41 (19.2)	2 (10.0)
>=70	5 (2.3)	0 (0.0)
Recipient sex - no. (%)		
Male	107 (50.0)	14 (70.0)
Female	107 (50.0)	6 (30.0)
HCT-CI - no. (%)		
0	85 (39.7)	7 (35.0)
1	32 (15.0)	3 (15.0)
2	28 (13.1)	5 (25.0)
3+	62 (29.0)	5 (25.0)
Missing	7 (3.3)	0 (0.0)
Disease status at time of HCT - no. (%)		
PIF	0 (0.0)	1 (5.0)
CR1	143 (66.8)	17 (85.0)
CR2	65 (30.4)	2 (10.0)
>=CR3	3 (1.4)	0 (0.0)
Relapse	3 (1.4)	0 (0.0)
Time from diagnosis to HCT - no. (%)		
Median (min-max)	5.9 (2.8-181.5)	8.8 (4.9-37.3)
<6 months	112 (52.3)	3 (15.0)
6-12months	35 (16.4)	14 (70.0)
>12 months	67 (31.3)	3 (15.0)
Product type - no. (%)		
Bone marrow	3 (1.4)	0 (0.0)
Peripheral blood	210 (98.1)	20 (100)
Umbilical cord blood	1 (0.5)	0 (0.0)
Year of HCT - no. (%)		

Characteristic	AML	ALL
2008-2009	112 (52.3)	7 (35.0)
2010-2011	34 (15.9)	3 (15.0)
2012-2013	34 (15.9)	6 (30.0)
2014-2015	15 (7.0)	1 (5.0)
2016-2017	11 (5.1)	2 (10.0)
2018-2019	6 (2.8)	1 (5.0)
2020-2021	1 (0.5)	0 (0.0)
2022-2023	1 (0.5)	0 (0.0)
Median follow-up of survivors (range), months - median (range)	95.1 (0.0-171.2)	79.0 (0.0-95.5)

Note: Due to ongoing data transition, conditioning intensities are being provided as estimates.
Conditioning intensity for AML cohort for 2013-2019: MAC 50.2%, RIC 31.2% and NMA 17.7%.
Conditioning intensity for ALL cohort for 2013-2019: MAC 76.6%, RIC/NMA 23.3%.

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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 has been written and reviewed by the Writing Committee. The plan is to finalize the manuscript and submit it for publication by April 2024.

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 including an extensive review of cytogenetic data. The plan is to finalize the data file and complete the analysis by July 2024.

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.

The analysis is nearly complete, and an abstract was submitted to EBMT. The manuscript is currently being written. The plan is to finalize the manuscript and submit it for publication by July 2024.

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 2024.

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.

The analysis has been completed and circulated to the Writing Committee for feedback. The manuscript is currently being written. The plan is to have a draft manuscript prepared over the next few months and submit it for publication in July 2024.

LK22-01: Impact of pre-allogeneic hematopoietic cell transplantation therapy in acute myeloid leukemia and myelodysplastic syndrome on post-transplant outcomes (N Ali)
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 and start datafile preparation by July 2024.

LK23-01: The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities. (Arjun L)
The purpose of this study is to:

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

Protocol development is currently in progress. The plan is to finalize the protocol and study population by July 2024.

LK23-02: Prognostic impact of cytogenetic and molecular risk classification in AML after hematopoietic stem cell transplant in adolescents and young adults. (Hannah L)
The purpose of this study is to:

(1) Describe the prognostic significance of ELN2022 cytogenetic risk stratification in AYA patients with AML receiving HSCT in CR1 or CR2.

(2) 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.
(3) 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.

Protocol development is currently in progress. The plan is to finalize the protocol and study population by July 2024.

LK23-03: Impact of donor source in second allogeneic hematopoietic cell transplant in patients with acute leukemia/MDS who relapsed after prior allograft during the current era (2014-2020). (Alexandre L)

The purpose of this study is to:

(1) Evaluate the impact of HCT-2 donor (related, unrelated, haplo identical or CB) on Leukemia-free Survival (LFS) at 1 year in patients transplanted during the period 2014-2020.
(2) Evaluate transplant outcomes after HCT-2 in the subgroups of patients who received unrelated CB grafts or had haplo-donors. Evaluate whether the development of GvHD after HCT-1 impacts the incidence of relapse after HCT-2.

Protocol development is currently in progress. The plan is to finalize the protocol and study population by July 2024.

Thank you for your ongoing support and interest in these studies.

Field	Response
Proposal Number	2309-02-CHOKR
Proposal Title	Outcomes of allogeneic stem cell transplantation for therapy related ALL
Key Words	ALL, therapy, allogeneic transplantation
Principal Investigator #1: - First and last name, degree(s)	Nora Chokr MD
Principal Investigator #1: - Email address	noc4001@med.cornell.edu
Principal Investigator #1: - Institution name	Weill Cornell Medicine
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
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
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Is ALL associated with prior genotoxic therapy associated with worse outcomes after allogeneic transplantation
RESEARCH HYPOTHESIS:	Therapy related ALL is associated with worse outcomes after allogeneic stem cell transplantation and than can be independent of cytogenetic and genetic abnormalities.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary - PFS/RFS - OS Secondary CI of relapse CI acute GVHD
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Most patients with ALL receive transplant in CR2 unless with a obvious high risk cytogenetic and genetic features. t-ALL is poorly defined. There is limited data that demonstrated worse outcomes in t-ALL regardless of genetic/cytogenetic abnormalities. This may help highlight this high risk group who will likely benefit from consolidation with alloHCT in CR1.

Field	Response
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.	Therapy related ALL is poorly defined. Similar to t-MDS/AML, the pathogenesis of t-ALL is attributed to the genotoxic effect of cytotoxic therapies on hematopoietic progenitor cells, but the exact mechanisms are less understood. Aldoss et al. reported the largest retrospective study from a single institution with analysis focused only on cases with prior exposure to cytotoxic therapies. The frequency of t-ALL was 10%, an important subset of patients showed cytogenetic abnormalities similar to those found in t-MDS/AML, and the outcome of t-ALL patients was poorer than that of the de novo ALL patients, especially for those who did not undergo alloHSCT. Some centers offer transplant in CR2 especially in the absence of high risk cytogenetic abnormalities and genetic mutations while others offer transplant in CR1, based on the assumption of the poor prognosis from retrospective studies, mirroring what occurs in t-MDS/AML. However, one study by Genzel et al could not identify an impact of prior genotoxic therapies on the prognosis of ALL. Saygin et al showed in a univariable analysis for OS in t-ALL patients, male sex, exposure to topoisomerase II inhibitors, and radiotherapy to be associated with poor survival, whereas achievement of CR/CRi after first-line therapy and undergoing HCT to be associated with better OS. Similarly, RFS after achievement of CR/CRi for patients who underwent HCT was significantly better than patients who did not undergo HCT (HR, 0.25; 95% CI, 0.07-0.86; P = .02). The multivariable analysis of OS demonstrated that performance of HCT was the only independent predictor of outcome in this cohort (HR, 0.41; 95% CI, 0.20-0.82; P = .01) More large data base studies are needed to compare outcomes of ALL with and without prior genotoxic therapy and establish prior therapy as an independent risk factor.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion Adults 18 years or older with ALL If prior history of malignancy, should have received genotoxic treatment (chemotherapy and or radiation) CR at time of allogeneic transplantation Exclusion Patients with prior history of malignancy who have not received genotoxic therapy Patients with active ALL at time of transplant Patients who are receiving a second transplant or beyond
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	therapy related ALL is a diagnosis of older patients

Field	Response
REFERENCES:	Saygin, C., Kishtagari, A., Cassaday, R. D., Reizine, N., Yurkiewicz, I., Liedtke, M., Stock, W., Larson, R. A., Levine, R. L., Tallman, M. S., Park, J. H., Kerr, C., Przychodzen, B., Sekeres, M. A., Kalaycio, M. E., Carraway, H. E., Hamilton, B. K., Sobecks, R., Gerds, A., … Advani, A. S. (2019, December 23). Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes. American Society of Hematology. Ribera, J.-M. (2018, October). Therapy-related acute lymphoblastic leukemia. Haematologica. https://www.ncbi.nlm.nih.gov/pmc/articles /PMC6165810/#b1-1031581 Aldoss, I., Stiller, T., Tsai, N.-C., Song, J. Y., Cao, T., Bandara, N. A., Salhotra, A., Khaled, S., Aribi, A., Al Malki, M. M., Mei, M., Ali, H., Spielberger, R., O'Donnell, M., Snyder, D., Slavin, T., Nakamura, R., Stein, A. S., Forman, S. J., … Pullarkat, V. (2018, October). Therapy-related acute lymphoblastic leukemia has distinct clinical and cytogenetic features compared to de novo acute lymphoblastic leukemia, but outcomes are comparable in transplanted patients. Haematologica.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-18-VASUDEVANNAMPOOTHIRI
Proposal Title	Outcomes and Predictors of outcomes of adult patients with therapy-related acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation.
Key Words	therapy related acute lymphoblastic leukemia; therapy related hematological malignancies
Principal Investigator #1: - First and last name, degree(s)	Ram Vasudevan Nampoothiri MD DM MRCP (UK)
Principal Investigator #1: - Email address	rvasudevan@toh.ca
Principal Investigator #1: - Institution name	The Ottawa Hospital
Principal Investigator #1: - Academic rank	Asst. Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Nil
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	What are the outcomes and predictors of outcomes of adults with therapy related acute lymphoblastic leukemia undergoing allogeneic stem cell transplantation
RESEARCH HYPOTHESIS:	We hypothesize that outcomes of therapy related ALL (overall survival, relapse free survival, cumulative incidence of relapse, non-relapse mortality) are comparable to previously reported outcomes of denovo high risk ALL after allogeneic hematopoietic stem cell transplant. We also hypothesize that pre-transplant cytogenetics and molecular profile, along with pre transplant minimal residual disease may be predictors for outcomes in therapy related ALL after allogeneic hematopoietic stem cell transplant.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Objective Assess overall survival of adult patients with therapy related acute lymphoblastic leukemia who underwent allogeneic hematopoietic stem cell transplantation. Secondary Objectives • Assess progression free survival and relapse rates of patients with therapy related acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation. • Assess pre transplant and post-transplant factors associated with poor overall survival and progression free survival in these patients. • Assess rates of, and factors associated with non-relapse mortality in these patients.
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.	With less than 100 cases reported in literature on Allogeneic Hematopoietic stem cell transplantation (HSCT) in therapy related acute lymphoblastic leukemia – results of the proposed study will provide preliminary evidence as to whether allogeneic bone marrow transplant is beneficial in patients with therapy related ALL and what the predictors for better outcomes are in this population. This will be a platform for prospective randomized studies to study the degree of benefit of the HSCT in this population in comparison to other treatment modalities.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Justification.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	106273
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	1. STUDY SUBJECTS - The study would comprise of all adult patients (>18 years of age) with therapy related acute lymphoblastic leukemia undergoing allogeneic HSCT from 01-Jan-2010 to 31-Dec-2023 reported to the CIBMTR 2. INCLUSION CRITERIA - All adult patients (>18 years of age) with therapy related acute lymphoblastic leukemia undergoing allogeneic HSCT during the study period reported to the CIBMTR. Therapy related acute lymphoblastic leukemia will be defined as acute lymphoblastic leukemia developing in patients who has prior exposure to therapy known to predispose to subsequent malignancy (chemotherapy, radiotherapy etc.) which may be given for a malignant or non-malignant disorder. 3. EXCLUSION CRITERIA - Patients with known inherent germline mutations and genetic disorders predisposing them to multiple neoplastic disorders (eg – Fanconi Anemia) - Patients with prior malignancy who did not undergo chemotherapy or radiotherapy.
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Therapy related ALL is rare in pediatric population and if they occur they are likely to be due to a diagnosed or undiagnosed genetic predisposing abnormality = exclusion criteria. Hence pediatric patients are excluded

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient Specific (including prior malignancy / treatment) • Age at transplant (Date of birth) • Gender • Race • Country of transplant (if available) • Significant comorbidities •Date of diagnosis of primary malignancy if applicable • Cytotoxic Treatment (chemo/RT) received received (Drugs/Dose/No of cycles) • Radiotherapy received of not • Latent period to diagnosis to t-ALL • Date of Diagnosis of t-ALL • Cytogenetic Abnormalities (Conventional cytogenetics / FISH) • Molecular Abnormalities (PCR/NGS) including MLL abnormalities & BCR-ABL Abnormalities • CNS involvement (Yes/No) • Risk Stratification • Induction & Consolidation Treatment received • Date of remission • Remission status / MRD status at transplant • Interval from diagnosis to transplant • Performance status (ECOG/Karnofksy) at transplant • HCT-CI Score prior to transplant Transplant information (Including conditioning regimens and GVHD Prophylaxis) • Transplant date •Donor type: MUD vs Haploidentical donor • HLA mismatch • Donor-recipient gender match • Donor-recipient ABO mismatch • Donor age (if available) • Conditioning regimen description MAC/RIC/NMA • GVHD Prophylaxis - Calcineurin based • T cell depletion (Y/N) • Stem cell source (BM or PBSC) Outcome Measures • Neutrophil engraftment date • Platelet engraftment date • VOD: Yes/No. Grade if available. Resolved: Yes/no • CMV reactivation: yes/no. Date of first reactivation • EBV reactivation: yes/no. • PTLD yes/no • Acute GVHD (aGVHD) • Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD) • Chronic GVHD (cGVHD) • Incidence of chronic GVHD (aGVHD) (subset evaluating moderate and severe cGVHD) • Death yes/no • Time to mortality • Day 100, 6 months and 2 year mortality • Treatment related mortality at 6 months and 1 year • Cause of mortality • Patient alive with no graft failure and absence of active GVHD: Yes/No • Graft failure (primary and secondary) • Date of the graft failure • Relapse yes/No • Date of

Field	Response
	Relapse • Molecular / Morphological relapse • Treatment Received for relapse • Second transplant: Yes/No. Date of the second transplant • Relapse of the primary malignancy
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	N/A
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.	N/A

REFERENCES:	1. Tang G, Zuo Z Fau - Thomas DA, Thomas Da Fau - Lin P, Lin P Fau - Liu D, Liu D Fau - Hu Y, Hu Y Fau - Kantarjian HM, et al. Precursor B-acute lymphoblastic leukemia occurring in patients with a history of. Haematologica. 2012;97(6):919-25 LID - 10.3324/haematol.2011.057752 [doi]. 2. Pagano L, Pulsoni A Fau - Tosti ME, Tosti Me Fau - Annino L, Annino L Fau - Mele A, Mele A Fau - Camera A, Camera A Fau - Martino B, et al. Acute lymphoblastic leukaemia occurring as second malignancy: report of the. Br J Haematol. 1999;106(4):1037-40. 3. Ishizawa S, Slovak Ml Fau - Popplewell L, Popplewell L Fau - Bedell V, Bedell V Fau - Wrede JE, Wrede Je Fau - Carter NH, Carter Nh Fau - Snyder DS, et al. High frequency of pro-B acute lymphoblastic leukemia in adults with secondary. Leukemia. 2003;17(6):1091-5. 4. Abdulwahab A, Sykes J Fau - Kamel-Reid S, Kamel-Reid S Fau - Chang H, Chang H Fau - Brandwein JM, Brandwein JM. Therapy-related acute lymphoblastic leukemia is more frequent than previously. Cancer. 2012;118(16):3962-7 LID - 10.1002/cncr.26735 [doi]. 5. Ganzel C, Devlin S, Douer D, Rowe JM, Stein EM, Tallman MS. Secondary acute lymphoblastic leukaemia is constitutional and probably not. Br J Haematol. 2015;170(1):50-5 LID - 10.1111/bjh.13386 [doi]. 6. Rosenberg AS, Brunson A, Paulus JK, Tuscano J, Wun T, Keegan THM, et al. Secondary acute lymphoblastic leukemia is a distinct clinical entity with. Blood Cancer J. 2017;7(9):e605 LID - 10.1038/bcj.2017.81 [doi]. 7. Swaika A, Frank RD, Yang D, Finn LE, Jiang L, Advani P, et al. Second primary acute lymphoblastic leukemia in adults: a SEER analysis of. Cancer Med. 2018;7(2):499-507 LID - 10.1002/cam4.266 [doi]. 8. Ribera JM. Therapy-related acute lymphoblastic leukemia. Haematologica. 2018;103(10):1581-3 LID - 10.3324/haematol.2018.200311 [doi] FAU - Ribera, Josep-Maria. 9. Aldoss I, Stiller T, Tsai NC, Song JY, Cao T, Bandara NA, et al. Therapy-related acute lymphoblastic leukemia has distinct clinical and. Haematologica. 2018;103(10):1662-8 LID - 10.3324/haematol.2018.193599 [doi]. 10. Aldoss I, Dagis A, Palmer J, Forman S, Pullarkat V. Therapy-related ALL: cytogenetic features and hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50(5):746-8 LID - 10.1038/bmt.2015.8

Field	Response
	[doi] FAU - Aldoss, I. 10. Shivakumar R, Tan W Fau - Wilding GE, Wilding Ge Fau - Wang ES, Wang Es Fau - Wetzler M, Wetzler M. Biologic features and treatment outcome of secondary acute lymphoblastic. Ann Oncol. 2008;19(9):1634-8 LID - 10.093/annonc/mdn182 [doi]. 11. Aldoss I, Stiller T, Song J, Al Malki M, Ali H, Salhotra A, et al. Philadelphia chromosome as a recurrent event among therapy-related acute. Am J Hematol. 2017;92(2):E18-E9 LID - 0.1002/ajh.24604 [doi] FAU - Aldoss, Ibrahim. 12. Kelleher N, Gallardo D, Gonzalez-Campos J, Hernandez-Rivas JM, Montesinos P, Sarra J, et al. Incidence, clinical and biological characteristics and outcome of secondary acute. Leuk Lymphoma. 2016;57(1):86-91 LID - 10.3109/10428194.2015.1040013 [doi]. 13. Vasudevan Nampoothiri R, Law AD, Lam W, et al. Outcomes of therapy-related acute lymphoblastic leukemia in adults after allogeneic stem cell transplantation. Eur J Haematol. 2020 Jul;105(1):24-29. doi: 10.1111/ejh.13403. Epub 2020 Mar 18. PMID: 32115767.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Not for publication or presentation ***Attachment 4b***

Table 1 – Available literature on Allogeneic hematopoietic stem cell transplant in patients with t-ALL

Study	t-ALL	Most common Cytogenetic abnormality	Allo HSCT n(%)	NRM of HSCT patients	2-year OS of HSCT patients
Aldoss et al.[9]	93	t (9;22)	49 (53.7)	28.5% (? time)	53.4%
Shivakumar et al.[11]	89+	11q23 rearrangement	14 (15.73)	NA	NA
Ganzel et al.[5]	23	t (9;22)	8 (34.8)*	NA	NA
Abdulwahab et al.[4]	23	11q23 rearrangement	5 (21.7)	20% (2 year)	60%
Kelleher et al.[12]	16	Hyperdiploidy (33%)	2 (12.5)	NA	NA
Vasudevan Nampoothiri et al[13]	18	11q23 rearrangement	18 (100)	33.3% (2 year)	51.8%

* - both secondary ALL(s-ALL) & t-ALL combined

\+ includes both own patients and that collected from literature.

Field	Response
Proposal Number	2310-50-MURTHY
Proposal Title	Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in Therapy related Acute Lymphoblastic Leukemia (tr-ALL)
Key Words	Therapy related Acute Lymphoblastic Leukemia (tr-ALL)
Principal Investigator #1: - First and last name, degree(s)	Hemant Murthy MD
Principal Investigator #1: - Email address	murthy.hemant@mayo.edu
Principal Investigator #1: - Institution name	Mayo Clinic Florida
Principal Investigator #1: - Academic rank	Associate Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Mohamed A. Kharfan Dabaja
Principal Investigator #2 (If applicable): - Email address:)	kharfandabaja.mohamed@mayo.edu
Principal Investigator #2 (If applicable): - Institution name:	Mayo Clinic Florida
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Hemant Murthy
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	LK 20-03: Outcomes of HCT for T-ALL
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Outcomes of HCT for tr-ALL
RESEARCH HYPOTHESIS:	Allogeneic hematopoietic cell transplantation (allo-HCT) is associated with durable remissions in patients with therapy related acute lymphoblastic leukemia (tr-ALL). Outcomes of allo-HCT in tr-ALL are similar to matched patient cohort with de novo ALL.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. To describe clinical outcomes of patients with tr-ALL undergoing allogeneic hematopoietic cell transplantation (Allo-HCT) including: • Overall Survival (OS) • Progression-free Survival (PFS) • Non-relapse mortality (NRM) • Cumulative incidence of acute graft versus host disease (aGVHD) • Cumulative incidence of chronic graft versus host disease (cGVHD) • Cumulative incidence of relapse/progression 2. To identify the impact of patient-, disease-, and transplant-related factors on the outcomes of PFS, OS, relapse and NRM for tr-ALL undergoing allo-HCT 3. To compare outcomes of patients with tr-ALL undergoing allo-HCT to similar patient cohort with de novo ALL undergoing allo-HCT. 4. Identify patient, disease, and therapy related factors that influence development of tr-ALL

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.	Therapy related leukemias represent a distinct entity resulting from prior exposure to cytotoxic therapies including chemotherapy and/or radiation therapy. Therapy-related myeloid neoplasms, which include therapy-related acute myeloid leukemia (t-AML) and therapy-related myelodysplastic syndrome (t-MDS) in general, carry poor cytogenetic and molecular features at the time of diagnosis, and carry poor prognosis. Allo-HCT can provide durable remissions in selected individuals with therapy related myeloid neoplasms, however there still exists high rate of relapse and poor overall and disease free survival(1). Therapy-related acute lymphoblastic leukemia (tr-ALL) is a recently recognized but poorly defined entity with the current literature being comprised mainly of retrospective registry data and case series with an estimated incidence of 3-9% of ALL cases (2–10) with the most common malignancies reported to be associated with tr-ALL include breast and plasma cell disorders(10–12). Tr-ALL is associated with an inferior survival outcome compared to de novo ALL, partly because it has been shown to harbor a predominance of high-risk genetic features compared with de novo ALL, mainly hypodiploidy/near triploidy, 11q23 (KMT2A) rearrangement, monosomies of chromosomes 5, 7 and 17, complex karyotype and even the Philadelphia chromosome(8,10,12,13). Additionally, patients with tr-ALL harbor mutations commonly seen in myeloid malignancies such as DNMT3A, IDH 1/2, RUNX1, and ASXL1. Finally, patients with tr-ALL were less likely to achieve a complete remission or achieve minimal residual disease (MRD) with induction therapy compared to patients with de novo ALL (10,12,14). The role of allogeneic hematopoietic cell transplantation (Allo-HCT) is not well described. Few studies have described alloHCT outcomes in tr-ALL (Table 1), with most HCT outcomes reported as part of larger reported outcomes of tr-ALL who either received or did not receive allo-HCT. Recently, Abdel Rahman and colleagues reported Mayo Clinic Experience of 69 patients with tr-ALL, including 34 who received allo-HCT. They found inferior OS in tr-ALL compared to de novo ALL, but OS was not significant when comparing allo-HCT recipients with tr-ALL compared to de novo ALL(14). Important questions remain regarding allo-HCT in this population, including conditioning intensity, choice of donor and gvhd prophylaxis, and CR1 vs other remission states to name a few. Given this emerging subset of patients with a high risk hematologic malignancy, limited studies with small sample sizes reporting increase benefit with allo-HCT, and the relative lack or limited transplant specific data and

Field	Response
	outcomes reported, there exists a need to provide more information regarding the role of allo-HCT in tr-ALL. This can be accomplished largely through the use of registry data. Thus we propose to utilize CIBMTR registry data to evaluate outcomes of allo- HCT recipients with tr-ALL and compare Allo-HCT outcomes between tr-ALL and de novo ALL.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_BY63U2d7EAzaXId
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	table 1.PNG
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	29724
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/png
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion Criteria Diagnosis of Acute lymphoblastic leukemia (tr-ALL and de novo) who received first Allo-HCT between 2008-2020 Exclusion Criteria Allo-HCT for any other etiology aside from ALL
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	unlikely pediatric pts would have therapy related neoplasm

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Variables to be described: (bolded variables will be considered in multivariate analysis) Patient-related: Age at transplant: continuous & by age group: decades Patient sex: male vs. female Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3 vs. missing Race: Caucasian vs. others vs. missing Disease-related: Disease state at time of transplant: CR1 vs CR2 vs PR vs SD vs PD Time from diagnosis to HCT Number of pre-transplant lines of therapy B cell vs T cell Ph+ vs Ph -ve Induction therapy: Hyper CVAD induction vs pediatric style induction vs other induction strategies BM involvement: (yes/no) CNS disease at time of diagnosis (yes/no) Cytogenetic abnormalities at diagnosis MRD status at time of allo-HCT (pos vs neg) Prior malignancy preceding diagnosis of ALL (tr-ALL only) Transplant-related: Cell source: bone marrow vs. peripheral blood vs. umbilical cord blood Transplant donor type: Match related donor vs. match unrelated donor vs. mismatch unrelated donor vs haploidentical donor vs cord blood Conditioning intensity: myeloablative vs. reduced intensity conditioning/non-myeloablative T-cell depletion: ATG/alemtuzumab (yes/no) Total Body Irradiation: TBI vs non-TBI based conditioning regimen Myeloablative: TBI vs non-TBI based conditioning regimen RIC/NMA: TBI vs non-TBI based conditioning regimen GVHD prophylaxis: CNI + MTX ± others except MMF, post Cy vs. CNI + MMF ±others except post Cy vs. CNI + others except MMF, MTX vs. missing vs. other Donor-recipient sex match: male-male vs. male-female vs. female-male vs. female-female vs. missing CMV serostatus matching (+/-, +/+, -/-, -/+) between donor and recipient ABO compatibility: Minor vs Major vs matched Year of transplant: continuous Post transplant treatment: DLI vs others vs None Prior auto HCT (yes vs no)

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Field	Response
	lymphoblastic leukemia (dnALL): Contemporary Mayo Clinic ALL cohort. 2020; 12. Saygin C, Kishtagari A, Cassaday RD, Reizine N, Yurkiewicz I, Liedtke M, et al. Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes. Blood Adv. 2019 Dec 23;3(24):4228–4237. 13. Aldoss I, Stiller T, Song J, Al Malki M, Ali H, Salhotra A, et al. Philadelphia chromosome as a recurrent event among therapy-related acute leukemia. Am J Hematol. 2017 Feb;92(2):E18–E19. 14. Abdel Rahman Z, Parrondo RD, Heckman M, Spiegel M, Miller KC, Sproat LO, et al. Comparative study of therapy-related (tALL) and de novo adult acute lymphoblastic leukemia (dnALL): Contemporary Mayo Clinic ALL cohort. JCO. 2020 May 20;38(15_suppl):7523–7523. 15. Vasudevan Nampoothiri R, Law AD, Lam W, Chen C, Al-Shaibani Z, Loach D, et al. Outcomes of Therapy Related Acute Lymphoblastic Leukemia in Adults after Allogeneic Stem Cell Transplantation. Eur J Haematol. 2020 Mar 1; 16. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995 Jun;15(6):825–828. 17. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389–401.e1. 18. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009 Dec;15(12):1628–1633.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Not for publication or presentation ***Attachment 4c***

Table 1: Selected studies of alloHCT in tr-ALL

Publication	Study	No. patients	Remission status at alloHCT (N)	Donor type	Regimen intensity (N)	Outcomes
Nampoothri et al. (15)	Toronto	18	CR1=16 CR2=2	MRD=5 MUD=10 Haplo= 3	MAC=8 RIC=10	2 year OS: 51.8% 2 year NRM: 33% 2 year relapse: 16.7%
Saygin et al. [12]	multicenter	42	CR1=35 CR2=7	MRD=12 MUD=18 Haplo= 2 UCB= 5 Other= 5	MAC=25 NMA= 7 Unk= 10	Median OS: 46 mos
Abdel-Rahman et al. (14)	Mayo	34	CR1= 27 CR2= 7	MRD=15 MUD=15 Haplo= 4	MAC=15 NMA=19	3 year OS: 48.6% 3 year NRM: 35.5% 3 year relapse: 31.1%
Aldoss et al.(10)	City of Hope	49	CR1=37 CR2 or other= 12	MRD =5 MUD=3 Other=3	MAC=8 RIC=3	2 year OS: 53.4% 2 year NRM: 28.5% relapse: NR

Characteristics of adult patients with ALL in 2008-2023

Characteristic	De novo	Therapy-related	Total
No. of patients	16770	1324	18094
No. of centers	378	198	379
Disease status - no. (%)			
CR	15608 (93.1)	1245 (94.0)	16853 (93.1)
Patients have chemotherapy or radiationtherapy if they have prior maligancy + Patients without second transplant	14821 (88.4)	**300 (22.7)**	15121 (83.6)
Patients without known inherent germline mutations and genetic disorders predisposing them to multiple neoplastic disorders - no. (%)			
Yes	16746 (99.9)	1322 (99.8)	18068 (99.9)
Patients have chemotherapy or radiationtherapy if they have prior maligancy	16626 (99.1)	**353 (26.7)**	16979 (93.8)
Year Group - no. (%)			
Others	3149 (18.8)	293 (22.1)	3442 (19.0)
2008-2020	13621 (81.2)	1031 (77.9)	14652 (81.0)
Prior Malignancy			
Breast cancer - no. (%)			
No	35 (0.2)	324 (24.5)	359 (2.0)
Yes	7 (0.0)	219 (16.5)	226 (1.2)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	70 (0.4)	398 (30.1)	468 (2.6)
CNS - no. (%)			
No	36 (0.2)	455 (34.4)	491 (2.7)
Yes	1 (0.0)	16 (1.2)	17 (0.1)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	75 (0.4)	470 (35.5)	545 (3.0)
Gastrointestinal malignancy - no. (%)			
No	36 (0.2)	430 (32.5)	466 (2.6)
Yes	1 (0.0)	56 (4.2)	57 (0.3)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	75 (0.4)	455 (34.4)	530 (2.9)
Genitourinary malignancy - no. (%)			

Characteristic	De novo	Therapy-related	Total
No	31 (0.2)	338 (25.5)	369 (2.0)
Yes	11 (0.1)	194 (14.7)	205 (1.1)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	70 (0.4)	409 (30.9)	479 (2.6)
Leukemia (includes acute or chronic leukemia) - no. (%)			
No	86 (0.5)	231 (17.4)	317 (1.8)
Yes	15 (0.1)	65 (4.9)	80 (0.4)
Not reported	16669 (99.4)	1028 (77.6)	17697 (97.8)
Lung cancer - no. (%)			
No	37 (0.2)	459 (34.7)	496 (2.7)
Yes	0 (0.0)	13 (1.0)	13 (0.1)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	75 (0.4)	469 (35.4)	544 (3.0)
Lymphoma - no. (%)			
No	93 (0.6)	201 (15.2)	294 (1.6)
Yes	9 (0.1)	97 (7.3)	106 (0.6)
Not reported	16612 (99.1)	348 (26.3)	16960 (93.7)
Not selected	56 (0.3)	678 (51.2)	734 (4.1)
MDS/MPN - no. (%)			
No	94 (0.6)	243 (18.4)	337 (1.9)
Yes	9 (0.1)	43 (3.2)	52 (0.3)
Not reported	16612 (99.1)	348 (26.3)	16960 (93.7)
Not selected	55 (0.3)	690 (52.1)	745 (4.1)
Melanoma - no. (%)			
No	33 (0.2)	428 (32.3)	461 (2.5)
Yes	9 (0.1)	62 (4.7)	71 (0.4)
Not reported	16658 (99.3)	383 (28.9)	17041 (94.2)
Not selected	70 (0.4)	451 (34.1)	521 (2.9)
Multiple myeloma / plasma cell disorder (PCD)- no. (%)			
Yes	7 (0.0)	81 (6.1)	88 (0.5)
Not reported	16682 (99.5)	493 (37.2)	17175 (94.9)
Not selected	81 (0.5)	750 (56.6)	831 (4.6)
Oropharyngeal cancer - no. (%)			
No	18 (0.1)	68 (5.1)	86 (0.5)

Characteristic	De novo	Therapy-related	Total
Yes	0 (0.0)	10 (0.8)	10 (0.1)
Not reported	16664 (99.4)	426 (32.2)	17090 (94.5)
Not selected	88 (0.5)	820 (61.9)	908 (5.0)
Sarcoma - no. (%)			
No	18 (0.1)	64 (4.8)	82 (0.5)
Yes	2 (0.0)	24 (1.8)	26 (0.1)
Not reported	16664 (99.4)	426 (32.2)	17090 (94.5)
Not selected	86 (0.5)	810 (61.2)	896 (5.0)
Thyroid cancer - no. (%)			
No	17 (0.1)	65 (4.9)	82 (0.5)
Yes	5 (0.0)	87 (6.6)	92 (0.5)
Not reported	16664 (99.4)	426 (32.2)	17090 (94.5)
Not selected	84 (0.5)	746 (56.3)	830 (4.6)
Other skin(Basal, squamous cell) cancer - no. (%)			
No	18 (0.1)	177 (13.4)	195 (1.1)
Yes	130 (0.8)	0 (0.0)	130 (0.7)
Not reported	16612 (99.1)	348 (26.3)	16960 (93.7)
Not selected	10 (0.1)	799 (60.3)	809 (4.5)
Other hematological - no. (%)			
No	18 (0.1)	61 (4.6)	79 (0.4)
Yes	53 (0.3)	96 (7.3)	149 (0.8)
Not reported	16612 (99.1)	348 (26.3)	16960 (93.7)
Not selected	87 (0.5)	819 (61.9)	906 (5.0)
Other solid tumor - no. (%)			
Yes	0 (0.0)	12 (0.9)	12 (0.1)
Not reported	16770 (100)	1312 (99.1)	18082 (99.9)
Patient Related			
Age at HCT - no. (%)			
Median (min-max)	38.9 (18.0-78.6)	56.9 (18.0-75.5)	40.2 (18.0-78.6)
18-29	5422 (32.3)	110 (8.3)	5532 (30.6)
30-39	3330 (19.9)	112 (8.5)	3442 (19.0)
40-49	3275 (19.5)	211 (15.9)	3486 (19.3)
50-59	2975 (17.7)	381 (28.8)	3356 (18.5)
60-69	1613 (9.6)	428 (32.3)	2041 (11.3)

Characteristic	De novo	Therapy-related	Total
>=70	155 (0.9)	82 (6.2)	237 (1.3)
Sex - no. (%)			
Male	9945 (59.3)	618 (46.7)	10563 (58.4)
Female	6824 (40.7)	706 (53.3)	7530 (41.6)
Not reported	1 (0.0)	0 (0.0)	1 (0.0)
Race - no. (%)			
White	10869 (64.8)	1036 (78.2)	11905 (65.8)
Black or African American	773 (4.6)	61 (4.6)	834 (4.6)
Asian	1399 (8.3)	57 (4.3)	1456 (8.0)
Native Hawaiian or other Pacific Islander	81 (0.5)	2 (0.2)	83 (0.5)
American Indian or Alaska Native	128 (0.8)	8 (0.6)	136 (0.8)
More than one race	142 (0.8)	7 (0.5)	149 (0.8)
Not reported	3378 (20.1)	153 (11.6)	3531 (19.5)
Reporting track - no. (%)			
TED	13829 (82.5)	1086 (82.0)	14915 (82.4)
CRF	2941 (17.5)	238 (18.0)	3179 (17.6)
US or Non-US - no. (%)			
US	10986 (65.5)	1046 (79.0)	12032 (66.5)
Non-US	5784 (34.5)	278 (21.0)	6062 (33.5)
Karnofsky score prior to HCT - no. (%)			
90-100	10955 (65.3)	696 (52.6)	11651 (64.4)
< 90	5522 (32.9)	605 (45.7)	6127 (33.9)
Not reported	293 (1.7)	23 (1.7)	316 (1.7)
HCT-CI - no. (%)			
0	6011 (35.8)	154 (11.6)	6165 (34.1)
1	2563 (15.3)	92 (6.9)	2655 (14.7)
2	2418 (14.4)	77 (5.8)	2495 (13.8)
3+	4839 (28.9)	969 (73.2)	5808 (32.1)
TBD, review needed for history of malignancies	48 (0.3)	27 (2.0)	75 (0.4)
TBD, inconsistencies between parent and sub-questions	4 (0.0)	0 (0.0)	4 (0.0)
NA, f2400 (pre-TED) not completed	4 (0.0)	0 (0.0)	4 (0.0)
Missing	883 (5.3)	5 (0.4)	888 (4.9)
Disease Related			
Disease status at time of HCT - no. (%)			
PIF	454 (2.7)	40 (3.0)	494 (2.7)

Characteristic	De novo	Therapy-related	Total
CR1	11552 (68.9)	1018 (76.9)	12570 (69.5)
CR2	3485 (20.8)	193 (14.6)	3678 (20.3)
>=CR3	571 (3.4)	34 (2.6)	605 (3.3)
Relapse	674 (4.0)	38 (2.9)	712 (3.9)
Not reported	34 (0.2)	1 (0.1)	35 (0.2)
Time from diagnosis to HCT - no. (%)			
<6 months	6679 (39.8)	667 (50.4)	7346 (40.6)
6-12months	5439 (32.4)	400 (30.2)	5839 (32.3)
>12 months	4652 (27.7)	257 (19.4)	4909 (27.1)
Transplant Related			
Donor type - no. (%)			
HLA-identical sibling	5697 (34.0)	345 (26.1)	6042 (33.4)
Other related	2570 (15.3)	200 (15.1)	2770 (15.3)
Well-matched unrelated (8/8)	4705 (28.1)	521 (39.4)	5226 (28.9)
Partially-matched unrelated (7/8)	1050 (6.3)	81 (6.1)	1131 (6.3)
Mis-matched unrelated (<= 6/8)	50 (0.3)	4 (0.3)	54 (0.3)
Unrelated (matching TBD)	1505 (9.0)	100 (7.6)	1605 (8.9)
Cord blood	995 (5.9)	70 (5.3)	1065 (5.9)
Not reported	198 (1.2)	3 (0.2)	201 (1.1)
Donor/recipient CMV serostatus - no. (%)			
+/+	6811 (40.6)	476 (36.0)	7287 (40.3)
+/-	1413 (8.4)	123 (9.3)	1536 (8.5)
-/+	3654 (21.8)	366 (27.6)	4020 (22.2)
-/-	3239 (19.3)	266 (20.1)	3505 (19.4)
CB - recipient +	697 (4.2)	53 (4.0)	750 (4.1)
CB - recipient -	283 (1.7)	17 (1.3)	300 (1.7)
CB - recipient CMV unknown	15 (0.1)	0 (0.0)	15 (0.1)
Not reported	658 (3.9)	23 (1.7)	681 (3.8)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)			
No drugs reported	28 (0.2)	2 (0.2)	30 (0.2)
MAC	12230 (72.9)	623 (47.1)	12853 (71.0)
RIC	2798 (16.7)	478 (36.1)	3276 (18.1)
NMA	1108 (6.6)	182 (13.7)	1290 (7.1)
TBD	593 (3.5)	35 (2.6)	628 (3.5)
N/A, F2400 (pre-TED) not submitted, drug dose not available	4 (0.0)	2 (0.2)	6 (0.0)
Not reported	9 (0.1)	2 (0.2)	11 (0.1)

Characteristic	De novo	Therapy-related	Total
Donor/recipient sex match - no. (%)			
M-M	5895 (35.2)	379 (28.6)	6274 (34.7)
M-F	3583 (21.4)	377 (28.5)	3960 (21.9)
F-M	3246 (19.4)	191 (14.4)	3437 (19.0)
F-F	2679 (16.0)	273 (20.6)	2952 (16.3)
CB - recipient M	573 (3.4)	32 (2.4)	605 (3.3)
CB - recipient F	422 (2.5)	38 (2.9)	460 (2.5)
Not reported	372 (2.2)	34 (2.6)	406 (2.2)
Product type - no. (%)			
BM	2703 (16.1)	140 (10.6)	2843 (15.7)
PB	13072 (77.9)	1114 (84.1)	14186 (78.4)
UCB	995 (5.9)	70 (5.3)	1065 (5.9)
GVHD prophylaxis - no. (%)			
None	105 (0.6)	6 (0.5)	111 (0.6)
Ex-vivo T-cell depletion	137 (0.8)	9 (0.7)	146 (0.8)
CD34 selection	214 (1.3)	13 (1.0)	227 (1.3)
PtCy + other(s)	3299 (19.7)	305 (23.0)	3604 (19.9)
PtCy alone	104 (0.6)	8 (0.6)	112 (0.6)
TAC + MMF +- other(s) (except PtCy)	1227 (7.3)	125 (9.4)	1352 (7.5)
TAC + MTX +- other(s) (except MMF, PtCy)	5147 (30.7)	456 (34.4)	5603 (31.0)
TAC + other(s) (except MMF, MTX, PtCy)	769 (4.6)	75 (5.7)	844 (4.7)
TAC alone	346 (2.1)	33 (2.5)	379 (2.1)
CSA + MMF +- other(s) (except PtCy,TAC)	1008 (6.0)	88 (6.6)	1096 (6.1)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	3354 (20.0)	163 (12.3)	3517 (19.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	28 (0.2)	0 (0.0)	28 (0.2)
CSA alone	759 (4.5)	25 (1.9)	784 (4.3)
Other(s)	240 (1.4)	15 (1.1)	255 (1.4)
Missing	33 (0.2)	3 (0.2)	36 (0.2)
Year of current transplant - no. (%)			
2008	888 (5.3)	29 (2.2)	917 (5.1)
2009	940 (5.6)	37 (2.8)	977 (5.4)
2010	1001 (6.0)	53 (4.0)	1054 (5.8)
2011	1020 (6.1)	49 (3.7)	1069 (5.9)
2012	1093 (6.5)	68 (5.1)	1161 (6.4)
2013	1051 (6.3)	66 (5.0)	1117 (6.2)
2014	1022 (6.1)	78 (5.9)	1100 (6.1)
2015	1047 (6.2)	85 (6.4)	1132 (6.3)
2016	1052 (6.3)	102 (7.7)	1154 (6.4)
2017	1138 (6.8)	131 (9.9)	1269 (7.0)

Characteristic	De novo	Therapy-related	Total
2018	1122 (6.7)	110 (8.3)	1232 (6.8)
2019	1161 (6.9)	129 (9.7)	1290 (7.1)
2020	1086 (6.5)	94 (7.1)	1180 (6.5)
2021	1150 (6.9)	99 (7.5)	1249 (6.9)
2022	1149 (6.9)	90 (6.8)	1239 (6.8)
2023	850 (5.1)	104 (7.9)	954 (5.3)
Median follow-up of survivors (range), months - median (range)	41.2 (0.0-176.6)	48.1 (0.0-174.3)	42.9 (0.0-176.6)

Field	Response
Proposal Number	2309-21-CHOKR
Proposal Title	Comparing outcomes of alternative donor transplantation in patients 65 years and older with myeloid malignancies
Key Words	cord blood, haploidentical, mismatched unrelated donors, allogeneic transplantation
Principal Investigator #1: - First and last name, degree(s)	Nora Chokr MD and Alexandra Gomez Arteaga MD
Principal Investigator #1: - Email address	noc4001@med.cornell.edu / alg9117@med.cornell.edu
Principal Investigator #1: - Institution name	Weill Cornell Medicine
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Mohamed Sorror
Principal Investigator #2 (If applicable): - Email address:)	msorror@fredhutch.org
Principal Investigator #2 (If applicable): - Institution name:	Fred Hutchinson Cancer Research Center
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Nora Chokr
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	Yes
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	To compare outcomes of older patients (65 yr and older) with no matched donors undergoing MMUD (7/8 mismatch at single locus) transplantation with PTCy vs haploidentical transplantation with PTCy vs cord blood transplantation
RESEARCH HYPOTHESIS:	Alternative donor transplantation in older patients is feasible and offer comparable leukemia free survival; PTCy regimens are less toxic with lower TRM

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary - Leukemia free survival - TRM -OS Secondary -Engraftment of neutrophils and platelets -CI of Relapse - CI primary graft failure - CI acute GVHD - CI chronic GVHD - Immune reconstitution - Hospital length of stay - Infection rate
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	As we are transplanting more patients in their 7th and 8th decade of life, this is a very pertinent clinical question because these patients even if they have a matched related donor, these donors are older in age. Many of these patients do not have fully matched donors in registries. Physicians often have to chose between MMUD 7/8 vs related haploidentical vs cord blood transplants. Cord blood transplantation is thought to be associated with slower immune reconstitution, higher risk of infections and higher overall TRM. Answering this question can give some insight regarding the better donor option in the absence of a matched donor.

Field	Response
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.	Consolidation with allogeneic transplant in CR1 for high grade myeloid malignancies is a standard practice. Many patients are diagnosed in their 7th and 8th decade of life. Older patients tend to have more comorbidities and are more frail especially after undergoing induction therapy. Sibling donors for these patients are old. A recent CIBMTR analysis showed that younger MUDs are associated less relapse and better DFS compared to older MSDs. Many of these older patient do not have fully matched MUDs. Different institutions have preferential practices when it comes to alternative donor transplantation. There is little data examining the toxicities, outcomes, and disease control amongst the available donor choices in these patients. Cord blood transplantation are presumed to have a better GVL effect as depicted by some publications. In a recent CIBMTR-Eurocord analysis, Weisdorf et al compared outcomes of patients 50 years and older undergoing stem cell transplantation with MUD (8/8 and 7/8) vs cord blood and found higher TRM and lower LFS with cord blood transplant compared to 8/8 MUD transplants. 7/8 MUDs had a higher TRM and similar LFS. UCB had the lowest rate of chronic GVHD. Three-year survival was 8/8 URD 43%, UCB 30% and 7/8 URD 37%. However, in this paper none of the patients received PTCy as part of the GVHD prophylaxis which introduced a major shift in practice across the US especially after BMT CTN 1703 and hence the paper did not explore haploidentical transplantation. We propose a comparison of outcomes between UCB vs haplo+PTCy vs MMUD 7/8+ PTCy to try to prioritize donor options in the absence of matched related or unrelated donors in older patients.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion - Age 65 and older - Allogeneic transplant recipients with high/very high risk MDS or AML - Recipients of cord blood transplantation, haploidentical transplantation (<7/8) + PTCy or MMUD (7/8, mismatched at a single locus) transplantation with PTCy Exclusion - Prior history of transplantation
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Focus is on older patients (geriatric population)
REFERENCES:	Alternative Donor Transplantation for Older Patients with Acute Myeloid Leukemia in First Complete Remission: a CIBMTR-Eurocord Analysis Weisdorf et al
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-25-KHAIRE
Proposal Title	Outcomes in patients with MDS and AML undergoing Allogeneic stem cell transplantation using older matched sibling donors vs younger unrelated donors with PTCy based GVHD prophylaxis strategies
Key Words	Allo-SCT, MUD, MSD, PTCY
Principal Investigator #1: - First and last name, degree(s)	Niranjan Khaire, MBBS, MD, DM.
Principal Investigator #1: - Email address	Niranjan.Khaire@uhn.ca
Principal Investigator #1: - Institution name	Princess Margaret Cancer Centre, University Of Toronto
Principal Investigator #1: - Academic rank	Clinical Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Arjun Law MBBS, MD, DM, DRCPC
Principal Investigator #2 (If applicable): - Email address:)	Arjun.Law@uhn.ca
Principal Investigator #2 (If applicable): - Institution name:	Princess Margaret Cancer Centre, University Of Toronto
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
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:	Arjun Law
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	LK23-01: Proposal accepted by Acute Leukemia Working Committee for outcomes of AML and MDS with chromosome 3 abnormalities. Currently in protocol development phase
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Chris Hourigan , Kristin Page , Nelli Benjanyan
RESEARCH QUESTION:	Has the use of Post Transplant Cyclophosphamide (PTCy) as Graft Versus Host Disease (GVHD) Prophylaxis changed the paradigm for optimal donor choice amongst patients with older matched siblings (MSD) versus younger matched unrelated donors (MUD) in terms of comparable or superior transplant outcomes?

Field	Response
RESEARCH HYPOTHESIS:	With the use of PTCY based GVHD prophylaxis, use of a younger MUD will lead to better outcomes compared with older matched sibling donors.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Outcome : Overall survival Secondary Outcomes : Relapse free Survival ; Cumulative incidence of relapse ; Non Relapse Mortality ; acute GVHD ; chronic GVHD and GVHD-free Relapse-free survival
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	In patients with MDS/AML despite evidence to suggest that choosing a younger unrelated donor is associated with lesser relapse, the benefit is offset by a higher risk of GVHD in contrast to older matched sibling donors who remain the default first choice. The widespread use of PTCy based GVHD platforms has significantly reduced the incidence and mortality due to GVHD. Completion of the aims of this study may provide conclusive proof that use of a young MUD donor may be a better option than an older MSD in the contemporary era where PTCy based GVHD prophylaxis is increasingly the norm in both situations.

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 selection of the optimal hematopoietic stem cell donor is critical for patients undergoing allogeneic hematopoietic cell transplantation (HCT) as potential curative treatment. Traditionally, human leukocyte antigen (HLA) matching has been prioritized over donor age during the selection process, favoring suitable HLA-matched sibling donors (MSD) over HLA-matched unrelated donors (MUD), regardless of their age. However, advancements in HLA typing technology and improvements in graft-versus-host disease (GVHD) prophylaxis have resulted in comparable outcomes between MSD and MUD HCT as reported by many groups (1-2). As a result, there is ongoing debate regarding the optimal donor choice for adult recipients who have both an older MSD and a younger MUD available. Previous studies have suggested that advanced donor age is an independent risk factor associated with unfavorable transplant outcomes due to increased incidence of GVHD and decreased progression-free survival (3-4), however it remains unclear whether these factors can overcome the benefits of genotypic similarity unique to MSD transplants. In a large study (5) of 2,172 patients >50 transplanted for leukemia or lymphoma, recipients of grafts from younger MUD had higher rates of acute (aGVHD) and chronic GVHD (cGVHD) compared to those who received grafts from older MSD. The effect of donor choice on relapse, non-relapse mortality (NRM) and overall survival (OS) was more complex, with better outcomes reported among recipients of MSD transplants in fitter patients, in contrast to individuals with lower performance scores who appeared to do equally well with older MSD and younger MUD. A retrospective study (6) the outcomes of 4,684 transplants for acute myeloid leukemia (AML) through the Center for International Blood and Marrow Transplant Research (CIBMTR) database, reported higher relapse rates among recipients of older MSD grafts compared to those using younger MUD. Despite the observed increase in relapse risk associated with MSD use, there was no difference in OS between the two groups, as the increased risk of relapse seen with MSD was largely offset by higher NRM associated with younger MUD. Interestingly, higher NRM seen with MUD was more apparent in earlier than recent transplants, suggesting that novel strategies for GVHD prophylaxis may improve our ability to deliver these types of transplants increasingly safely. Similarly, a study of 1,761 individuals with myelodysplastic syndrome (MDS) showed that the use of older MSD, compared to younger MUD, was associated with lower NRM, yet increased risk of relapse, leading to similar rates of OS

	between the two donor types (7). The debate about the choice between older MSD and younger MUD has been further fueled by the increasing availability of older sibling donors related to the referral of older recipients to transplant centers, driven by emerging novel therapies for high-risk MDS and AML, as well as advancements in reduced-intensity conditioning (RIC) regimens and supportive care. These older recipients are likely to have suitable sibling donors who are older compared to unrelated donors registered in the National Marrow Donor Program (NMDP), which focuses on recruiting individuals aged 18-35. Although several large studies have tried to answer this question, none of the prior studies have looked at contemporary practice post 2015 when PTCY based protocols are far more common. The use of PTCY has increased from 6% and 5% for MSD and MUD donors in 2015 to 22% and 27% in 2021. (8) The large retrospective CIBMTR database analysis included patients till 2017 and 2018, but excluded those with PTCY based prophylaxis (6,7) . In the era of PTCY based GVHD prophylaxis, it is important to revisit the question if PTCY sufficiently mitigates the higher risk of NRM and GVHD in MUD donors, so that overall young MUD donors provide better transplant outcomes than older MUD donors. References 1. Solomon SR, Sizemore CA, Zhang X, Brown S, Holland HK, Morris LE, et al. Impact of Donor Type on Outcome after Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia. Biology of Blood and Marrow Transplantation. 2016 Oct;22(10):1816–22. 2. Moore J, Nivison-Smith I, Goh K, Ma D, Bradstock K, Szer J, et al. Equivalent Survival for Sibling and Unrelated Donor Allogeneic Stem Cell Transplantation for Acute Myelogenous Leukemia. Biology of Blood and Marrow Transplantation. 2007 May;13(5):601–7 3. Bastida JM, Cabrero M, Lopez-Godino O, Lopez-Parra M, Sanchez-Guijo F, LopezCorral L, et al. Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome. Leuk Res. 2015 Aug 1;39(8):828–34. 4. Shaw BE, Logan BR, Spellman SR, Marsh SGE, Robinson J, Pidala J, et al. Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most. Biology of Blood and Marrow Transplantation. 2018 May;24(5):1049–56. 5. Alousi AM, Le-Rademacher J, Saliba RM, Appelbaum FR, Artz A, Benjamin J, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood. 2013 Mar 28;121(13):2567-73. 6. Abid MB, Estrada-Merly N, Zhang MJ, Chen K, Allan D, Bredeson C, Sabloff M, Guru

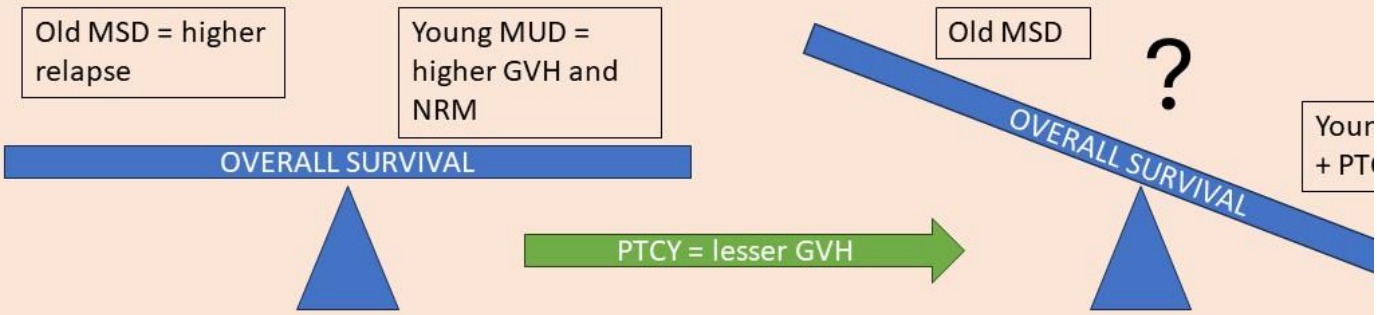
Field	Response
	Murthy GS, Badar T, Hashmi S, Aljurf M, Litzow MR, Kebriaei P, Hourigan CS, Saber W. Impact of Donor Age on Allogeneic Hematopoietic Cell Transplantation Outcomes in Older Adults with Acute Myeloid Leukemia. Transplant Cell Ther. 2023 Sep;29(9):578.e1-578.e9. 7. Guru Murthy GS, Kim S, Hu ZH, Estrada-Merly N, Abid MB, Aljurf M, et al. Relapse and Disease-Free Survival in Patients with Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors. JAMA Oncol. 2022 Mar 1;8(3):404. 8. Bolon YT, Atshan R, Allbee-Johnson M, Estrada-Merly N, Lee SJ. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2022.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_1rjYNio58p8w3o4
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Scientific Justification.png
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	79877
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/png
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion : 1. Underwent first Allo HCT for MDS or AML 2. Older MSD donor (age > 50) with any GVHD prophylaxis 3. Younger MUD donor (age<35) with PTCY based GVHD prophylaxis. Exclusion criteria : Alternative donors ; ex vivo T cell depletion ; CD 34 selection ; Second transplant.
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	1. MDS and AML are predominantly diseases of the elderly 2. Pediatric patients will by definition not have elderly siblings
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient Variable : Age , Sex, HCT-CI , KPS Disease variable : Therapy related , Antecedent hematological disorder, karyotype, IPSS-R (MDS) , Lines of RX before SCT , Disease status (CR1, CR2+,etc), Infusion Variables : D/R CMV , D/R sex , D/R ABO , Graft source , Conditioning regimen, Conditioning intensity , GVHD prophylaxis , Use of ATG/Campath, Transplant year
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 desc	Not Applicable

Field	Response
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	No
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.	No

Field	Response
REFERENCES:	1. Solomon SR, Sizemore CA, Zhang X, Brown S, Holland HK, Morris LE, et al. Impact of Donor Type on Outcome after Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia. Biology of Blood and Marrow Transplantation. 2016 Oct;22(10):1816–22. 2. Moore J, Nivison-Smith I, Goh K, Ma D, Bradstock K, Szer J, et al. Equivalent Survival for Sibling and Unrelated Donor Allogeneic Stem Cell Transplantation for Acute Myelogenous Leukemia. Biology of Blood and Marrow Transplantation. 2007 May;13(5):601–7 3. Bastida JM, Cabrero M, Lopez-Godino O, Lopez-Parra M, Sanchez-Guijo F, LopezCorral L, et al. Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome. Leuk Res. 2015 Aug 1;39(8):828–34. 4. Shaw BE, Logan BR, Spellman SR, Marsh SGE, Robinson J, Pidala J, et al. Development of an Unrelated Donor Selection Score Predictive of Survival after HCT: Donor Age Matters Most. Biology of Blood and Marrow Transplantation. 2018 May;24(5):1049–56. 5. Alousi AM, Le-Rademacher J, Saliba RM, Appelbaum FR, Artz A, Benjamin J, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood. 2013 Mar 28;121(13):2567-73. 6. Abid MB, Estrada-Merly N, Zhang MJ, Chen K, Allan D, Bredeson C, Sabloff M, Guru Murthy GS, Badar T, Hashmi S, Aljurf M, Litzow MR, Kebriaei P, Hourigan CS, Saber W. Impact of Donor Age on Allogeneic Hematopoietic Cell Transplantation Outcomes in Older Adults with Acute Myeloid Leukemia. Transplant Cell Ther. 2023 Sep;29(9):578.e1-578.e9. doi: 10.1016/j.jtct.2023.06.020. Epub 2023 Jul 3. PMID: 37406882; PMCID: PMC10528825. 7. Guru Murthy GS, Kim S, Hu ZH, Estrada-Merly N, Abid MB, Aljurf M, et al. Relapse and Disease-Free Survival in Patients with Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation Using Older Matched Sibling Donors vs Younger Matched Unrelated Donors. JAMA Oncol. 2022 Mar 1;8(3):404. 8. Bolon YT, Atshan R, Allbee-Johnson M, Estrada-Merly N, Lee SJ. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2022.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Not for publication or presentation ***Attachment 5b***

	Publication	study type	Population	Use of PTCY	Comparator	RFS	OS	old MSD vs Young MUD
1	Guru Murthy GS, et al JAMA Oncol 22	Retrospective CIBMTR analysis	n=1761 with age>50y MDS period 2011 to 2017	PTCY excluded	Old MSD (Age ≥ 50)(n=646) vs Young MUD (Age≤35)(n=1115)	HR 1.17, P=0.02 (Favours young MUD)	HR=1.13 , P=0.07 No statistical difference	Higher relapse (HR 1.62 , p<0.00 Lower NRM (HR 0.76 , P=0.02), Lower aGVH(HR 0.52 , P<0.001), Lower cGVH (HR 0.77, P=0.005), Lower GRFS post 12m (HR 1.42 , P=0.04)
2	Mariana Pinto Pereira et al. TCT 2023	Single centre retrospective, Canada	n=377 with AML and MDS Period 2010 to 2021	PTCY in 60.6% MUD and 40% MSD	Old MSD (Age ≥ 60)(n=85) vs Young MUD (Age≤30)(n=292)	HR = 0.73 , P = 0.18	HR = 0.73 , P = 0.21 No statistical difference	No statistically significant differe graft-vs-host disease (GVHD)- and relapse-free survival, non-re mortality, relapse, engraftment, failure or acute GVHD
3	Takaaki Konuma, et al. BMT 2023	Retrospective Japanese registry	n=1787 with age>50y MDS period 2014 to 2020	Nil.	MSD(n=214) vs MUD(562) vs 7/8MMUD(n=334) vs UCB(n=667)			Relapse lower in MUD vs MSD (HR=0.74 , P=0.047) Donor type showed no effect on RFS, GRFS
4	Muhammad Bilal Abid, et al. TCT 2023	Retrospective CIBMTR analysis	n=4684 with age>50y AML period 2011 to 2018	PTCY excluded	Old MSD (Age ≥ 50)(n=1736) vs Young MUD (Age≤35)(n=2948)	No Difference	No difference	Relapse lower in MUD vs MSD (HR=0.86, P=0.005) NRM higher in Young MUD betw 2011 to 2015 (HR1=1.24, P=0.16 difference in 2016-2018 (HR=0. P=0.017)



Characteristics of patients with AML and MDS

Characteristic	N (%)
No. of patients	12487
No. of centers	241
Patient age 65 and older with high/very high risk MDS or AML - no. (%)	
Yes	7928 (63.5)
Patients without prior history of transplantation + Recipients of cord blood transplantation, haploidentical transplantation (<7/8) + PTCy or MMUD (7/8, mismatched at a single locus) transplantation with PTCy	**1336** (10.7)
Patients with older MSD donor (age > 50) with any GVHD prophylaxis or younger MUD donor (age<35) with PTCY based GVHD prophylaxis. - no. (%)	
Yes	3284 (26.3)
Patients without ex-vivo T-cell depletion and CD34 selection + Patients without second transplant	**3176** (25.4)
Patients Cohorts - no. (%)	
Matched sibling Donors using PTCY	270 (2.2)
8/8 Matched unrelated Donors using PTCY	1479 (11.8)
7/8 and 6/8 Mismatched unrelated Donors using PTCY	390 (3.1)
Haploidentical Donors using PTCY	1701 (13.6)
Matched sibling Donors using non – PTCY based GVHD prophylaxis	2159 (17.3)
8/8 Matched unrelated Donors using non – PTCY based GVHD prophylaxis	5794 (46.4)
7/8 and 6/8 Mismatched unrelated Donors using non – PTCY based GVHD prophylaxis	554 (4.4)
Haploidentical Donors using non – PTCY based GVHD prophylaxis	140 (1.1)
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	68.9 (65.0-99.7)
65-69	7815 (62.6)
>=70	4672 (37.4)
Sex - no. (%)	
Male	7996 (64.0)
Female	4491 (36.0)
Race - no. (%)	
White	10675 (85.5)
Black or African American	340 (2.7)
Asian	351 (2.8)
Native Hawaiian or other Pacific Islander	11 (0.1)
American Indian or Alaska Native	17 (0.1)
More than one race	33 (0.3)
Not reported	1060 (8.5)

Characteristic	N (%)
Reporting track - no. (%)	
TED	8345 (66.8)
CRF	4142 (33.2)
US or Non-US - no. (%)	
US	10828 (86.7)
Non-US	1659 (13.3)
Karnofsky score prior to HCT - no. (%)	
90-100	6473 (51.8)
< 90	5800 (46.4)
Not reported	214 (1.7)
HCT-CI - no. (%)	
0	2458 (19.7)
1	1736 (13.9)
2	1697 (13.6)
3+	6425 (51.5)
TBD, review needed for history of malignancies	112 (0.9)
TBD, inconsistencies between parent and sub-questions	4 (0.0)
NA, f2400 (pre-TED) not completed	2 (0.0)
Missing	53 (0.4)
Patients without prior history of transplantation - no. (%)	
No	360 (2.9)
Yes	12127 (97.1)
Patients without second transplant - no. (%)	
No	420 (3.4)
Yes	12067 (96.6)
Disease Related	
Disease status at time of HCT - no. (%)	
CR1	6589 (52.8)
Not reported	5898 (47.2)
Risk level of MDS - no. (%)	
High/Very High	1339 (10.7)
Low/Intermediate	4559 (36.5)
Non MDS	6589 (52.8)
Time from diagnosis to HCT - no. (%)	
<6 months	5963 (47.8)
6-12months	4103 (32.9)
>12 months	2421 (19.4)
Transplant Related	
Donor age at HCT - no. (%)	

Characteristic	N (%)
Median (min-max)	32.0 (0.1-99.4)
<10	2 (0.0)
10-17	9 (0.1)
18-29	5383 (43.1)
30-39	2669 (21.4)
40-49	1512 (12.1)
50-59	873 (7.0)
60-69	1369 (11.0)
>=70	291 (2.3)
Not reported	379 (3.0)
Donor/recipient CMV serostatus - no. (%)	
+/+	4062 (32.5)
+/-	1317 (10.5)
-/+	3917 (31.4)
-/-	3074 (24.6)
Not reported	117 (0.9)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
No drugs reported	12 (0.1)
MAC	1964 (15.7)
RIC	7940 (63.6)
NMA	2165 (17.3)
TBD	363 (2.9)
N/A, F2400 (pre-TED) not submitted, drug dose not available	7 (0.1)
Not reported	36 (0.3)
Donor/recipient sex match - no. (%)	
M-M	5436 (43.5)
M-F	2647 (21.2)
F-M	2538 (20.3)
F-F	1832 (14.7)
Not reported	34 (0.3)
Product type - no. (%)	
BM	1010 (8.1)
PB	11477 (91.9)
Post-transplant Cy - no. (%)	
No	8644 (69.2)
Yes	3840 (30.8)
Missing	3 (0.0)
ATG/Campath - no. (%)	
ATG + CAMPATH	1 (0.0)

Characteristic	N (%)
ATG alone	2790 (22.3)
CAMPATH alone	310 (2.5)
No ATG or CAMPATH	9386 (75.2)
GVHD prophylaxis - no. (%)	
None	35 (0.3)
CD34 selection	39 (0.3)
PtCy + other(s)	3798 (30.4)
PtCy alone	36 (0.3)
TAC + MMF +- other(s) (except PtCy)	1608 (12.9)
TAC + MTX +- other(s) (except MMF, PtCy)	4127 (33.1)
TAC + other(s) (except MMF, MTX, PtCy)	747 (6.0)
TAC alone	261 (2.1)
CSA + MMF +- other(s) (except PtCy,TAC)	933 (7.5)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	610 (4.9)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	5 (0.0)
CSA alone	134 (1.1)
Other(s)	140 (1.1)
Missing	14 (0.1)
Year of current transplant - no. (%)	
2008	142 (1.1)
2009	176 (1.4)
2010	220 (1.8)
2011	302 (2.4)
2012	399 (3.2)
2013	514 (4.1)
2014	647 (5.2)
2015	715 (5.7)
2016	844 (6.8)
2017	898 (7.2)
2018	1155 (9.2)
2019	1250 (10.0)
2020	1226 (9.8)
2021	1372 (11.0)
2022	1522 (12.2)
2023	1105 (8.8)
Median follow-up of survivors (range), months - median (range)	36.4 (0.0-2196.9)

Field	Response
Proposal Number	2310-31-WUDHIKARN
Proposal Title	Differences in product characteristics, resource utilization and side effects profile of patients who received brexucabtagene autoleucel comparing between B-ALL and Mantle Cell Lymphoma
Key Words	Brexucabtagene autoleucel, mantle cell lymphoma, B cell acute lymphoblastic leukemia, toxicity, product attributes
Principal Investigator #1: - First and last name, degree(s)	Kitsada Wudhikarn
Principal Investigator #1: - Email address	kitsada.w@chula.ac.th
Principal Investigator #1: - Institution name	Chulalongkorn University
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Miguel-Angel Perales
Principal Investigator #2 (If applicable): - Email address:)	peralesm@mskcc.org
Principal Investigator #2 (If applicable): - Institution name:	Memorial Sloan Kettering Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Dr. Miguel-Angel Perales will be a senior mentor of this project
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
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Infection complication in patients with R/R LBCL CD19 CAR T cell therapy
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Lymphoma
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Are product characteristics, resource utilization and side effects profile of patients who received brexucabtagene autoleucel different between B-ALL and Mantle Cell Lymphoma?

Field	Response
RESEARCH HYPOTHESIS:	1. Patients with R/R MCL treated with brexucabtagene autoleucel have different side effects profile compared to those with B cell acute lymphoblastic leukemia 2. The characteristics, logistics and attributes of brexucabtagene autoleucel product are different between patients with mantle cell lymphoma and B cell acute lymphoblastic leukemia
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. To evaluate and compare the product attributes, logistics, efficacy and toxicity profile of brexucabtagene autoleucel between patients with mantle cell lymphoma and B cell acute lymphoblastic leukemia
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Brexucabtagene autoleucel is approved for adult patients with relapsed/refractory mantle cell lymphoma and B-ALL according based on two pivotal studies; ZUMA-2 and ZUMA-3 respectively. The patient characteristics in both trials were different. The median age of patients in ZUMA-2 was 65 years old whereas the median age of patients in ZUMA-3 was 40 years old. In the phase 2 ZUMA-2 study, brexucabtagene autoleucel was successfully manufactured for 71 patients but given to only 68 patients. Two patients had disease progression and died before receiving brexucabtagene autoleucel. The median time from apheresis to product delivery was 16 days. Cytopenia was the most common side effect in the ZUMA-2 study seen in 94%. Cytokine release syndrome and neurotoxicities were observed in 91% and 63%, respectively. Of all CRS and ICANS events, 15% and 31% were grade 3 or more. In the ZUMA-3 study where brexucabtagene autoleucel was given to 71 adult patients with relapsed/refractory B-ALL, the product was successfully manufactured for 65 patients (92%) but administered to only 55 patients (77%). CRS grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients. The median time from leukapheresis to product release was 13 days. As reported, there were evident difference of patients' characteristics, product manufacturing logistics and adverse events observed between these 2 trials despite the same product. These differences might be more obvious in the real-world setting warranting further description and exploration in order to improve product delivery and patient care. The knowledge from this study will highlight the differences in the real-world setting.

Field	Response
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.	Brexucabtagene autoleucel is approved for adult patients with relapsed/refractory mantle cell lymphoma and B-ALL according based on two pivotal studies; ZUMA-2 and ZUMA-3 respectively. The patient characteristics in both trials were different. The median age of patients in ZUMA-2 was 65 years old whereas the median age of patients in ZUMA-3 was 40 years old. In the phase 2 ZUMA-2 study, brexucabtagene autoleucel was successfully manufactured for 71 patients but given to only 68 patients. Two patients had disease progression and died before receiving brexucabtagene autoleucel. The median time from apheresis to product delivery was 16 days. Cytopenia was the most common side effect in the ZUMA-2 study seen in 94%. Cytokine release syndrome and neurotoxicities were observed in 91% and 63%, respectively. Of all CRS and ICANS events, 15% and 31% were grade 3 or more. In the ZUMA-3 study where brexucabtagene autoleucel was given to 71 adult patients with relapsed/refractory B-ALL, the product was successfully manufactured for 65 patients (92%) but administered to only 55 patients (77%). CRS grade 3 or higher occurred in 13 (24%) patients and neurological events of grade 3 or higher occurred in 14 (25%) patients. The median time from leukapheresis to product release was 13 days. As reported, there were evident difference of patients' characteristics, product manufacturing logistics and adverse events observed between these 2 trials despite the same product. These difference might be more obvious in the real-world setting warranting further description and exploration in order to improve product delivery and patient's care.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	1. All adult patients with r/r B cell acute lymphoblastic leukemia aged >18 years old who received brexucabtagene autoleucel 2. All adult patients with r/r Mantel cell lymphoma aged >18 years old who received brexucabtagene autoleucel
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Brexucabtagene autoleucel is approved for adult patients.

DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	All data are captured in the data collection form. Additional data collection is not required. Patient-Related • Age at CAR T cell • Gender: Male vs. Female • Ethnicity: Caucasian, Hispanic, African American, Asian Pacific Islander • Performance Status: Karnofsky score (>90% vs. 80-90% vs. <80%) • Hematopoietic Cell Transplant Comorbidity Index: 0-2 vs. 3-4 vs. high risk group (≥ 5) • Baseline platelet count pre-lymphodepletion: yes vs no • Body weight: kilogram • Height: cm Disease-Related • Diagnostic indication • Time from diagnosis to CAR T infusion • Disease risk index • IPI for mantle cell lymphoma • Stage for mantle cell lymphoma • Bulky disease for mantle cell lymphoma • Chromosomal abnormality for B-ALL • Risk group for B-A LL • Disease status at the time of CAR T-cell therapy • Baseline LDH pre lymphodepletion • Number of prior lines of treatments • Bridging therapy before CAR T cell • Time from last non-transplant therapy to CAR T cell infusion • Prior hematopoietic cell transplant before CAR T cell therapy CAR T cell Related • Time from leukapheresis to the release of CAR T cell product/CAR T cell infusion • Lymphodepletion Regimen for CAR T cells • CAR T cell dose Time-dependent • Neutrophil and platelet engraftment: Yes/No • Date of engraftment • Median time to neutrophil and platelet engraftment • Grade 4 organ toxicity: Yes/No • Date of organ toxicity grade 4 onset • Median time to grade 4 toxicity • CRS: Yes/No • Date of CRS onset • Median time to CRS • CRS grade (maximal grade) • Duration of CRS •ICANS: Yes/No • Median time to ICANS • ICANS grade (maximal grade) • Duration of ICANS • Received steroids: Yes/No • Received Tocilizumab: No vs. Yes 1 dose vs. Yes ≥2 doses • Time to the first dose of tocilizumab • Time to the first dose of steroid • Neutropenia grade 3 or more • Anemia grade 3 or more • Thrombocytopenia grade 3 or more • Infection grade 3 or more • Date of

Field	Response
	infection • Relapse/Progression: Yes/No • Date of relapse or progression • Alive status: Alive vs. Death • Date of last follow up or death
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 desc	None
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	No
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.	No
REFERENCES:	1. Shah BD 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 Aug 7;398(10299):491-502. 2. Shah BD et al. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood. 2021 Jul 8;138(1):11-22 3. Wang M et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020 Apr 2;382(14):1331-1342
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal
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.	Dr. Perales reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

Field	Response
Proposal Number	2310-33-WUDHIKARN
Proposal Title	Outcomes of adolescent and young adult (AYA) patients with relapsed/refractory B-ALL treated with tisagenlecleucel compared to brexucabtagene autoleucel
Key Words	Adolescent and young adult, B-cell acute lymphoblastic leukemia, CD19 Chimeric Antigen Receptor, Brexubactagene autoleucel
Principal Investigator #1: - First and last name, degree(s)	Kitsada Wudhikarn, MD
Principal Investigator #1: - Email address	kitsada.w@chula.ac.th
Principal Investigator #1: - Institution name	Chulalongkorn University
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Miguel-Angel Perales, MD
Principal Investigator #2 (If applicable): - Email address:)	peralesm@mskcc.org
Principal Investigator #2 (If applicable): - Institution name:	Memorial Sloan Kettering Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Infection complication in patients with r/r large B cell lymphoma receiving CD19 CAR T cell
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Do adolescent and young adult patients with r/r B-ALL treated with tisagelecleucel have different outcomes and toxicity profiles compared to those treated with brexucabtagene autoleucel?
RESEARCH HYPOTHESIS:	1. Adolescent and Young Adults with B-ALL treated with tisagenlecleucel had different outcomes compared to those treated with brexucabtagene autoleucel 2. Adolescent and Young Adults with B-ALL treated with tisagenlecleucel had different toxicity profiles compared to those treated with brexucabtagene autoleucel

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	To evaluate, compare the efficacy and toxicity profile of tisagenlecleucel and brexucabtagene autoleucel in adolescent and young adult patients with B-ALL: 1. Cumulative incidence of cytokine release syndrome: Time from CAR T cell infusion to the onset of CRS, and grade 2.Cumulative incidence of immune effector cell associated neurotoxicity syndrome: Time from CAR T cell infusion to the onset of ICANS, and grade 3. Cumulative incidence of infection 4. Cumulative incidence of grade ≥3 toxicities 5. Treatment related mortality (TRM) 6.Cumulative Incidence of Relapse (CIR) 7. Progression Free Survival (PFS) 8. Overall Survival (OS)
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Historically, the prognosis of relapsed and refractory B-ALL, especially in patients who relapsed after allogeneic HSCT is dismal. Most patients eventually die from progressive disease. Until recently, treatment options for these patients were limited. Over the past decade, several studies demonstrated the remarkable efficacy of CD19 CARC T cells in B-ALL. There are currently two FDA-approved CD19 CAR T cells for patients with relapsed/refractory B-ALL. Tisagenlecleucel, a CD19/4-1BB CAR T cell was initially approved in 2017 for pediatric and young adult (up to age of 25 years old) patients with relapsed/refractory B-ALL. Subsequently, in 2021, brexucabtagene autoleucel was approved for adult patients with relapsed/refractory B-ALL. It is known that adolescent and young adult (AYA) patients with ALL represent a unique subgroup of patients with ALL according to both disease biology and socioeconomic perspective. AYA patients have various age range definitions with some data referring to patients aged up to 40 years old. Historically, treatment patterns and outcomes of AYA patients also depend upon primary hematologists and chemotherapy regimens with patients treated with pediatric hematologists and pediatric-inspired chemotherapy regimens carrying better outcomes than adult hematologists or adult protocols. Currently, it is not known whether certain constructs of CD19 CAR T cells would influence outcomes in AYA patients with relapsed/refractory B-ALL. This study will describe the characteristics, toxicity profiles and outcomes of AYA patients treated with brexucabtagene autoleucel and tisagenlecleucel. This study will compare the similarities and differences between groups and will help us to better understand optimal CD19 CAR T cell products in this patient population.

Field	Response
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.	Historically, the prognosis of relapsed and refractory B-ALL, especially in patients who relapsed after allogeneic HSCT is dismal. Most patients eventually die from progressive disease. Until recently, treatment options for these patients were limited. Over the past decade, several studies demonstrated the remarkable efficacy of CD19 CARC T cells in B-ALL. There are currently two FDA-approved CD19 CAR T cells for patients with relapsed/refractory B-ALL. Tisagenlecleucel, a CD19/4-1BB CAR T cell was initially approved in 2017 for pediatric and young adult (up to age of 25 years old) patients with relapsed/refractory B-ALL. Subsequently, in 2021, brexucabtagene autoleucel was approved for adult patients with relapsed/refractory B-ALL. It is known that adolescent and young adult (AYA) patients with ALL represent a unique subgroup of patients with ALL according to both disease biology and socioeconomic perspective. AYA patients have various age range definitions with some data referring to patients aged up to 40 years old. Historically, treatment patterns and outcomes of AYA patients also depend upon primary hematologists and chemotherapy regimens with patients treated with pediatric hematologists and pediatric-inspired chemotherapy regimens carrying better outcomes than adult hematologists or adult protocols. Currently, it is not known whether certain constructs of CD19 CAR T cells would influence outcomes in AYA patients with relapsed/refractory B-ALL. This study will describe the characteristics, toxicity profiles and outcomes of AYA patients treated with brexucabtagene autoleucel and tisagenlecleucel.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	1. All adolescent and young adult patients aged 15-25 years old who were treated with Tisagenlecleucel 2. All adolescent and young adult patients aged 15-40 years old who were treated with Brexucabtagene autoleucel
Does this study include pediatric patients?	Yes

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient-Related •Age at CAR T cell • Gender: Male vs. Female • Ethnicity: Caucasian, Hispanic, African American, Asian Pacific Islander • Performance Status: Karnofsky score (90% vs. 80-80% vs. <80%) for adults and Lansky score (90-100 vs. <90) for pediatric patients • Hematopoietic Cell Transplant Comorbidity Index: 0-2 vs. 3 - 4 vs. high-risk group (≥ 5) • Baseline platelet count pre lymphodepletion • Body weight: kilogram • Height: cm Disease-Related • Time from diagnosis to CAR T infusion • Disease status at the time of CAR T cell infusion (morphologic disease or MRD positive disease) • Cytogenetic risk stratification (Ph+ or Ph- ALL and other high risk cytogenetic abnormalities i.e., MLL, hypodiploidy) • Disease risk index • Baseline LDH pre lymphodepletion • Number of prior lines of treatments • Previous exposure to blinatumomab (Yes vs. No) • Previous exposure to Inotuzumab ozogamycin (Yes vs. No) • Bridging therapy before CAR T cell • Time from last non-transplant therapy to CAR T cell infusion • Prior Allogeneic hematopoietic cell transplant before CAR T cell therapy • If allotransplant before CAR T cell, Time from alloHCT to CD19 CAR T cells CAR T cell-Related • Lymphodepletion Regimen for CAR T cells • Time between start of Lymphodepletion and CAR.T infusion • Type of CAR T cell product (Tisagenlecleucel, Brexucabtagene autoleucel) • CAR T cell dose • Inpatient vs Outpatient CAR T cell administration Time-dependent • Neutrophil and platelet engraftment: Yes/No • Median time to neutrophil and platelet engraftment • Grade ≥3 organ toxicity: Yes/No • Median time to grade ≥3 toxicity • CRS: Yes/No • Median time to CRS • CRS grade (maximal grade) • Duration of CRS •ICANS: Yes/No • Median time to ICANS • ICANS grade (maximal grade) • Duration of ICANS • Received steroids: Yes/No • Received Tocilizumab: No vs. Yes 1 dose vs. Yes ≥2 doses • ICU admission • Duration of ICU admission • Relapse/Progression: Yes/No • Alive status: Alive vs. Death

Field	Response
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 desc	No
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	No
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.	No
REFERENCES:	1. Maude SL, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439-448. 2. Levine JE, et al. Pooled safety analysis of tisagenlecleucel in children and young adults with B cell acute lymphoblastic leukemia. J Immunother Cancer. 2021 Aug;9(8):e002287. 3. Shah BD, 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 Aug 7;398(10299):491-502. 4. Shah BD, et al. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood. 2021 Jul 8;138(1):11-22. 5. Shah BD, et al. Matching-Adjusted Indirect Comparisons of Brexucabtagene Autoleucel with Alternative Standard Therapies for Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia in Adult Patients. Adv Ther. 2023 Oct 6 6. Shah BD, et al. Impact of prior therapies and subsequent transplantation on outcomes in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. J Immunother Cancer. 2023 Aug;11(8):e007118.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
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.	Dr. Perales reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of the American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee.

Field	Response
Proposal Number	2310-111-ABID
Proposal Title	CD19+CAR-T therapy vs allogeneic HCT for poor-risk B-cell ALL with post-induction MRD positivity
Key Words	CD19+CAR-T; allogeneic HCT; Measurable Residual Disease; Primary induction failure; high-risk ALL
Principal Investigator #1: - First and last name, degree(s)	Muhammad Bilal Abid, MD MS
Principal Investigator #1: - Email address	Bilal_abid@hotmail.com
Principal Investigator #1: - Institution name	Medical College of Wisconsin
Principal Investigator #1: - Academic rank	Assistant Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Frances Cervoni-Curet, MD
Principal Investigator #2 (If applicable): - Email address:)	FNCervoni@mdanderson.org
Principal Investigator #2 (If applicable): - Institution name:	U.T. M.D. Anderson Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Lymphoma / Myeloma Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
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:	Muhammad Bilal Abid, MD MS
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
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Dr. Abid participates in studies related to leukemia, CAR-T, and infections. Dr. Cervoni has not participated in CIBMTR studies.
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Wael Saber
RESEARCH QUESTION:	What is the optimal consolidation therapy for B-cell ALL patients with persistent disease after multiagent chemotherapy induction?

Field	Response
RESEARCH HYPOTHESIS:	The optimal consolidation strategy and sequence of CAR-T vs alloHCT remains unknown in high-risk B-ALL patients who are MRD+ after initial multiagent chemotherapy induction. In this highly selected high-risk B-ALL cohort, we hypothesize that CD19+CAR-T therapy confers similar outcomes (leukemia relapse, PFS, and OS) compared to alloHCT. This will further leave alloHCT as an additional salvage treatment in case of relapse post-CAR-T.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	-The overall study objective is to compare the efficacy and toxicity outcomes of CAR-T vs alloHCT consolidation in high-risk ALL patients who continue to have persistent disease (MRD+) after multiagent chemotherapy induction. Main study outcomes include: 1. Event-free survival: Composite endpoint with disease relapse and death of any cause. 2. Overall survival: Time to death of any cause will be an event for this outcome. Patients will be censored at the time of last follow-up. 3. Relapse: Disease relapse is the event. For cases with available phenotype information at the time of disease relapse, cases with CD19 negative blasts will be described. 4. Duration of response (DOR): This outcome is the interval from achieving complete remission at 90 days to the loss of this response. Only patients who achieve a CR at 90 days are included in this outcome. 5. CAR T-cell toxicity: Grades III-IV CRS according to ASTCT criteria will be the events for this outcome. Grades II-IV and III-IV ICANS according to ASTCT criteria will be the events for this outcome 6. Acute GVHD: Grades I-II, II-IV, and III-IV acute GVHD according to modified Glucksberg criteria will be the events for this outcome among patients who received an alloHCT. 7. Chronic GVHD: Occurrence of any chronic GVHD as reported by the transplant center will be the event for this outcome among recipients for alloHCT. 8. Transplant-related mortality: Deaths occurring in patients without disease relapse will be the event for this outcome among patients who received an alloHCT. 9. Causes of Death: Center reported primary and contributing COD will be described among patients who did or did not receive an alloHCT after CAR T cells.

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	The optimal consolidation strategy remains unknown in high-risk B-ALL patients who are MRD+ after initial multiagent chemotherapy induction. The decision between CAR-T vs alloHCT is often made on clinical grounds - based on the availability of a donor and the patient's fitness to withstand alloHCT-associated TRM. There is no head-to-head comparison between the 2 treatment modalities in the subset of B-ALL patients at a higher risk of disease relapse. The current study will examine if one modality is superior to the other and CIBMTR registry data provides the platform, in the absence of prospective data.

Field	Response
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 rates for children and young adults with de novo B-ALL approach 90% in the modern era with the intensification of multiagent chemotherapy, risk stratification, and further intensification for subgroups of patients at higher risk of relapse. Despite these improvements in outcome for the majority of patients, subgroups of patients remain at very high risk of relapse with current intensive chemotherapy regimens. Some of these patients are identified by the underlying genomics of the leukemic blasts, but many poor-risk ALL patients can be identified on the basis of a poor early response to therapy. Studies have shown MRD status to be the single most important independent prognostic indicator. AlloHCT serves as a consolidative therapy for acute leukemia and cures many patients with relapsed or high-risk disease. The therapeutic effect of alloHCT is driven by the direct cytotoxicity from the chemo-radiotherapy administered in the conditioning regimen, along with the graft-versus-leukemia (GVL) immune effect. Patients transplanted with a lower disease burden have better outcomes. Moreover, patients with mild to moderate GVHD have higher rates of long-term remissions, attributed to an immunologic response against host targets. The major effectors of GVL in ALL are T cells, but most of the antigens targeted by these alloreactive T-cells remain unknown. Loss of antigen-presenting mechanisms is a known mechanism of leukemic resistance to the GVL effect. CAR-T cells may offer a similar immune-monitoring long-term effect against leukemia, but a specific known antigen is being targeted by a CAR. Durable immunologic control following CAR T cells may result in prolonged remission or cure, if CAR effector cells are durable and functional and CAR target is essential for the leukemia. While an ongoing CIBMTR study shows that alloHCT consolidation appears safe and may improve remission duration following CD19+CAR-T therapy and should be performed as a consolidation and not as a treatment of disease relapse, the optimal consolidation strategy remains unknown in patients who are MRD+ after initial multiagent chemotherapy induction. The decision between CAR-T vs alloHCT is often made on clinical grounds - based on the availability of a donor and patient's fitness to withstand alloHCT-associated TRM but there is no head-to-head comparison between the 2 treatment modalities in the subset of B-ALL patients at a higher risk of disease relapse. Given the lack of prospective data, the CIBMTR registry provides the data and infrastructure to conduct such a study addressing a timely question.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Patients of all age groups with MRD+ B-ALL after induction who received alloHCT or CD19+CAR-T therapy from 2015 to 2021. This could include patients who are PIF, progressive disease, and CR1 with MRD+ disease. For the current analysis, those patients will be excluded who achieve CR1 and MRD- status after induction.
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	N/A
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	N/A
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	N/A
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.	N/A

REFERENCES:	1. Bader P, Kreyenberg H, Henze GHR, Eckert C, Reising M, Willasch A, et al. Prognostic value of Minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol. 2009;27:377–84. 2. Pulsipher MA, Carlson C, Langholz B, et al. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. Blood. 2015;125(22):3501-3508. 3. Pulsipher MA, Peters C, Pui C-H. High-risk pediatric acute lymphoblastic leukemia: to transplant or not to transplant? Biol Blood Marrow Transplant. 2011;17(suppl 1):S137-S148. 4. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood. 2015;126(8):964-971. 5. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206-3214. 6. Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. Lancet. 2005;366(9486):635-642. 7. Fagioli F, Quarello P, Zecca M, et al. Hematopoietic stem cell transplantation for children with high-risk acute lymphoblastic leukemia in first complete remission: a report from the AIEOP registry. Haematologica. 2013;98(8):1273-1281. 8. Maude SL, Laetsch TW, Buechner Jet al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378:439-448. 9. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-2138. 10. Curran KJ, Margossian SP, Kernan NA, et al. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. Blood. 2019;134(26):2361-2368. 11. Abid MB, Shah NN, Maatman TC, Hari PN. Gut microbiome and CAR-T therapy. Exp Hematol Oncol 2019; 8:31. 12. Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent to treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129:3322–31. 13. Lee DW, Stetler-Stevenson M, Yuan CM, Shah NN, Delbrook C, Yates B, et al. Long-term outcomes following CD19 CAR

Field	Response
	T cell therapy for B-ALL are superior in patients receiving a fludarabine/cyclophosphamide preparative regimen and post-CAR hematopoietic stem cell transplantation. Blood. 2016;128:218.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-206-MIRZA
Proposal Title	CD 19 CAR T cell therapy in Adult B-cell Acute lymphoblastic leukemia (B-ALL): Real world Evidence and Clinical Predictors of Toxicity and Efficacy.
Key Words	Tecartus, adult ALL, allo-HCT
Principal Investigator #1: - First and last name, degree(s)	Abu-Sayeef Mirza
Principal Investigator #1: - Email address	Sayeef.Mirza@moffitt.org
Principal Investigator #1: - Institution name	Moffitt Cancer Center
Principal Investigator #1: - Academic rank	Assistant Member
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Lohith Gowda
Principal Investigator #2 (If applicable): - Email address:)	lohith.gowda@yale.edu
Principal Investigator #2 (If applicable): - Institution name:	Yale Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No

Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	1) Co-Chair: Plasma Cell Disorder and Solid Organ Transplant Working Committee Study: Plasma Cell Leukemia: Impact of Stem Cell Transplant in the Era of Novel Drugs (Completed) (PMID: 32313109). 2) Co-Chair: Chronic Leukemia Working Committee Study: T- cell Prolymphocytic Leukemia: Allogeneic Stem Cell Transplant as Consolidation Therapy (Completed) (PMID: 35081472). 3) Co-Chair: Plasma Cell Disorder and Solid Organ Transplantation Working Committee Study: Risk factors for and characteristics of second primary malignancies following autologous hematopoietic cell transplant for multiple myeloma (Completed) (PMID; 36827681). 4) Co-Chair: Infection and Immune Reconstitution Working Committee Study: Incidence, Treatment and Outcome of infection in patients with B lymphoid neoplasm treated with CD19 Chimeric Antigen Receptor T cell (ongoing, ASH 2023 Submission). 5) Co-Chair: Acute Leukemia Working Committee Study: Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (ongoing) (mentee- Shallis). 6) Co-Chair: Infection and Immune Reconstitution Working Committee Study: COVID-19 in Hematopoietic Stem Cell Transplant and Cellular Therapy (ongoing) (PMID: 33482113). 7) Principal Investigator: Outcomes of Elderly Patients Receiving CD-19 Directed CAR-T Therapy for B cell Lymphomas (Ongoing) (Mentee- Dr. Abu Sayeef, Fellow in Hematology-Oncology, ASH 2022 Presentation, Publication under Review). 8) Co-Chair: 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 (ongoing) (Mentee- Dr. Abu Sayeef, Fellow in Hematology- Oncology). 9) Co-Chair: CD19-CAR-T therapy failure: Impact of subsequent therapy in patients with B-cell malignancies. (ongoing) (mentee- Dr. Abu-Sayeef Mirza) 10) Co-Chair: Outcomes of CD19 CAR-T in patients who received lymphodepleting chemotherapy using fludarabine containing versus other regimens. (ongoing) (Mentee- Dr. Abu-Sayeef Mirza) 11) Co-Chair: Infectious complications in patients with relapsed/refractory multiple myeloma receiving B-cell maturation antigen targeted chimeric antigen receptor T cells. (Approved by Committee) 12) Co-Chair: Real world experience of feasibility, safety, efficacy, and outcomes following anti-BCMA CAR T-cell therapy for

Field	Response
	patients with relapsed or refractory multiple myeloma. (Ongoing ASH 2023 presentation)
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	Yes
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	What is the efficacy of CD19-directed CAR T cell therapy in real-world adult patients with B-ALL and determine the predictors of its efficacy and toxicity?
RESEARCH HYPOTHESIS:	1) We hypothesize real-world outcomes for adult patients with B-ALL receiving CD19 CART is like registration trial data. 2) Patient (age/ethnicity etc;) and disease-related variables will identify subgroups that are most and least likely to benefit post-CD19 CAR-T for adult ALL patients. 3) Consolidative allogeneic hematopoietic stem cell Transplant post-CAR-T post CD 19 CART improves survival.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. Primary aim: Identify response rate, duration of remission, progression-free survival, and overall survival. Identify predictors of efficacy (PFS, OS, CRS and neurotoxocity) in recipients of CD 19 CAR-T cells for r/r ALL. 2. Secondary aims: a. Cumulative incidence of infections, immune recovery, relapse, and non-relapse mortality. b. Determine whether CAR-T cell therapy followed by consolidative allogeneic hematopoietic cell transplant (allo-HCT) results in superior progression free survival (PFS) and overall survival (OS) versus CAR-T cell therapy alone in patients with B-cell ALL.

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	In adult patients, B-cell Acute Lymphoblastic Leukemia (B-ALL) is a challenging disease with poor outcomes compared to kids. Until recent findings from the E-1910 study, induction chemotherapy followed by curative allogeneic hematopoietic cell therapy (allo-HCT) in CR1 was standard for eligible patients. Allo-HCT was offered because in the era of chemo alone the median overall survival was about 2-6 months for those with relapsed disease. The arrival of blinatumomab, and inotuzumab to relapsed space has changed the landscape of both upfront and relapsed settings. In addition, Brexucabtagene autoleucel (Tecartus) was recently FDA-approved for adult patients with r/r ALL. In the registration trial, the median DOR was about 7 months while 70% reached CR. Interestingly, adults > 60 years who historically were difficult to treat in relapsed setting had 100% CR rates. Until this publication came out such high response rates was unprecedented for those treating older adults. Considering only 65 patients in ZUMA-3 received CD 19 CART cells based on which FDA approved the product, real-world toxicity and efficacy of this product are highly desirable. Investigators of Zuma-3 as a part of subgroup analyses also reported in ASCO 2023 abstract (Ghobadi et al), age group cutoff that seems to suggest a potential benefit to using Tecartus even in younger patients that would be eligible to receive the other FDA-approved CART. While the response rates and DOR were impressive benefit of consolidative allo-HCT remains unknown. Some pediatric reports suggest allo-HCT is beneficial while a few other studies suggest it may not impact overall survival.
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.	As the number of available therapies for r/r ALL increases, how best to sequence FDA-approved therapies in r/r ALL without sacrificing on efficacy of individual therapies has become challenging. Now that blinatumomab may be increasingly used for consolidation, with or without measurable residual disease post-induction understanding real-world benefits with CD 19 CART cells is essential. This study will also clearly delineate if consolidative allo-HCT should be pursued among patients who achieve remission after CAR-T cell therapy.

PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Patient Eligibility Population: Adult r/r B-ALL patients receiving CD-19 directed CAR-T cell (TECARTUS) therapy. Exclusion: patients enrolled on clinical trials Data Requirements: CIBMTR report forms will be used for data analysis. Supplemental data if made available will also be used. Study period Jan 2019 to Dec 2023. Pre-CART: Time from diagnosis to CART, number of lines of induction/consolidation/relapse therapies used before CAR-T, HCTCI comorbidity index, KPS, disease status pre-CART. CD 19 expression status (bright, dim etc; if available), best response prior to CAR-T, best response to blinatumomab. Patient related: Age, sex, ethnicity Post CAR-T: Data on counts, infection, last follow up, relapse, time to relapse, info on subsequent therapy, CRS, neurotoxicity, date of last follow up, dead- Y/N, causes of death. If CD 19 and CD 22 status data is available we would seek that info. If allo-HCT after CAR-T (Y/N) was used then below data Donor: HLA matching level (matched vs mismatched- related/unrelated), Donor-recipient CMV/ABO matching status Recipient: KPS, HCT-CI, race, age, CMV, disease type/risk group Graft: peripheral blood or bone marrow with no ex-vivo T cell depletion. Therapy: Conditioning regimens (Intensity-MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-ASCT therapy to prevent relapse(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials) . Therapies used pre and post CART Disease related: Best response pre-transplant. Rates of grade 3 or 4 aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death. - Disease risk index - High risk cytogenetics: yes vs.no - Philadelphia Chromosome (yes vs. no) - Immunohistochemistry (IHC) if available - Number of prior therapy (before transplant): 1 vs. 2 vs. ≥ 3 - Disease status at the time of transplant: complete remission vs partial response vs. stable disease vs progressive disease - CNS involvement at diagnosis and transplant - Response to First line therapy - Lines of therapy before HCT - Remission status prior to HCT Transplant-related: - Year of transplant - Time from diagnosis to allogeneic transplantation: months - Timing of HCT: upfront (after induction), late (>1 line of therapy), unknown - Disease risk index at transplant - Mobilization regimen for allo-HCT - Conditioning regimen: myeloablative vs. reduced-intensity (RIC)/non-myeloablative (NMA) - Graft source (PBSCT versus marrow) - Donor type (matched related,

Field	Response
	matched unrelated, mismatched related/haploidentical related, mismatched unrelated, cord) - Neutrophil and platelet engraftment (days) - GVHD prophylactic regimen - Donor/Recipient ABO match - Donor/Recipient CMV match - Donor age Post-transplant-related: - Follow-up of survivors (months) - Response to transplant -100-day disease status - 30 and 100-day mortality - Date of post-transplant relapse - Date of death - Cause of death
Does this study include pediatric patients?	Yes

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	1650-1659. 13. Amrolia, P.J. and M. Pule, Chimeric antigen receptor T cells for ALL. Lancet, 2015. 385(9967): p. 488-90. 14. Brentjens, R.J., et al., CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med, 2013. 5(177): p. 177ra38. 15. Kochenderfer, J.N., et al., Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol, 2015. 33(6): p. 540-9. 16. Porter, D.L., et al., Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med, 2011. 365(8): p. 725-33. 17. June, C.H. and M. Sadelain, Chimeric Antigen Receptor Therapy. New England Journal of Medicine, 2018. 379(1): p. 64-73. 18. Brown, P.A. and B. Shah, Emerging Treatment Options for Acute Lymphoblastic Leukemia: Focus on CAR T-Cell Therapy. J Natl Compr Canc Netw, 2018. 16(5s): p. 651-655. 19. Wang, J., Y. Hu, and H. Huang, Acute lymphoblastic leukemia relapse after CD19-targeted chimeric antigen receptor T cell therapy. J Leukoc Biol, 2017. 102(6): p. 1347-1356. 20. Ghosh, A., I. Politikos, and M.A. Perales, Stop and go: hematopoietic cell transplantation in the era of chimeric antigen receptor T cells and checkpoint inhibitors. Curr Opin Oncol, 2017. 29(6): p. 474-483. 21. Wen, S., et al., CAR-T bridging to allo-HSCT as a treatment strategy for relapsed adult acute B-lymphoblastic leukemia: a case report. BMC Cancer, 2018. 18(1): p. 1143. 22. Hu, Y., et al., A retrospective comparison of allogenic and autologous chimeric antigen receptor T cell therapy targeting CD19 in patients with relapsed/refractory acute lymphoblastic leukemia. Bone Marrow Transplant, 2019. 54(8): p. 1208-1217. 23. Lee, D.W., et al., T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet, 2015. 385(9967): p. 517-528. 24. Maude, S.L., et al., Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med, 2014. 371(16): p. 1507-17. 25. Davila, M.L., et al., Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med, 2014. 6(224): p. 224ra25. 26. Park, J.H., et al., Implications of Minimal Residual Disease Negative Complete Remission (MRD-CR) and Allogeneic Stem Cell Transplant on Safety and Clinical Outcome of CD19-Targeted 19-28z CAR Modified T Cells in Adult Patients with Relapsed, Refractory B-Cell ALL. Blood, 2015. 126(23): p. 682-682. 27. Liu, J., et al., CAR-T

Field	Response
	cells and allogeneic hematopoietic stem cell transplantation for relapsed/refractory B-cell acute lymphoblastic leukemia. Immunotherapy, 2017. 9(13): p. 1115-1125. 28. Hay, K.A., et al., Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood, 2019. 133(15): p. 1652-1663. 29. Shadman, M., et al., Safety of allogeneic hematopoietic cell transplant in adults after CD19-targeted CAR T-cell therapy. Blood Adv, 2019. 3(20): p. 3062-3069.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-266-MIRZA
Proposal Title	Outcomes of B- Acute Lymphoblastic Leukemia Patients Receiving CD19 CAR-T with Prior Exposure to Blinatumomab.
Key Words	salvage, B-ALL, sequential therapy, CAR-T, survival
Principal Investigator #1: - First and last name, degree(s)	Sayeef Mirza
Principal Investigator #1: - Email address	sayeef.mirza@moffitt.org
Principal Investigator #1: - Institution name	Moffitt Cancer Center
Principal Investigator #1: - Academic rank	Assistant Member
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Nelli Bejanyan
Principal Investigator #2 (If applicable): - Email address:)	nelli.bejanyan@moffitt.org
Principal Investigator #2 (If applicable): - Institution name:	Moffitt Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Associate Member
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	sayeef mirza
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	CT21-01: PI
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	What is the impact of pharmacologic CD19 targeting prior to CD19 CAR-T infusion in B-ALL?
RESEARCH HYPOTHESIS:	We hypothesize that that use of blinatumomab pre-CART is associated with increased treatment failure and poor survival in management of relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL).

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. Primary aim: Evaluate progression free survival (PFS) (at 6 months and 12 months) in recipients of CD 19 CAR-T cells for r/r ALL stratified by prior blinatumomab use. 2. Secondary aims: a. Evaluate Overall survival (OS) at 6 months and 12 months in recipients of CD 19 CAR-T for r/r ALL stratified by prior blinatumomab use. b. Evaluate risk of cytokine release syndrome and neurotoxicity post-CART stratified by prior blinatumomab use. c. Cumulative incidence of infections, immune recovery, relapse, and non-relapse mortality. d. Identify prognostic markers that may predict best response at 3 months and PFS and OS at 6- and 12-months post CAR-T therapy stratified by prior blinatumomab use.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	As the number of available therapies for r/r ALL increases, how best to sequence FDA approved therapies in r/r ALL without sacrificing on efficacy of individual therapies has become challenging. While Blinatumomab is FDA approved for relapsed, MRD + ve disease and is prospectively studied in E1910 to eradicate MRD post induction, it remains to be seen if used as a bridge to CD19 CAR-T cell therapy, will it alter subsequent immune-vigilance? Collectively, the above studies highlight a growing armamentarium and concerns, when novel therapies competing against same target are used sequentially. Results from our proposed study will offer future direction on how best to sequence immunomodulatory drugs with either native T cells (allo-HCT) or genetically modified T cells (CAR-T). CIBMTR studies in the past have shown risk of VOD with inotuzumab prior to allografting and has changed practice. We remain optimistic signals from this study would also be practice changing albeit, with CAR-T cell therapy.

Field	Response
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.	Despite the high initial remission rate (about 85%-90%) for acute lymphoblastic leukemias (ALL), relapses are not infrequent and overall survival (OS) in adults is low (about 30%-40%). A few decades ago, LALA-87, LALA-94 and MRC-ECOG trials showed the utility of ASCT in first complete remission for standard and high-risk groups. For those with relapse/refractory disease, outcomes were generally poor in that era with short lasting remissions in the range of 18%-44% with salvage chemotherapy. The median overall survival was about 2-6 months with chemo-regimens. However, if the patient had donor availability and achieved second CR (CR), the 5-year OS was 33% in the LALA study[1]. This was confirmed again in the MRC/ECOG 2993 study where the 5 year OS was 23%, 16% and 4% for patients receiving matched sibling, matched unrelated donor ASCT, and chemotherapy, respectively.[2, 3] A study conducted at MD Anderson Cancer Center reported 1 and 2 year OS of 17% and 10%, respectively, for those who relapse after ASCT despite receiving different salvage options including a second ASCT[4]. Collectively, these results underline an unmet need to improve response rates in r/r ALL, which could then be translated with additional interventions to improve OS benefit. Arrival of monoclonal antibodies and antibody drug conjugates have modified the landscape of r/r ALL management.[5-7] In Tower trial, remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard of care (SOC) group, both with respect to CR (34% vs. 16%, P<0.001) and with respect to CR with full, partial, or incomplete hematologic recovery (Cri- 44% vs. 25%, P<0.001). Median OS was 7.7 m vs 4.0 months in favor of blina (28249141).[7, 8] With the advent of CAR-T, we now have a viable alternative cellular approach to regain remission in kids and adults with r/r ALL.[5, 9] Unexpectedly, a recent study presented at ASH 2020 has raised concerns about blunting CD19 expression prior to CAR-T with blinatumomab as this group experienced higher relapse, inferior relapse free survival, compared to those not treated with blina, which begs the question whether there is early loss of immune surveillance.[10] Since, ELIANA (registration) trial excluded patients with prior blina exposure, it is not possible to extrapolate from that study about the significance of prior blinatumomab treatment on long term immune-surveillance. In contrast, the more recent adult CAR-T approval study permitted use of blinatumomab and impressively, rates of CR (56.4%) in ZUMA-3 trial (small n) was higher than that reported in blinatumomab registration trial.[11]

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Pediatric and Adult r/r B-ALL patients receiving CD-19 directed CAR-T cell therapy.
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	CIBMTR report forms will be used for data analysis. Supplemental data if made available will also be used. Study period Jan 2011 to Dec 2023. Pre-CART: Time from diagnosis to CART, number of lines of induction/consolidation/relapse therapies used before CAR-T, HCTCI comorbidity index, KPS, disease status pre-CART. CD 19 expression status (bright, dim etc; if available), best response prior to CAR-T, best response to blinatumomab. Patient related: Age, sex, ethnicity Post CAR-T: Data on counts, infection, last follow up, relapse, time to relapse, info on subsequent therapy, CRS, neurotoxicity, date of last follow up, dead-Y/N, causes of death. If CD 19 and CD 22 status data is available we would seek that info. If allo-HCT after CAR-T (Y/N) was used then below data Donor: HLA matching level (matched vs mismatched-related/unrelated), Donor-recipient CMV/ABO matching status Recipient: KPS, HCT-CI, race, age, CMV, disease type/risk group Graft: peripheral blood or bone marrow with no ex-vivo T cell depletion. Therapy: Conditioning regimens (Intensity- MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-ASCT therapy to prevent relapse(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials) Disease related: Best response pre-transplant. Rates of grade 3 or 4 aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death.
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.	We want to collaborate with European colleagues with a combined CIBMTR and EBMT analysis.

Field	Response
REFERENCES:	1. Tavernier, E., et al., Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia, 2007. 21(9): p. 1907-14. 2. Rowe, J.M., et al., Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood, 2005. 106(12): p. 3760-7. 3. Fielding, A.K., et al., Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood, 2007. 109(3): p. 944-50. 4. Poon, L.M., et al., Outcomes of adults with acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2013. 19(7): p. 1059-64. 5. Shah, N.N., et al., Long-Term Follow-Up of CD19-CAR T-Cell Therapy in Children and Young Adults With B-ALL. J Clin Oncol, 2021. 39(15): p. 1650-1659. 6. Li, L., et al., Treatment response, survival, safety, and predictive factors to chimeric antigen receptor T cell therapy in Chinese relapsed or refractory B cell acute lymphoblast leukemia patients. Cell Death & Disease, 2020. 11(3): p. 207. 7. Salhotra, A., et al., Outcomes of Allogeneic Hematopoietic Cell Transplantation after Salvage Therapy with Blinatumomab in Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant, 2020. 26(6): p. 1084-1090. 8. Kantarjian, H., et al., Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. New England Journal of Medicine, 2017. 376(9): p. 836-847. 9. Grupp, S.A., et al., Tisagenlecleucel for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: Updated Analysis of the ELIANA Clinical Trial. Biology of Blood and Marrow Transplantation, 2019. 25(3): p. S126-S127. 10. Taraseviciute, A., et al., Pre-CAR Blinatumomab Is Associated with Increased Post-CD19 CAR Relapse and Decreased Event Free Survival. Blood, 2020. 136(Supplement 1): p. 13-14. 11. 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.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	Yes, I have conflicts of interest pertinent to this proposal

Field	Response
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.	Dr. Bejanyan reports consulting, advisory role or research funding with Magenta Therapeutics, Medexus Pharmaceuticals, CTI BioPharma, CareDx Pharma, Orca Bio, Sanofi, AlloVir and CRISPR Therapeutics.

Characteristics of patients with B-cell ALL with CT in 2015-2021

Characteristic	N (%)
No. of patients	577
No. of centers	101
All adolescent and young adult patients aged 15-25 years old who were treated with Tisagenlecleucel, or aged 15-40 years old who were treated with Brexucabtagene autoleucel - no. (%)	
No	352 (61.0)
Yes	225 (39.0)
All adult patients with r/r B cell acute lymphoblastic leukemia who received brexucabtagene autoleucel, or adult patients with r/r Mantel cell lymphoma who received brexucabtagene autoleucel - no. (%)	
No	567 (98.3)
Yes	10 (1.7)
CT population	
Age at CT - no. (%)	
Median (min-max)	14.0 (0.4-66.0)
<10	185 (32.1)
10-17	207 (35.9)
18-29	176 (30.5)
30-39	4 (0.7)
50-59	2 (0.3)
60-69	3 (0.5)
Recipient Sex - no. (%)	
Male	345 (59.8)
Female	232 (40.2)
Recipient race - no. (%)	
White	408 (70.7)
Black or African American	36 (6.2)
Asian	19 (3.3)
American Indian or Alaska Native	3 (0.5)
Other	25 (4.3)
More than one race	49 (8.5)
Not reported	37 (6.4)
Karnofsky performance score prior to CT - no. (%)	
90-100	347 (60.1)
80-90	98 (17.0)
10-80	93 (16.1)

Characteristic	N (%)
Not reported	39 (6.8)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	347 (60.1)
1 - Symptomatic but completely ambulatory	157 (27.2)
2 - Symptomatic, <50% in bed during the day	31 (5.4)
3 - Symptomatic,>50% in bed, but not bedbound	3 (0.5)
Not reported	39 (6.8)
Country - no. (%)	
US	540 (93.6)
Others	37 (6.4)
CAR-T product type - no. (%)	
Kymriah	567 (98.3)
Tecartus	10 (1.7)
Sorror/HCT-CI comorbidity score group - no. (%)	
0	235 (40.7)
1	127 (22.0)
2	67 (11.6)
3+	142 (24.6)
TBD, unclear lineage of prior hematologic malignancies	2 (0.3)
NA, not collected for early revisions of f4000	2 (0.3)
Not reported	2 (0.3)
MRD status - no. (%)	
No	535 (92.7)
Yes	42 (7.3)
Prior HCT - no. (%)	
No	410 (71.1)
Yes	158 (27.4)
Not reported	9 (1.6)
Time from the latest prior HCT to current CT - no. (%)	
>= 0 to < 6 months	16 (2.8)
>= 6 to < 12 months	40 (6.9)
>= 12 months	98 (17.0)
Not reported	423 (73.3)
Subsequent HCT since the CT infusion - no. (%)	
No	356 (61.7)
Yes	197 (34.1)
Not reported	24 (4.2)
Time from CT to subsequent HCT - no. (%)	

Characteristic	N (%)
<6 months	492 (85.3)
6-12months	50 (8.7)
>12 months	35 (6.1)
Time from initial diagnosis to CT - no. (%)	
0-12 months	118 (20.5)
12-36 months	177 (30.7)
36-60 months	127 (22.0)
>60 months	155 (26.9)
Year of CT - no. (%)	
2017	8 (1.4)
2018	125 (21.7)
2019	173 (30.0)
2020	161 (27.9)
2021	110 (19.1)
Median follow-up of survivors (range), months - median (range)	30.9 (1.1-65.0)

Characteristics of patients with B-cell ALL with HCT in 2015-2021

Characteristic	N (%)
No. of patients	6927
No. of centers	312
Patients with MRD+ - no. (%)	
No	4937 (71.3)
Yes	1990 (28.7)
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	39.2 (0.2-78.4)
<10	594 (8.6)
10-17	671 (9.7)
18-29	1303 (18.8)
30-39	993 (14.3)
40-49	1121 (16.2)
50-59	1224 (17.7)
60-69	899 (13.0)
>=70	122 (1.8)

Characteristic	N (%)
Sex - no. (%)	
Male	3911 (56.5)
Female	3016 (43.5)
Race - no. (%)	
White	4710 (68.0)
Black or African American	304 (4.4)
Asian	501 (7.2)
Native Hawaiian or other Pacific Islander	30 (0.4)
American Indian or Alaska Native	79 (1.1)
More than one race	80 (1.2)
Not reported	1223 (17.7)
Reporting track - no. (%)	
TED	5702 (82.3)
CRF	1225 (17.7)
US or Non-US - no. (%)	
US	4991 (72.1)
Non-US	1936 (27.9)
Karnofsky score prior to HCT - no. (%)	
90-100	4474 (64.6)
< 90	2327 (33.6)
Not reported	126 (1.8)
HCT-CI - no. (%)	
0	2380 (34.4)
1	1054 (15.2)
2	992 (14.3)
3+	2473 (35.7)
TBD, review needed for history of malignancies	17 (0.2)
TBD, inconsistencies between parent and sub-questions	1 (0.0)
Missing	10 (0.1)
Prior CT - no. (%)	
No	6723 (97.1)
Yes	204 (2.9)
Time from prior ct to hct - no. (%)	
<6 months	141 (2.0)
6-12months	44 (0.6)
>12 months	19 (0.3)
Not Reported	6723 (97.1)
Subsequent CT - no. (%)	

Characteristic	N (%)
No	6711 (96.9)
Yes	216 (3.1)
Time from subsequent ct to hct - no. (%)	
<6 months	6 (0.1)
6-12months	47 (0.7)
>12 months	163 (2.4)
Not Reported	6711 (96.9)
Disease Related	
Disease status at time of HCT - no. (%)	
PIF	187 (2.7)
CR1	5901 (85.2)
>=CR3	604 (8.7)
Relapse	230 (3.3)
Not reported	5 (0.1)
Time from diagnosis to HCT - no. (%)	
<6 months	3138 (45.3)
6-12months	2563 (37.0)
>12 months	1226 (17.7)
Transplant Related	
Donor type - no. (%)	
HLA-identical sibling	2021 (29.2)
Other related	1452 (21.0)
Well-matched unrelated (8/8)	2289 (33.0)
Partially-matched unrelated (7/8)	418 (6.0)
Mis-matched unrelated (<= 6/8)	15 (0.2)
Unrelated (matching TBD)	288 (4.2)
Cord blood	444 (6.4)
Donor/recipient CMV serostatus - no. (%)	
+/+	2926 (42.2)
+/-	637 (9.2)
-/+	1607 (23.2)
-/-	1250 (18.0)
CB - recipient +	316 (4.6)
CB - recipient -	123 (1.8)
CB - recipient CMV unknown	5 (0.1)
Not reported	63 (0.9)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
No drugs reported	8 (0.1)

Characteristic	N (%)
MAC	4939 (71.3)
RIC	1330 (19.2)
NMA	517 (7.5)
TBD	129 (1.9)
Not reported	4 (0.1)
Donor/recipient sex match - no. (%)	
M-M	2337 (33.7)
M-F	1631 (23.5)
F-M	1307 (18.9)
F-F	1180 (17.0)
CB - recipient M	256 (3.7)
CB - recipient F	188 (2.7)
Not reported	28 (0.4)
Product type - no. (%)	
BM	1533 (22.1)
PB	4950 (71.5)
UCB	444 (6.4)
ATG/Campath - no. (%)	
ATG + CAMPATH	2 (0.0)
ATG alone	1579 (22.8)
CAMPATH alone	161 (2.3)
No ATG or CAMPATH	5185 (74.9)
GVHD prophylaxis - no. (%)	
None	46 (0.7)
Ex-vivo T-cell depletion	143 (2.1)
CD34 selection	105 (1.5)
PtCy + other(s)	1749 (25.2)
PtCy alone	35 (0.5)
TAC + MMF +- other(s) (except PtCy)	517 (7.5)
TAC + MTX +- other(s) (except MMF, PtCy)	2168 (31.3)
TAC + other(s) (except MMF, MTX, PtCy)	282 (4.1)
TAC alone	125 (1.8)
CSA + MMF +- other(s) (except PtCy,TAC)	366 (5.3)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	1198 (17.3)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	17 (0.2)
CSA alone	105 (1.5)
Other(s)	65 (0.9)
Missing	6 (0.1)

Characteristic	**N (%)**
Year of current transplant - no. (%)	
2015	891 (12.9)
2016	962 (13.9)
2017	1037 (15.0)
2018	1021 (14.7)
2019	1038 (15.0)
2020	959 (13.8)
2021	1019 (14.7)
Median follow-up of survivors (range), months - median (range)	37.3 (0.0-102.6)

Field	Response
Proposal Number	2310-42-GONZALEZMOSQUERA
Proposal Title	Safety and efficacy of CAR-T cell therapy in relapsed/refractory acute lymphoblastic leukemia with central nervous system involvement
Key Words	CAR-T, CNS, ALL
Principal Investigator #1: - First and last name, degree(s)	Luis Gonzalez Mosquera, MD
Principal Investigator #1: - Email address	lgonza11@hfhs.org
Principal Investigator #1: - Institution name	Henry Ford Health
Principal Investigator #1: - Academic rank	Hematology/oncology fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Shatha Farhan, MD
Principal Investigator #2 (If applicable): - Email address:)	sfarhan1@hfhs.org
Principal Investigator #2 (If applicable): - Institution name:	Henry Ford Health / Wayne State University
Principal Investigator #2 (If applicable): - Academic rank:	Clinical assistant professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	Yes
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:	Shatha Farhan, MD
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Shatha Farhan: CT22-2 PI CK20-01 participated in reviewing concept, data analysis and manuscript prep CK17-02 participated in reviewing concept, data analysis and manuscript prep
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Will CART cell therapy be an effective and safe option for patients with refractory/relapsed ALL and have CNS involvement?
RESEARCH HYPOTHESIS:	CAR-T cell therapy can be a safe and effective option in relapsed/refractory acute lymphoblastic leukemia with CNS involvement.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary objective - To evaluate progression free survival of CAR T-cell therapy in relapsed/refractory ALL with central nervous system involvement. Secondary objectives - To evaluate overall survival of CAR T-cell therapy in relapsed/refractory ALL with central nervous system involvement. - To evaluate non relapse mortality of CAR T-cell therapy in relapsed/refractory ALL with central nervous system involvement. - To evaluate demographic, disease and product associated risk factors related with dismal outcome. - To evaluate safety of CAR T-cell therapy in R/R ALL with CNS involvement, evaluate development of ICANS, and risk factors associated with it development. - To evaluate the influence of prior lines used of therapy (types and number used) in the efficacy of CAR T-cell in R/R ALL with CNS involvement. - To evaluate difference of response between the different CAR T-cell therapies used.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Give clinicians real-world data to have certainty of the use of CAR-T cell therapy in ALL with CNS involvement. There have been small trials and few patient papers showing their utility, so we want to provide robust evidence of how effective and safe they can be in the before-mentioned situation.

Field	Response
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 central nervous system (CNS) is the most frequently affected extramedullary site at diagnosis (< 5%) and at relapse (up to 30% to 40%)1. Cranial irradiation plus intrathecal chemotherapy is the mainstay of treatment of CNS involvement2. However, short- and long-term toxicities can make these interventions prohibitively risky, particularly for older adults3. For relapsed or refractory disease, the FDA approved Tisagenlecleucel and Brexucabtagene CAR-T cell therapies for the treatment of B cell precursor ALL. However, data for its safety and efficacy in CNS involvement relapse is scarce, partly due to the concern of CAR-T cell induced neurotoxicity, having CAR-T cell clinical trials excluding patients with CNS involvement. One Chinese retrospective study that included 48 patients with relapsed/refractory B-ALL with CNS-3 involvement showed an 85.4 % remission rate in CNS, with a median event-free survival of 8.7 months (95% CI, 3.7-18.8), and a median overall survival of 16.0 months (95% CI, 13.5-20.1). Severe neurologic events (grade 3-4) were seen in 11 patients (22.9%) with higher preinfusion disease burden in CNS4. A post hoc analysis from five pediatric clinical (included young adults) trials using CAR-T cell therapy, with 66 patients having CNS positive disease, showed no difference in complete response at 28 days (64 [97%] of 66 vs. 121 [94%] of 129; p=0 ·74) and relapse free survival when it was compared with patients with no CNS disease at relapse (60% [95% CI 49–74] vs 60% [51–71]; p=0·50). Also, there was no difference in the incidence of neurotoxicity (any grade, 53 [41%] vs 38 [58%]; p=0·20)5. In conclusion, despite the advancements in the last years concerning the use of CAR T-cell therapies for relapsed/refractory ALL, information about its use in relapsed/refractory ALL with CNS involvement is still scarce. As outlined in the previous paragraph, some small patient population studies showed that they are safe and can achieve a response in ALL with CNS disease; however, there is still a need for extensive prospective studies and evaluation in the real world. Therefore, we aim to collect data from real-world patients and evaluate their safety and response.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: a. Patients with diagnosis of acute lymphoblastic leukemia with CNS2 and CNS3 involvement b. Received at least one line of treatment. c. Received any FDA approved CAR-T cell for ALL d. June 2012 to June 2022 Exclusion criteria a. Patients with a diagnosis of acute lymphoblastic leukemia with CNS1 b. Not received FDA-approved CAR-T cell for ALL

Field	Response
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Baseline characteristics (prior CAR-T administration) - Date of birth - Sex - Cytogenetics o BCR-ABL+? (Y/N) o MLL rearrangements? (Y/N) o Other high-risk cytogenetics? (Y/N) - Number of prior treatment lines - List of prior treatment lines - Prior blinatumomab? (Y/N) o Refractory to blinatumomab? (Y/N) o Relapsed after blinatumomab? (Y/N) - Prior inotuzumab-ozogamicin? (Y/N) - Prior allo-HCT? (Y/N) - Number of prior allo-HCT: 1, 2, etc. o Date of prior allo-HCT o Myeloablative conditioning? (Y/N) o TBI? (Y/N) o Absence of extramedullary disease? (Y/N) o Date of relapse after allo-HCT CAR-T cell therapy: - CAR-T product - cell dose - Disease status at time of infusion - CRP and Ferritin at infusion - lymphodepletion prior to CAR-T (Y/N) - LD agent and dose - Bridging therapy - Response to CAR-T Disease treatment-related: - Complications related to CAR-T cell therapy CRS (y/n) and ASTCT grading , ICANS y/n and ASTCT grading - Side effects related to conditioning chemotherapy (sepsis, any other organ dysfunction beyond expected for CART (respiratory, cardiac, hepatic, etc.) - Duration of hospitalization post CAR-T cell therapy- Prolonged cytopenia - CRS treatment or prevention drugs – Y/N - B cell and T cell recovery markers at D 100, 180 and 365 - CRES/Neurotoxicity (Y/N and grade) - Cytopenias - Infectious complications Disease status • best response to the cellular therapy • date of best response to the cellular therapy • was a disease relapse or progression Date of progression Date of death or last follow-up Statistical analyses will be discussed with statisticians. Descriptive data will be reported as medians and ranges for continuous variables, and number and percent for categorical variables. Patients will be censored at last follow up if no events occurred. For time-to-event analysis, the Kaplan-Meier estimator method will be used. The starting point for time-to –event analysis will be the date of CART19 infusion. Progression-free survival (PFS): Survival without recurrence or tumor progression. Recurrence of progression of disease and death would be counted as events. Those who survive without recurrence or progression would be censored at the time of last contact Death of any cause will be the event for analysis of OS. Non-relapse mortality will be defined as the time from CART19 infusion to death in the absence of prior relapse or progression. Patients who did not have an event will be censored at the date of last follow-up.

Field	Response
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	No need of biological samples.
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.	N/A
REFERENCES:	1 Cancela CS, Murao M, Viana MB, de Oliveira BM. Incidence and risk factors for central nervous system relapse in children and adolescents with acute lymphoblastic leukemia. Rev Bras Hematol Hemoter. 2012;34(6):436-41. 2 Larson RA. Managing CNS disease in adults with acute lymphoblastic leukemia. Leuk Lymphoma. 2018 Jan;59(1):3-13. 3 Kopmar NE, Cassaday RD. How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia. Blood. 2023 Mar 23;141(12):1379-1388. 4 Qi Y, Zhao M, Hu Y, et al. Efficacy and safety of CD19-specific CAR T cell-based therapy in B-cell acute lymphoblastic leukemia patients with CNSL. Blood. 2022 Jun 9;139(23):3376-3386. 5 Leahy AB, Newman H, Li Y, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials. Lancet Haematol. 2021 Oct;8(10):e711-e722.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Characteristics of patients receiving CAR-T with ALL and CNS2 and CNS3 involvement

Characteristic	N (%)
No. of patients	71
No. of centers	42
Age at CT - no. (%)	
Median (min-max)	15.2 (0.7-58.1)
<10	25 (35.2)
10-17	17 (23.9)
18-29	24 (33.8)
30-39	3 (4.2)
50-59	2 (2.8)
Recipient Sex - no. (%)	
Male	47 (66.2)
Female	24 (33.8)
Recipient race - no. (%)	
White	51 (71.8)
Black or African American	5 (7.0)
Asian	6 (8.5)
Other	1 (1.4)
More than one race	5 (7.0)
Missing	3 (4.2)
Karnofsky performance score prior to CT - no. (%)	
90-100	42 (59.2)
80-90	12 (16.9)
10-80	14 (19.7)
Not reported	3 (4.2)
Country - no. (%)	
US	70 (98.6)
Others	1 (1.4)
Disease status (based on hematological test results) - no. (%)	
Primary induction failure	8 (11.3)
1st complete remission	1 (1.4)
2nd complete remission	3 (4.2)
>= 3rd complete remission	5 (7.0)
1st relapse	18 (25.4)
2nd relapse	21 (29.6)
>= 3rd relapse	15 (21.1)
ECOG performance status prior to CT - no. (%)	
0-Asymptomatic	42 (59.2)
1 - Symptomatic but completely ambulatory	21 (29.6)

Characteristic	**N (%)**
2 - Symptomatic, < 50% in bed during the day	4 (5.6)
3 - Symptomatic, > 50% in bed, but not bedbound	1 (1.4)
Not reported	3 (4.2)
CAR-T product type - no. (%)	
Kymriah	64 (90.1)
Tecartus	7 (9.9)
Sorror/HCT-CI comorbidity score group - no. (%)	
0	35 (49.3)
1	18 (25.4)
2	5 (7.0)
3+	12 (16.9)
Not reported	1 (1.4)
Time from initial diagnosis to CT - no. (%)	
0-12 months	16 (22.5)
12-36 months	27 (38.0)
36-60 months	10 (14.1)
>60 months	18 (25.4)
Year of CT - no. (%)	
2017	2 (2.8)
2018	11 (15.5)
2019	16 (22.5)
2020	19 (26.8)
2021	16 (22.5)
2022	7 (9.9)
Median follow-up of survivors (range), months - median (range)	26.4 (3.6-59.1)

Study title:

Sequencing of chimeric antigen receptor T-cell therapy and allogeneic transplantation in adult patients with B-cell acute lymphoblastic leukemia

Investigators:

Donna Eng, Princess Margaret Cancer Centre
Joshua Fein, Weill Cornell Medicine/New York Presbyterian Hospital
Alexandra Gomez Arteaga, Weill Cornell Medicine/New York Presbyterian Hospital
Mohamed Kharfan-Dabaja, Mayo Clinic Florida
Leland Metheny, University Hospitals Seidman Cancer Center
Razan Mohty, University of Alabama at Birmingham
Hassan Sibai, Princess Margaret Cancer Centre
Jiasheng Wang, University Hospitals Seidman Cancer Center

Research hypothesis:

The sequencing of allogeneic stem cell transplantation (allo-HCT) and CAR-T in adult patients (≥ 18 years) with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) remains controversial. We hypothesize that outcomes including response, overall survival (OS) and toxicities are affected by combining these two therapies.

Specific objectives/outcomes to be investigated: (Primary/secondary, max 200 words)

Primary outcomes (two separate manuscripts):

1. To evaluate OS of patients with R/R B-ALL who received consolidative allo-HCT after CAR-T in comparison to those who did not.

2. To evaluate OS and distinct toxicity profile of R/R B-ALL patients who receive CAR-T after previously receiving allo-HCT.

Secondary outcomes:

1. To determine the following outcomes in patients who did or did not receive consolidative allo-HCT following CAR-T
    a. Leukemia-free survival (LFS)
    b. Non-relapse mortality (NRM)
    c. Relapse incidence (RI)
    d. Graft-versus-host-disease free/relapse free survival (GRFS)
    e. Association between key subsets and overall survival benefit of consolidative allo-HCT
        i. Age
        ii. Disease risk defined by???
        iii. MRD (at what time???)
    f. Association between time from CAR-T to consolidative allo-HCT and overall survival
2. To determine the following outcomes in patients who received CAR-T after prior allo-HCT
    a. LFS

   b. NRM
   c. RI
   d. Incidence of CRS and ICANS
   e. GvHD incidence
   f. Association between time from allo-HCT to CAR-T and overall survival
3. To establish a dedicated data repository for future exploration of therapy sequencing in B-ALL disease subsets.

Participant selection criteria:

Inclusion:

- Relapsed/refractory B-cell ALL
- Recipient of brexu-cel
- Age ≥ 18 years at time of CAR-T infusion

Scientific impact:

Allogeneic HCT has traditionally played a critical consolidative role in the management of patients achieving response following relapse of B-cell ALL. Over the past decade, CD19-directed CAR-T therapy has emerged as an effective treatment of relapsed or refractory disease. It remains controversial whether patients benefit from allo-HCT consolidation after response to CAR-T. Similarly, the unique safety and effectiveness profile of CAR-T from transduced donor T-cells in patients who have previously undergone allo-HCT for B-ALL is poorly characterized. The approval of brexucabtagene autoleucel (brexu-cel) for adult patients with R/R B-ALL significantly broadened the set of patients eligible for CAR-T for this indication. However, relapse after CAR-T remain relatively high. In the ZUMA-3 registration trial for brexu-cel, relapse-free survival among patients who achieved CR or CR with incomplete hematologic recovery was 14 months.[1] In the same cohort, among patients who subsequently underwent allo-HCT, the median relapse-free survival was overlapping (11.6 vs 11.7 months),[2] though other cohorts have shown improved outcomes with allo-HCT consolidation.[3] One study identified longer time-interval between CAR-T and allo-HCT to be predictive of worse NRM and OS, a finding which could influence the timing of post-CAR-T consolidation.[4] Given the rarity of R/R B-ALL, characterization of real-world outcomes across the extensive CIBMTR registry dataset will offer critical and clinically actionable insight into whether, to whom, and how to incorporate consolidation in the management of these patients. Alongside this clinical conundrum, allo-HCT remains a standard consolidation strategy in first CR for patients with high-risk disease features; therefore, a significant subset of CAR-T recipients have previously undergone allo-HCT. The ZUMA-3 trial included 23 patients (42%) who had received prior allo-HCT. While a subset analysis in the trial did not show difference in outcome between patients with and without history of allo-HCT, there is compelling biological rationale to anticipate differences in both the graft-versus-host and host-versus-graft directions. These real-world data will allow us to elucidate the unique outcomes of post-allo-HCT CAR-T cells.

Scientific justification:

Adult relapsed/refractory B-cell ALL remains a clinical challenge, with long-term OS as low as 12% for adults older than 45 years, and only modestly higher for young(er) adults.[5] The introduction of CAR-T cell therapy has raised the possibility of markedly improved outcomes for patients with R/R B-ALL. Among adult patients treated with brexu-cel on the ZUMA-3 trial, the 1-year overall survival was 71% (95%

confidence interval: 57-82),[1] with three-quarters of patients achieving MRD-negative CR. Nearly half (42%) of these patients had previously been treated with allo-HCT, and 10 (23%) of patients were reported to proceed to subsequent consolidative allo-HCT as of the most recently-updated data. Both allo-HCT and CAR-T represent potentially curative therapies, and understanding their ideal sequencing and interaction is crucial to optimizing therapy in these challenging clinical situations.

Despite the successes of CAR-T in the relapsed/refractory disease setting, subsequent relapse remains frequent and with limited salvage options. Consolidation with allo-HCT after CAR-T response is a strategy which has been variably applied both in clinical trials and standard-of-care practice. Results in both prospective and retrospective studies have been mixed: prospectively, Jiang and colleagues studied 21 patients of all ages with MRD-negative disease after CAR-T and found significant improvement in relapse-free survival (multivariable hazard ratio [HR] 0.17 [95% CI 0.07-0.43], $p < 0.001$), but no statistically significant difference in overall survival (HR 0.36 [95% CI 0.12-1.07], $p = 0.066$). Non-relapse mortality was not described and may account in part for this difference.[6] In a study of patients with high-risk cytogenetic or molecular features, Zhang and colleagues retrospectively compared 75 patients of all ages who received CAR-T followed by allo-HCT to 27 patients who received only CAR-T; they identified a marked and statistically significant difference in overall survival (79% versus 32% at 1-year, $p < 0.0001$).[3] An ongoing CIBMTR study exploring this question in patients eligible for tisagenlecleucel (age ≤ 26 years) found low non-relapse mortality (9%) and significant reduction in relapse incidence (multivariable HR 0.37, $p = 0.037$), but again without demonstration of a difference in disease-free (HR 0.46, $p = 0.057$) and overall survival (HR 0.75, $p = 0.51$) when published as an abstract (manuscript pending).[7]

Among patients with high-risk features, allo-HCT as consolidation in first complete remission remains common practice. As these are patients at high risk of relapse, CAR-T following allo-HCT and potentially using donor T-cell as substrate accounts for a meaningful proportion of CAR-T treatment in B-ALL. In patients with mixed chimerism, especially upon relapse, this raises intriguing possibilities of graft-versus-leukemia allogenicity as well as recurrence of graft-versus-host or even host-versus-graft effects. At least one case of biopsy-proven CAR-T-derived graft-versus-host disease has been described, in an account by Gardner and colleagues.[8] While short-term follow-up of small numbers of trial patients has not demonstrated a difference in overall survival (ZUMA-3 1-year OS: 79% prior allo-HCT vs. 65% without[1]), the duration of response may defer between patients with and without prior allo-HCT in the real-world setting with longer follow-up. Similarly, the toxicity profile of CAR-T in prior allo-HCT recipients, including incidence and severity of cytokine release syndrome, neurotoxicity, hematologic toxicity, and infections may plausibly differ from transplant-naïve patients.

The results of this study will address urgent clinical questions. Consolidative allo-HCT after CAR-T exposes patients to substantial risk of treatment-related morbidity and mortality. Demonstrating an overall survival benefit would answer the critical question of whether consolidative allo-HCT is necessary for long-term disease-free survival. The potential to identify patient subsets with greater or lesser likelihood of benefit will aid in personalizing therapy. Understanding the unique safety and efficacy profile of CAR-T following allo-HCT will inform prophylaxis and surveillance strategies and may provide novel insights into underlying graft-versus-leukemia biology.

Data requirements:

Patient-related (form/question)
Age at CART infusion (calculated)
Age at allo-HCT (calculated)
Sex (2400/2)
Ethnicity (2400/3)
Race (2400/4)
Performance status (Karnofsky) (2400/82)
HCT-CI and individual component comorbidities (2400/100-105)
Pre-CART organ function: AST, ALT, Bilirubin, LDH, Creatinine (2000/4-20)
Pre-allo-HCT organ function (if relevant): AST, ALT, Bilirubin, LDH, Creatinine (2000/4-20)
Disease-related
Time (years) from diagnosis to CART, allo-HCT (calculated)
ALL classification (2402/104)
Predisposing condition [specifically Down syndrome) (2402/105-6)
Cytogenetics and molecular markers (2402/109-164)
Presence of CNS disease (2402/166)
Prior therapies [especially blinatumomab exposure] (2011/37; 2400/146)
Disease status at CART infusion (2402/167)
Disease status at allo-HCT (2402/167)
Presence of MRD (2402/169-179)
CART-related
Cellular therapy product (4003/1 or 4100/1)
Plan for subsequent HCT (4001/2-4)
Lymphodepletion (4001/7)
CART outcome
Best response to CART (4100/12)
Time to relapse/progression (calculated)
GvHD occurrence and severity [in patients with prior allo] (4100/27-43)
CRS occurrence, grade, and onset (4100/47; calculated grade and time to onset)
ICANS occurrence, grade, and onset (4100/81; calculated grade and time to onset)
Hematologic recovery (4101/11-20)
Allo-HCT-related
Donor: relationship, HLA match (2400/calculated)
Graft source (2400/45)
Donor age (2400/65)
Donor-recipient sex match (2400/67)
Donor and recipient CMV serostatus (2400/70, 86)
Conditioning intensity and TBI (2400/123, 124, 125)
In vivo t-cell depletion—ATG vs Campath (2400/135)
GvHD prophylaxis (2400/141)
Post-allo-HCT maintenance therapy planned (2450/100)
Allo-HCT outcome
Time to relapse/progression (calculated)
Presence of MRD (2111/48-70)
GvHD occurrence and severity (2450/18-43)
Overall outcomes
Time until most recent follow-up and vital status at most recent follow-up (calculated)
Primary cause of death (2900/4)

References:

1. Shah BD, Ghobadi A, Oluwole OO, 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):491-502.
2. 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.
3. Zhang X, Lu XA, Yang J, et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. *Blood Adv*. 2020;4(10):2325-2338.
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5. Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120(10):2032-2041.
6. Jiang H, Li C, Yin P, et al. Anti-CD19 chimeric antigen receptor-modified T-cell therapy bridging to allogeneic hematopoietic stem cell transplantation for relapsed/refractory B-cell acute lymphoblastic leukemia: An open-label pragmatic clinical trial. *American Journal of Hematology*. 2019;94(10):1113-1122.
7. Park JH, Nikiforow S, Kim S, et al. Impact of Allogeneic Hematopoietic Cell Transplantation (HCT) As Consolidation Following CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy for Treatment of Relapsed Acute Lymphoblastic Leukemia (ALL). *Blood*. 2021;138:3880.
8. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood*. 2017;129(25):3322-3331.

Characteristics of adult patients with B-cell ALL

Characteristic	CAR-T Only	With Prios AlloHCT	With Subsequent AlloHCT	With Prior&Post AlloHCT	Total
No. of patients	267	139	81	22	509
No. of centers	90	73	51	18	121
Time from CAR-T to Allo-SCT - no. (%)					
0-3 months	5 (1.9)	1 (0.7)	24 (29.6)	2 (9.1)	32 (6.3)
3-6 months	11 (4.1)	2 (1.4)	30 (37.0)	7 (31.8)	50 (9.8)
>6 months	19 (7.1)	4 (2.9)	27 (33.3)	13 (59.1)	63 (12.4)
Not reported	232 (86.9)	132 (95.0)	0 (0.0)	0 (0.0)	364 (71.5)
Age at CT - no. (%)					
Median (min-max)	29.7 (18.0-84.3)	35.2 (18.3-77.1)	23.3 (18.0-68.1)	23.0 (18.6-64.5)	29.1 (18.0-84.3)
18-29	134 (50.2)	53 (38.1)	59 (72.8)	19 (86.4)	265 (52.1)
30-39	39 (14.6)	26 (18.7)	7 (8.6)	0 (0.0)	72 (14.1)
40-49	27 (10.1)	21 (15.1)	2 (2.5)	1 (4.5)	51 (10.0)
50-59	22 (8.2)	25 (18.0)	11 (13.6)	0 (0.0)	58 (11.4)
60-69	33 (12.4)	12 (8.6)	2 (2.5)	2 (9.1)	49 (9.6)
>=70	12 (4.5)	2 (1.4)	0 (0.0)	0 (0.0)	14 (2.8)
Patients age group(18-26, >26) - no. (%)					
18-26	110 (41.2)	41 (29.5)	55 (67.9)	16 (72.7)	222 (43.6)
>26	157 (58.8)	98 (70.5)	26 (32.1)	6 (27.3)	287 (56.4)
Recipient Sex - no. (%)					
Male	155 (58.1)	81 (58.3)	56 (69.1)	12 (54.5)	304 (59.7)
Female	112 (41.9)	58 (41.7)	25 (30.9)	10 (45.5)	205 (40.3)
Recipient race - no. (%)					
White	187 (70.0)	101 (72.7)	68 (84.0)	17 (77.3)	373 (73.3)
Black or African American	25 (9.4)	9 (6.5)	5 (6.2)	2 (9.1)	41 (8.1)
Asian	12 (4.5)	5 (3.6)	1 (1.2)	1 (4.5)	19 (3.7)
Native Hawaiian or other Pacific Islander	1 (0.4)	0 (0.0)	1 (1.2)	0 (0.0)	2 (0.4)
American Indian or Alaska Native	4 (1.5)	1 (0.7)	0 (0.0)	0 (0.0)	5 (1.0)
Other	3 (1.1)	4 (2.9)	1 (1.2)	2 (9.1)	10 (2.0)
More than one race	26 (9.7)	11 (7.9)	1 (1.2)	0 (0.0)	38 (7.5)
Missing	9 (3.4)	8 (5.8)	4 (4.9)	0 (0.0)	21 (4.1)
Karnofsky performance score prior to CT - no. (%)					

Characteristic	CAR-T Only	With Prios AlloHCT	With Subsequent AlloHCT	With Prior&Post AlloHCT	Total
90-100	105 (39.3)	50 (36.0)	49 (60.5)	12 (54.5)	216 (42.4)
80-90	80 (30.0)	44 (31.7)	22 (27.2)	6 (27.3)	152 (29.9)
10-80	62 (23.2)	32 (23.0)	6 (7.4)	4 (18.2)	104 (20.4)
Not reported	20 (7.5)	13 (9.4)	4 (4.9)	0 (0.0)	37 (7.3)
Country - no. (%)					
US	265 (99.3)	133 (95.7)	80 (98.8)	21 (95.5)	499 (98.0)
Others	2 (0.7)	6 (4.3)	1 (1.2)	1 (4.5)	10 (2.0)
What was the disease status (based on hematological test results)? - no. (%)					
Primary induction failure	36 (13.5)	2 (1.4)	18 (22.2)	2 (9.1)	58 (11.4)
1st complete remission	40 (15.0)	3 (2.2)	13 (16.0)	0 (0.0)	56 (11.0)
2nd complete remission	36 (13.5)	19 (13.7)	8 (9.9)	5 (22.7)	68 (13.4)
>= 3rd complete remission	19 (7.1)	30 (21.6)	6 (7.4)	2 (9.1)	57 (11.2)
1st relapse	77 (28.8)	25 (18.0)	21 (25.9)	6 (27.3)	129 (25.3)
2nd relapse	42 (15.7)	32 (23.0)	12 (14.8)	0 (0.0)	86 (16.9)
>= 3rd relapse	17 (6.4)	28 (20.1)	3 (3.7)	7 (31.8)	55 (10.8)
ECOG performance status prior to CT - no. (%)					
Asymptomatic	105 (39.3)	50 (36.0)	49 (60.5)	12 (54.5)	216 (42.4)
Symptomatic but completely ambulatory	126 (47.2)	69 (49.6)	26 (32.1)	9 (40.9)	230 (45.2)
Symptomatic,<50% in bed during the day	14 (5.2)	7 (5.0)	2 (2.5)	0 (0.0)	23 (4.5)
Symptomatic,>50% in bed,but not bedbound	2 (0.7)	0 (0.0)	0 (0.0)	1 (4.5)	3 (0.6)
Not reported	20 (7.5)	13 (9.4)	4 (4.9)	0 (0.0)	37 (7.3)
CAR-T product type - no. (%)					
Kymriah	98 (36.7)	40 (28.8)	52 (64.2)	18 (81.8)	208 (40.9)
Tecartus	169 (63.3)	99 (71.2)	29 (35.8)	4 (18.2)	301 (59.1)
Sorror/HCT-CI comorbidity score group - no. (%)					
0	51 (19.1)	42 (30.2)	25 (30.9)	7 (31.8)	125 (24.6)
1	62 (23.2)	21 (15.1)	16 (19.8)	5 (22.7)	104 (20.4)
2	36 (13.5)	26 (18.7)	13 (16.0)	4 (18.2)	79 (15.5)
3	116 (43.4)	50 (36.0)	26 (32.1)	6 (27.3)	198 (38.9)
TBD, unclear lineage of prior hematologic malignancies	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)

Characteristic	CAR-T Only	With Prios AlloHCT	With Subsequent AlloHCT	With Prior&Post AlloHCT	Total
NA, not collected for early revisions of f4000	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Not reported	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Time from initial diagnosis to CT - no. (%)					
0-12 months	90 (33.7)	15 (10.8)	32 (39.5)	3 (13.6)	140 (27.5)
12-36 months	96 (36.0)	50 (36.0)	22 (27.2)	10 (45.5)	178 (35.0)
36-60 months	37 (13.9)	33 (23.7)	10 (12.3)	2 (9.1)	82 (16.1)
>60 months	44 (16.5)	41 (29.5)	17 (21.0)	7 (31.8)	109 (21.4)
Year of CT - no. (%)					
2017	3 (1.1)	0 (0.0)	2 (2.5)	0 (0.0)	5 (1.0)
2018	15 (5.6)	15 (10.8)	4 (4.9)	4 (18.2)	38 (7.5)
2019	30 (11.2)	13 (9.4)	19 (23.5)	7 (31.8)	69 (13.6)
2020	36 (13.5)	7 (5.0)	15 (18.5)	4 (18.2)	62 (12.2)
2021	19 (7.1)	9 (6.5)	14 (17.3)	3 (13.6)	45 (8.8)
2022	84 (31.5)	61 (43.9)	26 (32.1)	3 (13.6)	174 (34.2)
2023	80 (30.0)	34 (24.5)	1 (1.2)	1 (4.5)	116 (22.8)
Median follow-up of survivors (range), months - median (range)	12.7 (1.5-69.4)	12.1 (1.2-60.0)	27.9 (2.4-61.5)	22.9 (7.3-48.9)	13.1 (1.2-69.4)

Field	Response
Proposal Number	2310-93-ARSLAN
Proposal Title	Comparison of FluFTBI and other myeloablative Conditioning Regimens for Haploidentical and mismatched unrelated Hematopoietic Cell Transplant with Post-Transplant Cyclophosphamide in Patients with Acute Leukemia
Key Words	FluTBI, PTCy, Myeloablative, MAC, haplo, MMUD
Principal Investigator #1: - First and last name, degree(s)	Shukaib Arslan, MD
Principal Investigator #1: - Email address	sarslan@coh.org
Principal Investigator #1: - Institution name	City of Hope National Medical Center
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Monzr M. Al Malki
Principal Investigator #2 (If applicable): - Email address:)	malmalki@coh.org
Principal Investigator #2 (If applicable): - Institution name:	City of Hope National Medical Center
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	Yes
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:	Shukaib Arslan, MD
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	PI for PROP 2110-308
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	What is the impact of conditioning regimen on outcomes of patients undergoing haplo- or MMUD HCT for acute leukemia with MAC?

Field	Response
RESEARCH HYPOTHESIS:	We hypothesize that in patients with acute leukemia, outcomes of haploidentical and MMUD hematopoietic cell transplant with post-transplant cyclophosphamide (PTCy) are better with conditioning therapy comprising fludarabine with FTBI as compared to other conditioning therapies used as myeloablative conditioning (MAC).
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. Evaluate HCT outcomes in patients with AML and ALL who underwent haploHCT or MMUD HCT with PTCy with MAC consisting of either FluFTBI or other MAC and were registered in the Center for International Blood and Marrow Transplant Research (CIBMTR). 2. Compare the overall survival (OS) between the two groups of MAC. 3. Compare non-relapse-mortality (NRM). 4. Compare relapse rate and progression-free-survival (PFS) and leukemia-free-survival (LFS)
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Allogeneic hematopoietic cell transplantation (HCT; alloHCT) is a potentially curative therapy available for patients with acute leukemia. Although HLA matched siblings (MSD) have been the preferred donor choice for HCT in general, such donors are available for <30% of the patients. For the patients who lack an MSD, similar transplant outcomes have been reported by using MUD1,2. The likelihood of identifying an 8/8 MUD for the Caucasian population is about 70%, the probability of finding such donors falls to <20% for African American and other ethnic minorities and even more challenging for mixed-race individuals3,4. The use of haploidentical donor for HCT has made transplant available to a much larger group of patients. Single institution reports have suggested comparable outcomes with the use of haploHCT and MSD or MUD HCT5-7. Large retrospective studies have reported comparable outcomes of haplo- and MUD HCT for AML and ALL8,9. Relapse is a significant problem after allo-HCT10. A recently published phase III randomized study compared outcomes MAC versus RIC alloHCT for patients with AML and MDS11. Among patients with AML, 18-month OS was significantly higher with MAC vs. RIC.

SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.	Allogeneic HCT is the only curative therapy available for patients with high-risk acute leukemia. However, it is associated with significant risks of transplant-related mortality/morbidities due to graft-versus-host disease (GVHD), infections, and regimen-related toxicities. Although HLA matched siblings (MSD) have been the preferred donor choice for HCT in general, such donors are available for <30% of the patients. Also, as discussed before, the likelihood of finding a MUD for ethnic minorities and patients of mixed races is much lower as compared to the white population. The identification of a MUD and stem cell procurement can take an average of 3-4 months from the start of donor search12. More than 95% of patients have at least 1 HLA-haploidentical first-degree donor with an average number of haploidentical donors available per patient of 2.713,14 Recent advances in haplo-HCT with the use of PTCy have improved donor availability to these groups with comparable HCT outcomes with lower rates of NRM and similar rates of GVHD as compared to fully matched donors15,16. HCT offers the benefit of using high dose chemotherapy with or without radiation therapy to eliminate the leukemic clone and replace the abnormal hematopoietic system with a healthy donor hemopoiesis offering a graft-versus-leukemia effect (GVL). Several studies have shown that myeloablative conditioning (MAC) regimens have lower risk of disease relapse, higher relapse free survival and overall survival as compared to reduced intensity conditioning (RIC) regimens 17 11 18. High dose cyclophosphamide (CY) and total body irradiation (CY-TBI) has been used since the early 1970s to treat AML. Substituting etoposide with cyclophosphamide along with TBI improved outcomes ALL patients undergoing matched sibling donor (MSD) transplant 19. Since then, different agents have been combined with TBI, including cytarabine, melphalan, and busulfan, with no evidence of superiority in outcome compared to CY-TBI 20 21. Also, chemotherapy only MAC regimens such as busulfan with cyclophosphamide (Bu-Cy) and busulfan with cytarabine (Bu-Cyt) were compared in a phase III randomized study and resulted in similar outcomes 22. Similarly, groups have compared chemotherapy-based vs radiation-based regimens. Meta-analysis of 5 prospective randomized control trials compared chemo-based regimen Bu-Cy with chemo-radiation based regimens with TBI and they documented survival and disease-free survival benefit with TBI-based regimens over Bu-CY, but these differences were not statistically significant 23. Similarly, Socie et al., showed that in patients with AML, there was a nonsignificant 10% lower survival rate with Bu-CY compared to CY-TBI due to better disease-free survival

	24. A small prospective study reported the feasibility of fludarabine and TBI-based conditioning for haplo transplant 25,26. To date, there is no other study which has looked at fludarabine with FTBI as a myeloablative conditioning regimen in a matched or mismatched setting. A well-matched donor (related or unrelated) is still considered the preferred option for patients undergoing HCT, however, due to availability ranging from 13 to 51%, especially in patients of minority and mixed ancestry, many patients will rely on mismatched (related or unrelated) donor to access this life sustaining procedure. Gagelmann et al., did a systematic review and meta-analysis and looked at overall haplo stem cell transplant with posttransplant cyclophosphamide (PTCy) therapy versus another donor transplantation 27. They showed that the overall pooled OR for all-cause mortality for haplo-HCT was 1.06 compared with matched unrelated donors (MUDs). Haplo-HCT was associated with increased non-relapse mortality (NRM) when compared to matched related donor (MRD) with OR of 1.20 but associated with better outcome when compared with MUDs (OR of 0.75) and mismatched unrelated donor (MMUD) (OR of 0.51). For disease relapse, Haplo-HCT was associated with similar outcomes when compared to MRD (OR of 1.01) and MMUD (OR of 1.06) but was associated with increased risk of relapse when compared MUDs (OR of 1.2). Overall, haplo stem cell transplantation with PTCy appeared to be associated with increased GRFS, with a pooled OR of 0.80. The study did not find any confounding association between conditioning regimen in the meta-regression. The effect of conditioning therapy in this population is not well studied. Thus, several studies have shown feasibility of haplo transplantation with PTCy as a potential alternative to MUD transplantation with the advantages of having a better chance of donor availability, faster graft acquisition, shorter times of collection and availability of repeated donations if needed. A phase II National Marrow and Donor Program (NMDP) sponsored study showed that there was no significant difference in outcomes with MMUD as compared to haplo-HCT when PTCy was used for GVHD prophylaxis. A pilot study reported promising outcomes of MMUD-HCT with TBI-based MAC, as well as RIC, using PTCy-based GVHD prophylaxis. The optimal myeloablative HCT conditioning regimen in haplo and MMUD where higher intensity GVHD prophylaxis is used remains unknown. We propose a study to compare the outcome of haploHCT and MMUD HCT using PTCy with FluFTBI conditioning versus other myeloablative conditioning therapies in patients with acute leukemia.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Patients with AML and ALL, aged 6-60 who underwent MAC haploHCT with PTCy from 2005 through 2022 will be included in this study to allow at least a three-year follow-up period. We plan to exclude patients who received ex-vivo T cell depletion for haplo-HCT.
Does this study include pediatric patients?	Yes
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient characteristics (age, gender, KPS, HCT-CI), disease-specific characteristics (prior treatment, blood and marrow blasts), HCT-related variables (conditioning regimen, GVHD prophylaxis, graft source, donor-recipient sex match, donor-recipient CMV status). Outcome measures will include GVHD (acute GVHD grade 2-4, chronic GVHD at 1, 3, and 5 years post-HCT), NRM, relapse, PFS/LFS, and OS (assessed at 100 days, six months, 1 year and 3-year time), and cause of death. The study will be a retrospective analysis of patients who underwent MAC haploHCT or MMUD HCT using PTCy for AML and ALL from 2005 through 2022. Descriptive analyses of patient-, disease- and donor-variables will be performed. Kaplan-Meier curves will be used for OS and PFS. Cumulative incidence curves will be used for NRM, relapse, and GVHD. Probabilities of OS, DFS, NRM, relapse, and GVHD at specified time points and 95%CIs will be estimated from these curves. Multivariate analyses for survival (OS, DFS), NRM, relapse, and GVHD will be performed using the Cox proportional hazards model and the proportional sub-distribution hazards model for competing risks adjusting for the effects of covariates whenever appropriate. The covariates to be evaluated will include patient-specific variables (age, gender, KPS, HCT-CI), disease-related variables (disease diagnosis, time from diagnosis to HCT, pre-HCT treatment, diseases status at HCT), and transplant-related variables (graft source, GVHD prophylaxis, conditioning regimen (FluFTBI vs. other MAC regimens), donor-recipient sex match, donor-recipient CMV serostatus, donor-recipient ABO typing, year of transplantation).

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Field	Response
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CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Characteristics of patients with MAC haploHCT with PTCy in 2008-2022 without ex-vivo T cell depletion

Characteristic	N (%)
No. of patients	3714
No. of centers	241
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	34.7 (6.1-60.0)
<10	200 (5.4)
10-17	428 (11.5)
18-29	954 (25.7)
30-39	613 (16.5)
40-49	709 (19.1)
50-59	810 (21.8)
Sex - no. (%)	
Male	2071 (55.8)
Female	1643 (44.2)
Race - no. (%)	
White	2279 (61.4)
Black or African American	481 (13.0)
Asian	256 (6.9)
Native Hawaiian or other Pacific Islander	19 (0.5)
American Indian or Alaska Native	34 (0.9)
More than one race	98 (2.6)
Not reported	547 (14.7)
Reporting track - no. (%)	
TED	2886 (77.7)
CRF	828 (22.3)
US or Non-US - no. (%)	
US	2724 (73.3)
Non-US	990 (26.7)
Karnofsky score prior to HCT - no. (%)	
90-100	2542 (68.4)
< 90	1102 (29.7)
Not reported	70 (1.9)
HCT-CI - no. (%)	
0	1206 (32.5)
1	621 (16.7)
2	592 (15.9)
3+	1274 (34.3)

Characteristic	N (%)
TBD, review needed for history of malignancies	20 (0.5)
Missing	1 (0.0)
Disease Related	
Primary disease - no. (%)	
AML	2130 (57.4)
ALL	1584 (42.6)
Disease status at time of HCT - no. (%)	
PIF	237 (6.4)
CR1	2206 (59.4)
CR2	948 (25.5)
>=CR3	160 (4.3)
Relapse	161 (4.3)
Not reported	2 (0.1)
Time from diagnosis to HCT - no. (%)	
<6 months	1518 (40.9)
6-12months	1030 (27.7)
>12 months	1166 (31.4)
Transplant Related	
Donor type - no. (%)	
Haplo	3274 (88.2)
Partially-matched unrelated (7/8)	397 (10.7)
Mis-matched unrelated (<= 6/8)	43 (1.2)
Donor/recipient CMV serostatus - no. (%)	
+/+	2030 (54.7)
+/-	338 (9.1)
-/+	798 (21.5)
-/-	519 (14.0)
Not reported	29 (0.8)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
MAC	3714 (100)
Donor/recipient sex match - no. (%)	
M-M	1313 (35.4)
M-F	905 (24.4)
F-M	758 (20.4)
F-F	738 (19.9)
Product type - no. (%)	
BM	1001 (27.0)
PB	2713 (73.0)
Year of current transplant - no. (%)	
2009	12 (0.3)

Characteristic	N (%)
2010	26 (0.7)
2011	38 (1.0)
2012	41 (1.1)
2013	53 (1.4)
2014	84 (2.3)
2015	185 (5.0)
2016	222 (6.0)
2017	356 (9.6)
2018	414 (11.1)
2019	475 (12.8)
2020	563 (15.2)
2021	599 (16.1)
2022	646 (17.4)
Median follow-up of survivors (range), months - median (range)	34.0 (0.0-168.1)

Field	Response
Proposal Number	2310-97-ALI
Proposal Title	Low-intensity or chemotherapy-free regimens versus high-intensity regimens prior to allo-HCT for adults with newly diagnosed Ph+ ALL
Key Words	acute lymphoblastic leukemia, Philadelphia chromosome, allogeneic stem cell transplant, Tyrosine kinase inhibitors.
Principal Investigator #1: - First and last name, degree(s)	Alaa Ali
Principal Investigator #1: - Email address	alaa.ali@gunet.georgetown.edu
Principal Investigator #1: - Institution name	Georgetown Lombardi Comprehensive Cancer Center
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
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
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Outcomes of CD19 CAR-T in patients who received lymphodepleting chemotherapy using fludarabine-containing versus other regimens. co-PI
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Are the outcomes of newly diagnosed adult Ph+ ALL patients that are consolidated with allo-HCT in first remission non inferior (or better) when patients are induced with low-intensity or chemotherapy-free regimens compared to high-intensity induction regimens?
RESEARCH HYPOTHESIS:	Induction with low-intensity or chemotherapy-free regimens is feasible even when allo-HCT is planned in first remission and produces non-inferior or better outcomes after transplant compared to induction with high-intensity regimens. This less intensive induction approach may result in shorter inpatient hospitalization, better functional status, and possibly improved non-relapse mortality and overall survival following allo-HCT

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Compare newly diagnosed adult patients with Ph+ ALL that are induced with high-intensity chemotherapy (hyperCVAD or other multiagent regimens) vs low-intensity or chemotherapy-free regimens (TKI + steroids, TKI, TKI + vincristine + dexamethasone, or blinatumomab +/- TKI) followed by allo HCT in first remission in terms of: Primary endpoint: overall survival and leukemia free survival. Secondary endpoints: - NRM - Incidence rate of acute and chronic GVHD, infection, non-infectious pulmonary, liver, renal and cardiac toxicities, and TMA - Total number of inpatient days in the first 100 days. - Measures of functional status after transplant
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If the aim of the project is completed, it will provide treating clinicians with more evidence (although retrospective) that low-intensity or chemotherapy-free regimens are still feasible or possibly preferable for Ph+ ALL induction, even when allo-HCT is planned in first remission

Field	Response
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 remission induction of Ph+ ALL in adult patients (age>39), NCCN guidelines recommend a variety of regimens that range in intensity from TKI plus high-intensity regimens (such as hyper-CVAD or other multiagent chemotherapy) to low-intensity or even chemotherapy-free regimens (such as TKI + steroids +/- vincristine or TKI +/- blinatumomab). No randomized trials have directly compared the two approaches, but low-intensity and chemotherapy-free regimens seem to achieve high and comparable rates of complete remissions (CR) (1,2,3,4, 5,6,7). Although these low-intensity or chemotherapy-free regimens are frequently used in older or medically unfit patients that may be considered initially transplant ineligible, the medical fitness of a subset of these patients improves as their underlying disease is treated and they ultimately proceed to transplant. The outcomes of consolidation with allo-HCT after each of these induction approaches has not been compared prospectively or retrospectively (using a large patient sample). Although intensive chemotherapies may achieve deeper molecular responses before transplant (8,9), this benefit may be offset by substantial treatment-related morbidity and mortality. The high rates of CR with little toxicity that the low-intensity or chemotherapy-free regimens produce may enable patients to proceed with post-remission consolidation including allo-HCT with little morbidity/organ damage and better medical fitness. Therefore, resulting in shorter inpatient days, better functional recovery, and possibly better non-relapse mortality and overall survival after transplant.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: - Newly diagnosed Ph+ ALL patients older than 39 y.o that underwent allo-HCT in first remission. - Received induction therapy with: - Multiagent chemotherapy regimen or - Steroids/TKI, Blinatumomab +/- TKI, TKI + vincristine + dexamethasone, or TKI alone Exclusion criteria: - Ph - ALL - Relapsed/refractory ALL - Age 39 or younger
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Treatment of pediatric and AYA ALL is typically different with the use of more intensive pediatric regimens and less utilization of allo-HCT in pediatric ALL

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Forms: 2011, 2111, 2100, 2402 Presence of additional cytogenetics abnormality (other than t(9:22)): yes vs no If yes, 1 vs 2 vs 3 vs 4 or more Specify additional cytogenetics abnormality Molecular testing done? Yes vs no. If yes, what abnormality was identified? WBC at diagnosis >50K: yes vs no Extramedullary disease: yes vs no Induction chemotherapy used (high-intensity vs low-intensity/chemotherapy-free) Number of cycles of induction required to achieve CR? CNS prophylaxis prior to transplant: yes vs no Disease status at time of transplant MRD testing done? Yes vs no If yes, what method was used? MRD status before transplant (positive vs negative) Age: 40-50 vs 51-65, >65 Sex: male vs female Race: caucasian vs african american vs hispanic vs asian vs other KPS at time of transplant: ≥90 vs <90 Conditioning regimen: myeloablative vs RIC/NMA. TBI vs non-TBI Graft type: bone marrow vs peripheral blood vs cord blood Donor type: HLA matched sibling vs matched unrelated donor vs mismatched unrelated donor vs haplo CMV status: +/+ vs +/- vs -/+ vs -/- Gender mismatch: yes vs no GVHD prophylaxis: calcineurin inhibitor/MTX vs calcineurin inhibitor/MMF vs PTCy based Acute GVHD prior to day 100: none vs grade I-II vs grade III-IV Chronic GVHD: none vs mild vs moderate vs severe Maintenance therapy post transplant: yes vs no Post transplant therapy: TKI vs IT chemo vs DLI vs other Death: yes vs no Cause of death: relapse vs non-relapse Disease relapse after transplant: Yes vs no. Duration of CR after allo Clinically significant infection: yes vs no Non-infectious pulmonary abnormality/disorder following transplant: yes vs no Non-infectious liver abnormality/disorder following transplant: yes vs no Non-infectious renal abnormality/disorder following transplant: yes vs no Non-infectious cardiac abnormality/disorder following transplant: yes vs no TMA: yes vs no Total number of inpatient days Requirement for unplanned admission after transplant: yes vs no Functional status after transplant Work status: full time vs part time due to illness vs unemployed due to illness Medical disability: yes vs no

Field	Response
REFERENCES:	1. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer 2007;109:2068-2076. 2. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521-6528 3. Delannoy A, Delabesse E, Lheritier V, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. Leukemia 2006;20:1526-1532 4. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-3678 5. Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the Gimema LAL1811 phase II prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2017;130:99 6. Foà R, Bassan R, Vitale A, et al. Dasatinib-Blinatumomab for PhPositive Acute Lymphoblastic Leukemia in Adults. N Engl J Med 2020;383:1613-1623 7. Short NJ, Kantarjian H, Konopleva M, et al. Updated results of a phase II study of ponatinib and blinatumomab for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2021;138(suppl 1):2298. doi:10. 1182/blood-2021-153795 8. Ravandi F, Jorgensen JL, O'Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. Br J Haematol 2016;172(3):392–400 9. Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016;128(4):504–7.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-186-CHERGUI
Proposal Title	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).
Key Words	Philadelphia Positive Acute lymphoblastic leukemia (Ph+ ALL), Tyrosine Kinase Inhibitors (TKI), Allogenic Stem Cell Transplant (Allo-HCT)
Principal Investigator #1: - First and last name, degree(s)	Adel Chergui, DO
Principal Investigator #1: - Email address	adel_chergui@brown.edu
Principal Investigator #1: - Institution name	Brown Univeristy/Lifespan Cancer Institute
Principal Investigator #1: - Academic rank	Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Ari Pelcovits, MD
Principal Investigator #2 (If applicable): - Email address:)	ari_pelcovits@brown.edu
Principal Investigator #2 (If applicable): - Institution name:	Brown University/Lifespan Cancer Institute
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
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:	Adel Chergui (adel_chergui@brown.edu)
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
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Dr. Pelcovits has been involved in the following project: 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
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No

Field	Response
RESEARCH QUESTION:	How does the type and intensity of induction therapy, in the era of tyrosine kinase inhibitors (TKIs), affect the clinical outcomes for patients with Ph+ ALL that undergo allo-SCT?
RESEARCH HYPOTHESIS:	Adult patients with Ph+ ALL receiving TKIs and steroids alone (low intensity) as their induction regimen prior to Allo-SCT will have the same survival outcomes with lower treatment related complications than patients receiving TKIs in combination with chemotherapy (high intensity) for their initial induction therapy.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. Compare overall survival (OS) of patients undergoing allo-SCT for Ph+ ALL based on receipt of either low intensity or high intensity initial induction therapy. 2. Compare treatment related mortality (TRM) post allo-SCT based on receipt of either low intensity or high intensity initial induction therapy. 3. Compare incidence of graft versus host disease post allo-SCT based on receipt of either low intensity or high intensity initial induction therapy. 4. Compare leukemia free survival post allo-SCT based on receipt of either low intensity or high intensity initial induction therapy.
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 development of targeted therapies in Ph+ ALL has allowed the advent of low intensity (TKI only) induction therapies prior to Allo-SCT. We propose to describe the impact of low intensity induction regimens compared to high intensity therapies on outcomes of patients with Ph+ ALL undergoing Allo-SCT. We hypothesize that overall survival outcomes will not differ between the two. This information will help guide clinical decision making for initial choice of induction therapy prior to Allo-SCT.

Field	Response
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.	Prior to the advent of tyrosine kinase inhibitors (TKI) in the last two decades treatment for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) consisted of induction chemotherapy followed by allogenic stem cell transplant (Allo-SCT). The long-term outcomes in adults the pre-TKI era were suboptimal with estimated long term survival rates ranging from 10-35% [1]. With the advent of TKIs disease outcomes improved. TKIs including imatinib, dasatinib, nilotinib and ponatinib were incorporated to high and low intensity chemotherapy-based regimens with outcomes from first and second generation TKIs increasing 5 year survival rates to 40-65% [1]. More recently chemotherapy free regimens were developed combining TKIs (ponatinib or dasatinib) and blinatumomab, a bispecific anti-CD3/CD19, in the front line setting for Ph+ ALL showing 1 year survival rate of 80% for dasatinib and 93% for ponatinib. [2, 3] Despite recent improvement in outcomes due to novel therapies, allo-SCT remains the only established treatment with curative intent. In light of recent improvement in induction therapy work has been done to update results from allo-SCT in Ph +ALL in the era of targeted therapies. [4-8]. Herein we propose to characterize the outcomes of patients who underwent allo-SCT in the era of targeted therapies and less intensive induction regimens. We specifically will be looking at overall survival, leukemia free survival, non-relapse mortality, treatment-related mortality and GVHD based on the intensity and type of induction therapy given prior to allo-SCT. We hypothesize that patients who received low intensity induction regimens with TKIs have similar outcomes and fewer treatment related adverse events than those who received high intensity regimens prior to Allo-SCT.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion Criteria 1) Adult patients aged >18 years with Ph+ ALL who underwent allogenic transplant treated from 2001 to the present. 2) Receipt of TKI (Imatinib, dasatinib, ponatinib, nilotinib) containing low intensity or high intensity induction regimens. a. Low Intensity defined as any of the following: i. TKI + steroid (dexamethasone or prednisone) ii. TKI + steroid (dexamethasone or prednisone) + vincristine alone. iii. TKI + Blinatumomab b. High intensity defined as any of the following: i. TKI (Imatinib, dasatinib, ponatinib, nilotinib) + Hyper-CVAD ii. TKI + any chemotherapy regimen containing any combination of the following: daunorubicin, asparaginase, cyclophosphamide, idarubicin, vincristine.

Field	Response
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	We will not be including pediatric patients since Ph+ is very rare in the pediatric population.
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Data will be collected from data collection forms. The following variables will be evaluated from the forms: Patient specific data: - Age, gender, race, socioeconomic data, karnofsky performance status (KPS), HCT-comorbidity index, CMV status. Donor Specific data: - Age, gender, HLA match level (fully matched/ 1-alelle mismatched/haploidentical/umbilical cord blood), ABO compatibility, CMV status. Disease specific data: - Date of diagnosis of hematologic malignancy, best response pre-transplant, WBC at diagnosis, was CNS prophylaxis given, cytogenetics, FISH, extramedullary disease presence. Pre-transplant: - Time from diagnosis to transplant, number of lines of therapy and types of induction/consolidation therapy before Allo-SCT (TKI alone, TKI plus chemo, chemo alone) HCT-comorbidity index, disease status pre-transplant (CR1 vs. CR2 vs. active disease), MRD status (positive/negative). Transplant related data: - Conditioning regimen, conditioning intensity (myeloablative vs. reduced intensity vs. non-myeloablative), donor type, graft source, GVHD prophylaxis. Post-transplant data: - Follow up duration, relapse (yes/no), time to relapse/relapse free survival, maintenance post Allo-SCT therapy to prevent relapse, death, cause of death, time to death/overall survival, time to neutrophil recovery, time to platelet recovery, aGVHD, cGVHD.
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	N/A
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.	N/A

Field	Response
REFERENCES:	1. Jabbour, E., et al., Treatment of Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia—From Intensive Chemotherapy Combinations to Chemotherapy-Free Regimens: A Review. JAMA Oncology, 2022. 8(9): p. 1340-1348. 2. Foà, R., et al., Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. N Engl J Med, 2020. 383(17): p. 1613-1623. 3. Short, N.J., et al., Updated Results of a Phase II Study of Ponatinib and Blinatumomab for Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood, 2021. 138(Supplement 1): p. 2298-2298. 4. Kebriaei, P., et al., Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. Biol Blood Marrow Transplant, 2012. 18(4): p. 584-92. 5. Hulegårdh, E., et al., Outcome after HSCT in Philadelphia chromosome positive acute lymphoblastic leukemia in Sweden: a population-based study. Med Oncol, 2014. 31(8): p. 66. 6. Brissot, E., et al., Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. Haematologica, 2015. 100(3): p. 392-9. 7. Nishiwaki, S., et al., Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph+ALL: a study from the adult ALL WG of the JSHCT. Bone Marrow Transplant, 2016. 51(1): p. 43-50. 8. Candoni, A., et al., Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the Era of Tyrosine Kinase Inhibitors: A Registry-Based Study of the Italian Blood and Marrow Transplantation Society (GITMO). Biol Blood Marrow Transplant, 2019. 25(12): p. 2388-2397.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Characteristics of patients with ALL in 2008-2020

Characteristic	N (%)
No. of patients	1418
No. of centers	170
Patients older than 39 in first remission - no. (%)	
No	741 (52.3)
Yes	677 (47.7)
Patients with chemotherapy regimen - no. (%)	
No	240 (16.9)
Yes	1178 (83.1)
Patients with Blinatumomab - no. (%)	
Yes	58 (4.1)
Not reported	1360 (95.9)
Patients with TKI - no. (%)	
Yes	789 (55.6)
Not reported	629 (44.4)
Patients with Blinatumomab - no. (%)	
Yes	58 (4.1)
Patients with TKI	47 (3.3)
Patients with TKI - no. (%)	
Yes	789 (55.6)
Patients with steroid	104 (7.3)
Patients with TKI - no. (%)	
Yes	789 (55.6)
Patients with steroid and Vincristine	16 (1.1)
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	43.5 (18.0-74.4)
18-29	294 (20.7)
30-39	289 (20.4)
40-49	327 (23.1)
50-59	310 (21.9)
60-69	186 (13.1)
>=70	12 (0.8)
Sex - no. (%)	
Male	767 (54.1)
Female	651 (45.9)
Race - no. (%)	
White	1027 (72.4)
Black or African American	128 (9.0)

Characteristic	N (%)
Asian	135 (9.5)
Native Hawaiian or other Pacific Islander	13 (0.9)
American Indian or Alaska Native	8 (0.6)
More than one race	12 (0.8)
Not reported	95 (6.7)
US or Non-US - no. (%)	
US	1249 (88.1)
Non-US	169 (11.9)
Karnofsky score prior to HCT - no. (%)	
90-100%	870 (61.4)
< 90%	538 (37.9)
Not reported	10 (0.7)
HCT-CI score - no. (%)	
0	435 (30.7)
1	221 (15.6)
2	235 (16.6)
3+	512 (36.1)
TBD, review needed for history of malignancies	1 (0.1)
NA, f2400 (pre-TED) not completed	1 (0.1)
Missing	13 (0.9)
Disease Related	
Disease status at time of HCT - no. (%)	
PIF	51 (3.6)
CR1	1050 (74.0)
CR2	211 (14.9)
>=CR3	35 (2.5)
Relapse	71 (5.0)
Time from diagnosis to HCT - no. (%)	
<6 months	677 (47.7)
6-12months	430 (30.3)
>12 months	311 (21.9)
Transplant Related	
Donor type - no. (%)	
HLA-identical sibling	363 (25.6)
Other related	220 (15.5)
Well-matched unrelated (8/8)	406 (28.6)
Partially-matched unrelated (7/8)	106 (7.5)
Mis-matched unrelated (<= 6/8)	12 (0.8)
Unrelated (matching TBD)	21 (1.5)
Cord blood	288 (20.3)

Characteristic	N (%)
Not reported	2 (0.1)
Donor/recipient CMV serostatus - no. (%)	
+/+	464 (32.7)
+/-	118 (8.3)
-/+	279 (19.7)
-/-	253 (17.8)
CB - recipient +	200 (14.1)
CB - recipient -	87 (6.1)
CB - recipient CMV unknown	1 (0.1)
Not reported	16 (1.1)
Conditioning regimen intensity - no. (%)	
MAC	1010 (71.2)
RIC	198 (14.0)
NMA	157 (11.1)
TBD	20 (1.4)
Missing	33 (2.3)
Donor/recipient sex match - no. (%)	
M-M	390 (27.5)
M-F	297 (20.9)
F-M	227 (16.0)
F-F	214 (15.1)
CB - recipient M	148 (10.4)
CB - recipient F	140 (9.9)
Not reported	2 (0.1)
Product type - no. (%)	
Bone marrow	212 (15.0)
Peripheral blood	918 (64.7)
Umbilical cord blood	288 (20.3)
ATG/Campath - no. (%)	
ATG alone	241 (17.0)
CAMPATH alone	21 (1.5)
No ATG or CAMPATH	1115 (78.6)
Not reported	41 (2.9)
GVHD prophylaxis - no. (%)	
None	39 (2.8)
Ex-vivo T-cell depletion	11 (0.8)
CD34 selection	26 (1.8)
PtCy + other(s)	209 (14.7)
PtCy alone	8 (0.6)
TAC + MMF +- other(s) (except PtCy)	212 (15.0)

Characteristic	N (%)
TAC + MTX +- other(s) (except MMF, PtCy)	477 (33.6)
TAC + other(s) (except MMF, MTX, PtCy)	87 (6.1)
TAC alone	29 (2.0)
CSA + MMF +- other(s) (except PtCy,TAC)	175 (12.3)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	116 (8.2)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	6 (0.4)
CSA alone	7 (0.5)
Other(s)	13 (0.9)
Missing	3 (0.2)
TX year - no. (%)	
2008	216 (15.2)
2009	149 (10.5)
2010	101 (7.1)
2011	101 (7.1)
2012	78 (5.5)
2013	104 (7.3)
2014	122 (8.6)
2015	128 (9.0)
2016	103 (7.3)
2017	86 (6.1)
2018	113 (8.0)
2019	79 (5.6)
2020	38 (2.7)
Median follow-up of survivors (range), months - median (range)	60.6 (1.6-151.0)

Field	Response
Proposal Number	2310-122-SAYYED
Proposal Title	Impact of pre-transplant blinatumomab on allogeneic hematopoietic cell transplant (HCT) outcomes in patients with B-cell acute lymphoblastic leukemia (ALL)
Key Words	allogeneic HCT, blinatumomab, ALL
Principal Investigator #1: - First and last name, degree(s)	Ayman Sayyed
Principal Investigator #1: - Email address	ayman.sayyed@uhn.ca
Principal Investigator #1: - Institution name	Princess Margaret Cancer Centre, University of Toronto and Northern Ontario School of Medicine
Principal Investigator #1: - Academic rank	Clinical Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Ivan Pasic
Principal Investigator #2 (If applicable): - Email address:)	Ivan.Pasic@uhn.ca
Principal Investigator #2 (If applicable): - Institution name:	Princess Margaret Cancer Centre, University of Toronto
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
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:	Ivan Pasic
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Does pre-transplant blinatumomab improve transplant outcomes in B-cell ALL patients who undergo allogeneic HCT?
RESEARCH HYPOTHESIS:	Pre-transplant blinatumomab improves transplant outcomes by decreasing non-relapse mortality (NRM).

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary outcome: Overall survival (OS) Secondary outcomes: NRM, cumulative incidence of relapse (CIR), leukaemia-free-survival (LFS), cumulative incidence of acute graft-vs-host disease (GVHD) and chronic GVHD, GVHD-free and relapse-free survival (GRFS).
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If this study confirms that blinatumomab improves transplant outcomes, this will trigger further studies aimed at characterizing subgroups of patients who draw the most benefit from blinatumomab as well as identifying the optimal number of blinatumomab cycles before allogeneic HCT. Ultimately, this will help clinicians decide which ALL patients to offer blinatumomab to as well as the optimal duration of treatment.

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.	Blinatumomab is a bispecific monoclonal antibody which has shown effectiveness in controlling refractory B-cell ALL and achieving minimal residual disease (MRD) negativity [1]. Blinatumomab binds to CD3-positive cytotoxic T cells and to CD19-positive B cells, leading to T-cell activation and elimination of CD19 positive blasts [2, 3]. Recent data shows that blinatumomab improves survival when used in consolidation in Philadelphia (Ph)-negative ALL patients who achieve MRD negativity after induction chemotherapy, suggesting that addition of blinatumomab to consolidation in adult patients may represent a new standard of care for Ph-negative ALL patients [4]. In a phase II trial of newly diagnosed Ph-positive ALL patients, frontline therapy with blinatumomab and ponatinib resulted in an impressive 93% 2-year event-free survival (EFS) and OS. There were no relapses or leukaemia-related deaths in this cohort [5]. In a paediatric multi-centre, open-label, randomized, phase 3 trial of children with high-risk first-relapse Ph-negative B-ALL, addition of blinatumomab to consolidation chemotherapy before allogeneic HCT resulted in improved 2-y EFS; enrolment was terminated early due to the benefit of blinatumomab [6]. In another paediatric open-label, single-arm expanded access study (RIALTO) studying the safety of blinatumomab in relapsed/refractory B-cell ALL, no blinatumomab-related fatal adverse events were reported. For patients achieving CR after 2 cycles of blinatumomab, 73.5% proceeded to allogeneic HCT. Patients who received allogeneic HCT after blinatumomab had a 1-y OS of 87% [7]. A pooled analysis of long-term follow-up data from two phase 2 studies that evaluated blinatumomab in heavily pretreated adults with Ph-negative, relapsed/refractory B-ALL revealed that cure after blinatumomab therapy is most common in patients undergoing HSCT in CR; median OS in this subgroup was 18.1 months with a 3-year survival rate of 37.2% [8]. Achieving MRD negativity before allogeneic HCT is a predictor of prolonged survival, however scant data is available about outcomes of adults who received pre-transplant blinatumomab for this purpose. Subgroup analysis of patients undergoing allogeneic HCT after blinatumomab in BLAST study reported a 5-yr survival of 50% for complete MRD responders [9]. A multi-centre study of 106 patients who underwent allogeneic HCT after blinatumomab for relapsed/refractory B-ALL reported a 2-yr progression-free survival (PFS) and OS of 48% and 58%, with the cumulative incidence of grade 2-4 and 3-4 acute GVHD at three months of 24.7% and 9.9% and moderate-severe chronic GVHD at two years of 24.5% [10]. As blinatumomab increases the fraction of B-ALL

	patients eligible for allogeneic HCT, understanding how these individuals do post-transplant compared to those who received traditional chemotherapy is becoming increasingly important. We presented our experience with transplant outcomes of B-ALL patients who received pre-transplant blinatumomab at Princess Margaret Hospital, Toronto, Canada as an oral presentation at the 49th annual meeting of the European Society for Blood and Marrow Transplantation in 2023. We reported that patients who receive pre-transplant blinatumomab have superior survival compared to those who do not. The observed survival advantage associated with blinatumomab is likely related to the very low risk of NRM seen in this group of individuals: 3.2% vs. 43.0 % at two years (HR 0.06, 95% CI: 0.008-0.47, P=0.007) Figure. The reduction in TRM appears to stem from a reduction in the rates of GVHD and infections among blinatumomab recipients. The single transplant-related death in our blinatumomab group was from SOS/VOD in a patient who also received inotuzumab, a known risk factor for this complication, as a bridge to allogeneic HCT [11-13]. The effect of blinatuomamb on TRM (and OS) is confirmed in MVA suggesting that the reduction in TRM possibly reflects lower burden of treatment-related toxicity experienced by patients who receive less cytotoxic agents during induction. Our cohort included 19 patients who received pre-transplant blinatumomab followed by dual T-cell depletion (TCD) for GHVD prophylaxis. In MVA including pre-transplant blinatumomab and TCD, only blinatumomab remained associated with superior TRM indicating that pre-transplant blinatumomab represents a safe and feasible option for induction for a wide range of transplant patients, irrespective of which method of GVHD prophylaxis they subsequently receive. To our knowledge, this is the largest series of patients who received pre-transplant blinatumomab followed by dual TCD for GHVD prophylaxis to date. We report higher incidence of relapse at two years among blinatumomab recipients: 34.4% vs. 14.4% (HR 2.6, 95% CI: 1.2-5.9, P=0.02). This observation was not confirmed in MVA, but could be related to the higher proportion of patients in ≥CR2 (54.8% vs. 20.9%, P<0.001), those with primary induction failure (41.9% vs. 7.0%, P<0.001), and those with DRI of high or above (64.5% vs. 19.8%, P<0.001) among blinatumomab recipients compared to other individuals. Although blinatumomab recipients had lower rates of grade 2-4 and grade 3-4 aGVHD in univariate analyses, this effect was not confirmed in MVA. MVA identified PTCy as the major factor in the reduction of grade 2-4 and grade 3-4 aGVHD and more patients in the blinatumomab arm, compared to the non-blinatumomab arm, received PTCy

Field	Response
	(80.6% vs. 32.6%, P<0.001). This research raises a number of intriguing questions looking into what constitutes the most superior salvage treatment before transplant in individuals with relapsed/refractory B-cell ALL, the optimal number of blinatumomab cycles in the pre-transplant setting and into the dynamics of post-transplant immune reconstitution in the setting of blinatumomab and dual TCD. Along the same line, the best sequence of treatment options before allogeneic HCT in ALL patients remains unclear. The most superior approach is likely the one that achieves MRD negativity with minimal treatment-related toxicity, leading to low rates of both relapse and TRM post-transplant. The combination of chemotherapy and blinatumomab before transplant provides a very attractive treatment option for this purpose. Incorporation of blinatumomab to chemotherapy-based consolidation has shown excellent results in paediatrics [15], however more work is needed to identify sub-groups of adult patients who will get the benefit of low TRM without an increased risk of relapse. The present study represents one such addition to the growing evidence suggesting that pre-transplant blinatumomab is safe and effective in adult patients with B-cell ALL.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_1es1z4nzp6Ya0dS
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Figure.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	92690
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion: All adult patients (age >=18) who received first allogeneic HCT for B-cell ALL are included. Exclusion: none
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	As the biology and molecular profile of B-ALL is different in pediatrics and adults, we aim to get a more homogeneous group by excluding pediatric patients.

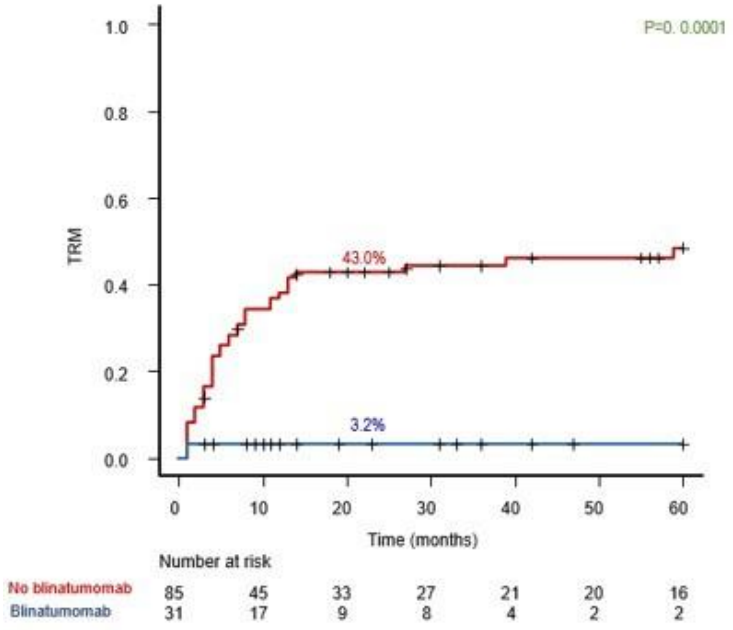
Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient variables : age , sex. Disease variables : cytogenetics, genetic mutations, at diagnosis, WBC count, blasts percentage in the peripheral blood and bone marrow, extramedullary involvement, CNS disease, Philadelphia status, lines of therapy before HCT including TKI, CNS prophylaxis , number of blinatumomab cycles pre-transplant, disease status (CR1, CR2+ ,etc), MRD status before HCT (By flow), post transplant MRD. Transplant variables: donor type, graft source, conditioning regimen and intensity, use of TBI-based conditioning, GVHD prophylaxis, T-cell depletion, transplant year .
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 desc	No
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No
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 o	No
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.	No

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. Dreier, T., et al., Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. Int J Cancer, 2002. 100(6): p. 690-7. 3. Hoffmann, P., et al., Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct. Int J Cancer, 2005. 115(1): p. 98-104. 4. Litzow, M.R., et al., Consolidation Therapy with Blinatumomab Improves Overall Survival in Newly Diagnosed Adult Patients with B-Lineage Acute Lymphoblastic Leukemia in Measurable Residual Disease Negative Remission: Results from the ECOG-ACRIN E1910 Randomized Phase III National Cooperative Clinical Trials Network Trial. Blood, 2022. 140(Supplement 2): p. LBA-1-LBA-1. 5. Short, N., et al., S114: PONATINIB AND BLINATUMOMAB FOR PATIENTS WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA: UPDATED RESULTS FROM A PHASE II STUDY. HemaSphere, 2022. 6: p. 15-16. 6. Locatelli, F., et al., Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA, 2021. 325(9): p. 843-854. 7. Bolanos-Meade, J., et al., HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood, 2012. 120(22): p. 4285-91. 8. Young, G., et al., Recognition of common childhood malignancies. American family physician, 2000. 61: p. 2144-54. 9. Gokbuget, N., et al., Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma, 2020. 61(11): p. 2665-2673. 10. Badar, T., et al., Multi-institutional study evaluating clinical outcome with allogeneic hematopoietic stem cell transplantation after blinatumomab in patients with B-cell acute lymphoblastic leukemia: real-world data. Bone Marrow Transplant, 2021. 56(8): p. 1998-2004. 11. Agrawal, V., et al., Post-Transplantation Sinusoidal Obstruction Syndrome in Adult Patients with B Cell Acute Lymphoblastic Leukemia Treated with Pretransplantation Inotuzumab. Transplant Cell Ther, 2023. 29(5): p. 314-320. 12. Ladha, A., G. Mannis, and L. Muffly, Hepatic veno-occlusive disease in allogeneic stem cell transplant recipients with prior exposure to gemtuzumab ozogamicin or inotuzumab ozogamicin. Leuk Lymphoma, 2021. 62(2): p. 257-263. 13. Kantarjian, H.M., et al., Hepatic adverse event profile of

Field	Response
	inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol, 2017. 4(8): p. e387-e398
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Not for publication or presentation ***Attachment 11a***

TRM



	HR (95% CI)	p value
Blinatumomab No blinatumomab	0.06 (0.008-0.47)	0.007

MVA	HR (95% CI)	p-value
Blinatumomab	0.08 (0.01-0.58)	0.01
Age >=40	3.27 (1.59-6.72)	0.001
TBI-based conditioning	0.74 (0.22-2.48)	0.62
Mismatched unrelated donor	2.73 (1.41-5.29)	0.003
TCD	0.69 (0.38-1.25)	0.22
Indication of transplant (High-risk features)	1.26 (0.69-2.30)	0.46
Donor: male	1.82 (0.99-3.35)	0.053

Cause of TRM	Blinatumomab (n= 1)	No blinatumomab (n=39)
VOD/SOS	1	2
Respiratory failure/hemorrhage	0	5
Infection	0	15
GVHD	0	11
Cardiomyopathy	0	1
Diffuse Leukoencephalopathy	0	1
Graft failure	0	1
Secondary cancer	0	1
Unknown	0	2

Field	Response
Proposal Number	2310-187-CHERGUI
Proposal Title	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.
Key Words	B- Cell Acute lymphoblastic leukemia (B-ALL), Minimal Residual Disease (MRD), Allogeneic stem cell transplant (Allo-SCT), Reduced intensity (RIC) vs. Myeloablative (MAC) conditioning, Blinatumumab, CAR-T, immunotherapy
Principal Investigator #1: - First and last name, degree(s)	Adel Chergui, DO
Principal Investigator #1: - Email address	adel_chergui@brown.edu
Principal Investigator #1: - Institution name	Brown University/Lifespan
Principal Investigator #1: - Academic rank	Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	John L. Reagan
Principal Investigator #2 (If applicable): - Email address:)	john_reagan@brown.edu
Principal Investigator #2 (If applicable): - Institution name:	Brown University/Lifespan Cancer Institute
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Adel Chergui (adel_chergui@brown.edu)
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Dr. Reagan has been involved in the following project: 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
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No

Field	Response
RESEARCH QUESTION:	What are the outcomes of patients with B-cell acute lymphoblastic leukemia (B-ALL) undergoing allogenic stem cell transplant (Allo-SCT) who received immunotherapy agents (Blinatumumab or CAR-T) compared to those who receive conventional chemotherapy alone based on conditioning intensity and MRD status?
RESEARCH HYPOTHESIS:	We hypothesize that patients that have received immunotherapy agents, defined as blinatumomab or CAR-T, and achieved CR1 with MRD negative status prior to Allo-SCT with reduced intensity conditioning (RIC) have similar outcomes to patients who received multi-agent chemotherapy and achieved CR1 with MRD negative status and proceeded to Allo-SCT with myeloablative conditioning (MAC).
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary Objective: - To compare overall survival (OS) of patients with B-ALL in CR1 who received immunotherapy agents prior to Allo-SCT to those who received chemotherapy based on conditioning intensity (RIC vs. MAC) and MRD status. Secondary Objective: In B-ALL patients in CR1 who received immunotherapy agents (defined as blinatumomab or CAR-T) prior to transplant compared to those who received chemotherapy we will compare: - Treatment related mortality (TRM) - Leukemia free survival (LFS) - Rates of aGVHD and cGVHD - Describe OS, TRM, LFS based on the following: oAge (15-39 vs. 40-59 vs. 60+) o Philadelphia chromosome status (positive vs. negative) o Minimal residual disease status (positive vs. negative)
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	We will investigate the effect on treatment outcomes of patients with B-ALL in CR1 that underwent Allo-SCT that received novel immunotherapy agents (Blinatumumab or CAR-T) based on conditioning intensity and MRD status. This will be done to determine if reduced intensity conditioning (RIC) will yield similar outcomes to myeloablative conditioning (MAC) in this setting. The results of the study will aid in clinical decision making in the choice of induction agents and conditioning regimens in the era of novel targeted therapy.

Field	Response
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.	Current induction therapies in acute lymphoblastic leukemia can lead to high rates of remission in 75-90% of adults but without consolidation many relapse. Hematopoietic stem cell transplant remains an established curative modality for certain subsets of patients with acute lymphoblastic leukemia [1] Myeloablative conditioning (MAC) is typically the preferred regimen for patients who are candidates for intensive chemotherapy, but is associated with high treatment related mortality (TRM), especially in older patients. Reduced intensity conditioning (RIC) has been considered and has been investigated in multiple studies showing lower TRM but with higher relapse rates. [2-5]. Relapse rates after transplant are affected by a variety of factors but one of interest is the presence of graft versus host disease (GvHD). Multiple studies have shown that in ALL GvHD confers some protection from relapse[6, 7]. This would indicate that a Graft versus tumor (GVT) plays a role in the prevention of relapse in ALL after transplant. Furthermore, it was shown that patients with mild GvHD had better overall survival and outcomes in ALL [8]. Improved survival in patients with GvHD in ALL supports the rational for novel therapy in ALL particularly immunotherapy agents. Recent trials have shown that immunotherapy agents such as Blinatumomab and CAR-T have improved outcomes in relapsed and refractory ALL [9]. In our study we will investigate the effect that immunotherapy for ALL given prior to Allo-SCT has on outcomes post-transplant depending on conditioning regimen intensity and MRD status. We hypothesize that patients who achieve MRD negative status with immunotherapy and underwent RIC may have similar outcomes than patients who achieved MRD negative status with multiagent chemotherapy undergoing MAC.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: - Patients aged >15 years with B-ALL who underwent allogenic transplant after achieving CR1 from 2010 to the present.
Does this study include pediatric patients?	Yes

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Data will be collected from data collection forms. The following variables will be evaluated from the forms: Patient specific data: - Age, gender, race, socioeconomic data, karnofsky performance status (KPS), HCT-comorbidity index, CMV status. Donor Specific data: - Age, gender, HLA match level (fully matched/ 1-alelle mismatched/haploidentical/umbilical cord blood), ABO compatibility, CMV status. Disease specific data: - Date of diagnosis of hematologic malignancy, best response pre-transplant, WBC at diagnosis, was CNS prophylaxis given, cytogenetics, FISH, extramedullary disease presence. Pre-transplant: - Time from diagnosis to transplant, number of lines of therapy and types of induction/consolidation therapy before Allo-SCT (TKI alone, TKI plus chemo, chemo alone, blinatumomab, inotuzumab, and CAR-T) HCT-comorbidity index, disease status pre-transplant (CR1 vs. CR2 vs. active disease), MRD status (positive/negative). Transplant related data: - Conditioning regimen, conditioning intensity (myeloablative vs. reduced intensity vs. non-myeloablative), donor type, graft source, GVHD prophylaxis. Post-transplant data: - Follow up duration, relapse (yes/no), time to relapse/relapse free survival, maintenance post Allo-SCT therapy to prevent relapse, death, cause of death, time to death/overall survival, time to neutrophil recovery, time to platelet recovery, aGVHD, cGVHD.
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	N/A
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.	N/A

Field	Response
REFERENCES:	1. Khazal, S. and P. Kebriaei, Hematopoietic cell transplantation for acute lymphoblastic leukemia: review of current indications and outcomes. Leuk Lymphoma, 2021. 62(12): p. 2831-2844. 2. Marks, D.I., et al., The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. Blood, 2010. 116(3): p. 366-74. 3. Tanaka, J., et al., Reduced-intensity vs myeloablative conditioning allogeneic hematopoietic SCT for patients aged over 45 years with ALL in remission: a study from the Adult ALL Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Bone Marrow Transplant, 2013. 48(11): p. 1389-94. 4. Abdul Wahid, S.F., et al., Comparison of reduced-intensity and myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and acute lymphoblastic leukemia: a meta-analysis. Stem Cells Dev, 2014. 23(21): p. 2535-52. 5. Mohty, M., et al., Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood, 2010. 116(22): p. 4439-43. 6. Passweg, J.R., et al., Graft-versus-leukemia effects in T lineage and B lineage acute lymphoblastic leukemia. Bone Marrow Transplant, 1998. 21(2): p. 153-8. 7. Stern, M., et al., Sensitivity of hematological malignancies to graft-versus-host effects: an EBMT megafile analysis. Leukemia, 2014. 28(11): p. 2235-40. 8. Yeshurun, M., et al., The impact of the graft-versus-leukemia effect on survival in acute lymphoblastic leukemia. Blood Adv, 2019. 3(4): p. 670-680. 9. Paul, S., et al., Treatment of relapsed/refractory acute lymphoblastic leukemia. Clin Adv Hematol Oncol, 2019. 17(3): p. 166-175.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Field	Response
Proposal Number	2310-199-CONNOR
Proposal Title	Impact of bridging therapy on outcomes after allogeneic stem cell transplantation for patients with ALL in second or greater complete remission
Key Words	Allogeneic hematopoietic stem cell transplant, Acute lymphoblastic leukemia, Salvage therapy, Targeted agents, CAR-T, Inotuzumab, Blinatumomab
Principal Investigator #1: - First and last name, degree(s)	Matthew Connor, MD
Principal Investigator #1: - Email address	matthew.connor@pennmedicine.upenn.edu
Principal Investigator #1: - Institution name	University of Pennsylvania
Principal Investigator #1: - Academic rank	Fellow, PGY-5
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Noelle Frey
Principal Investigator #2 (If applicable): - Email address:)	noelle.frey@pennmedicine.upenn.edu
Principal Investigator #2 (If applicable): - Institution name:	University of Pennsylvania
Principal Investigator #2 (If applicable): - Academic rank:	Associate Professor
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Matthew Connor
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Do adults with relapsed or refractory (r/r) B cell acute lymphoblastic leukemia (ALL) who go to allogeneic hematopoietic cell transplant (HCT) in second or greater complete remission (CR2+) after salvage with CD19-targeted chimeric antigen receptor T cell therapy (CART19) have different durability of remission and survival outcomes compared to patients transplanted in CR2+ after other modern salvage strategies?

Field	Response
RESEARCH HYPOTHESIS:	Adult ALL patients who receive CART19 as part of a successful salvage strategy to achieve CR2+ may have improved relapse free survival (RFS) after consolidative HCT compared to alternative modern bridging approaches including novel monoclonal antibody therapies or combination chemo/antibody therapies.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	The objective of this investigation is to determine if salvage strategy utilized to achieve CR2+ in patients with r/r ALL impacts RFS after consolidative HCT. Primary outcome: Relapse free survival (RFS) in patients receiving pre-HCT CART19 compared to those receiving pre-HCT novel monoclonal antibody or combination chemo/antibody therapies Secondary outcomes: Overall survival (OS) Incidence of relapse Non-relapse mortality (NRM) Incidence of graft-versus-host disease, acute (aGVHD) and chronic (cGVHD) Incidence of hepatic sinusoidal obstruction syndrome (SOS) Subgroup analyses based on specific last salvage therapy and cytogenetic/molecular risk groups
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Patients with r/r ALL have historically poor outcomes, and the introduction of novel targeted salvage therapies that successfully induce CR has revolutionized care. Achievement of CR2+ then opens up the opportunity to proceed to a potentially curative HCT. With multiple novel therapies available in the modern era, there is currently a lack of data regarding outcomes following HCT comparing pre-transplant salvage strategies. This study will be the first to describe and compare real-world outcomes in this patient population to better inform clinical care in the salvage setting in CR2+ patients who plan to undergo HCT.

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.	Adult patients with ALL who relapse following first minimal residual disease negative (MRD-) complete remission (CR1) have poor prognosis. Historically, salvage chemotherapy has resulted in complete response rates of 18-47% [1-4], and consolidation with allogeneic hematopoietic cell transplant is recommended in eligible patients to maintain second or subsequent remission. With chemotherapy-based salvage, about 20-40% of patients transplanted in CR2 achieve durable remissions [4-6]. The last decade has seen the incorporation of multiple novel targeted therapies for the treatment of relapsed ALL. Blinatumomab (blin) is a bispecific T-cell engaging monoclonal antibody targeting the pan-B-cell marker CD19. Blin first gained accelerate FDA approval for r/r ALL in December 2014 based on phase 2 data showing a 69% CR/CRh rate [7], and then full approval in the r/r setting in July 2017 after the pivotal TOWER trial demonstrated 44% v. 25% CR/CRi, 7.3 v. 4.6 month median event-free survival (EFS), and 7.7 v. 4.0 month median OS compared to standard-of-care salvage chemotherapy [8]. Inotuzumab ozogamicin (ino) is a monoclonal antibody-drug-conjugate targeting the B-cell marker CD22 expressed in the majority of ALL. Ino was approved for r/r ALL in October 2017 following the phase III INO-VATE 1022 trial which showed 80.7% v. 29.4% CR/CRi, 5.0 v. 1.8 month median progression-free survival, and 7.7 v. 6.2 month median OS versus standard chemotherapy salvage [9]. Ino can also be utilized in the salvage setting with combination chemotherapy such as with the “mini-hyper-CVD” regimen – dose-reduced hyperfractionated cyclophosphamide, vincristine, and dexamethasone with alternating cycles of dose-reduced methotrexate and cytarabine – with this regimen demonstrating a 78% overall response rate (ORR) with 59% CR and 50% 2-year OS in phase II data [10]. CART19 has been successful in r/r ALL in both pediatric and adult patients. Tisagenlecleucel was initially approved in August 2017 for use in r/r ALL in pediatric and young adult patients up to age 25 based on results of the ELIANA trial phase 1-2a data showing ORR of 81% at 3 months, all with MRD- [11]. Median EFS on long-term follow-up was 24 months, median OS was not reached, and no patients who consolidated with HCT had relapsed in a small sample size of 8 evaluable patients [12]. More recently in October 2021, brexucabtagene autoleucel was approved for use in adults with r/r ALL based on phase 2 data from the ZUMA-3 trial showing 71% CR/CRi rate, 11.6 month median RFS, and 18.2 month median OS; 11 patients went on to HCT [13]. Furthermore, a recent post-hoc analysis of the phase 1/2 PLAT-02 trial of

Field	Response
	41BB-CD19 CAR T in pediatric and young adult patients demonstrated high rates of leukemia-free survival in patients who underwent consolidative HCT [14]. Novel agents have improved the ability to achieve a second or subsequent complete remission and have shown success when utilized as bridging therapy to curative HCT [14-17]. There is, however, no consensus recommendation for preferred salvage therapy after relapse, including in current NCCN guidelines [18]. It is uncertain whether choice of bridging therapy in the modern era affects post-transplant outcomes, in particular the durability of remission. Depth of remission prior to HCT is clearly an important prognostic factor based on data on MRD-status at transplant [19]. While blin and ino monotherapy are excellent salvage strategies, they are not typically viewed as curative in the relapse setting outside of bridging to further consolidation. Tisagenlecleucel and brexucabtagene autoleucel have been shown to produce some durable long-term remissions in clinical trials even without consolidative HCT and can be effective salvage options for those ineligible or averse to HCT [11-13,20]. Thus, different salvage therapies may produce different depths of remission prior to transplantation. This study will investigate whether choice of bridging strategy is associated with longer post-transplant remissions and differential long-term outcomes.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion: 1. Age group: 18 years and older 2. Disease category: Acute lymphoblastic leukemia 3. Disease status at transplant: 2nd or subsequent remission 4. Transplant year: 2015-2023 5. First allogeneic transplant Exclusion: 1. Age group: < 18 years old 2. Prior receipt of allogeneic HCT 3. Disease category: T cell ALL, NK cell lymphoblastic leukemia/lymphoma
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	This study aims to guide salvage therapies in adult patients specifically. Management of relapse differs significantly in the pediatric population, and is not the target of this proposed study.

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient data: Age at HCT Sex Race Region Year of HCT HCT-CI KPS Disease specific: Extramedullary disease at diagnosis (Yes/No) CNS disease at diagnosis (Yes/No) Philadelphia Chromosome (Yes/No) Disease Cytogenetics Disease Molecular Mutations Remission status at transplant (CR, CRi, MLFS) MRD status at transplant (MRD+/MRD-) Previous lines of therapy (induction, consolidation, maintenance, salvage) Specific systemic therapy prior to transplant Dates of start/stop systemic therapy prior to transplant Best response to lines of therapy prior to transplant Time last systemic therapy to transplant CART19 pre-transplant Time CART19 to transplant Donor specific: Donor age Donor sex HLA match level (full match, less than full match, haploidentical, umbilical cord blood) Donor CMV matching (CMV+/CMV-) ABO match (compatible/major mismatch/minor mismatch) Transplant specific: Year of HCT Donor type (matched sibling/MUD/haploidentical/umbilical cord) Graft source (Peripheral blood/bone marrow/umbilical cord blood) Conditioning regimen Myeloablative (Yes/No) GVHD prophylaxis regimen Time from diagnosis to transplant Time to most recent relapse to transplant Post-transplant specific: Follow-up time Best response to HCT Post-transplant maintenance Acute GVHD (Yes/No) Acute GVHD grade Acute GVHD grade 3-4 Time to aGVHD grade 3-4 Chronic GVHD (Yes/No) Chronic GVHD grade Chronic GVHD grade moderate-severe Time to cGVHD grade moderate-severe Sinusoidal obstruction syndrome (Yes/No) Current disease status Relapse post-transplant (Yes/No) Time to relapse post-transplant Death (Yes/No) Cause of death (TRM, relapse, GVHD-related) Time to death post-transplant
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 desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
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 o	N/A

Field	Response
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.	N/A

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Field	Response
	ZUMA-3. J Immunother Cancer. 2023 Aug;11(8):e007118. doi: 10.1136/jitc-2023-007118.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	Yes, I have conflicts of interest pertinent to this proposal
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.	Noelle Frey: Consultancies - Kite, Sana, Pfizer, Autolus

Characteristics of patients with B-cell ALL with CT in 2015-2021

Characteristic	N (%)
No. of patients	577
No. of centers	101
All adolescent and young adult patients aged 15-25 years old who were treated with Tisagenlecleucel, or aged 15-40 years old who were treated with Brexucabtagene autoleucel - no. (%)	
No	352 (61.0)
Yes	225 (39.0)
All adult patients with r/r B cell acute lymphoblastic leukemia who received brexucabtagene autoleucel, or adult patients with r/r Mantel cell lymphoma who received brexucabtagene autoleucel - no. (%)	
No	567 (98.3)
Yes	10 (1.7)
CT population	
Age at CT - no. (%)	
Median (min-max)	14.0 (0.4-66.0)
<10	185 (32.1)
10-17	207 (35.9)
18-29	176 (30.5)
30-39	4 (0.7)
50-59	2 (0.3)
60-69	3 (0.5)
Recipient Sex - no. (%)	
Male	345 (59.8)
Female	232 (40.2)
Recipient race - no. (%)	
White	408 (70.7)
Black or African American	36 (6.2)
Asian	19 (3.3)
American Indian or Alaska Native	3 (0.5)
Other	25 (4.3)
More than one race	49 (8.5)
Not reported	37 (6.4)
Karnofsky performance score prior to CT - no. (%)	
90-100	347 (60.1)
80-90	98 (17.0)
10-80	93 (16.1)

Characteristic	N (%)
Not reported	39 (6.8)
ECOG performance status prior to CT - no. (%)	
0 - Asymptomatic	347 (60.1)
1 - Symptomatic but completely ambulatory	157 (27.2)
2 - Symptomatic, <50% in bed during the day	31 (5.4)
3 - Symptomatic,>50% in bed, but not bedbound	3 (0.5)
Not reported	39 (6.8)
Country - no. (%)	
US	540 (93.6)
Others	37 (6.4)
CAR-T product type - no. (%)	
Kymriah	567 (98.3)
Tecartus	10 (1.7)
Sorror/HCT-CI comorbidity score group - no. (%)	
0	235 (40.7)
1	127 (22.0)
2	67 (11.6)
3+	142 (24.6)
TBD, unclear lineage of prior hematologic malignancies	2 (0.3)
NA, not collected for early revisions of f4000	2 (0.3)
Not reported	2 (0.3)
MRD status - no. (%)	
No	535 (92.7)
Yes	42 (7.3)
Prior HCT - no. (%)	
No	410 (71.1)
Yes	158 (27.4)
Not reported	9 (1.6)
Time from the latest prior HCT to current CT - no. (%)	
>= 0 to < 6 months	16 (2.8)
>= 6 to < 12 months	40 (6.9)
>= 12 months	98 (17.0)
Not reported	423 (73.3)
Subsequent HCT since the CT infusion - no. (%)	
No	356 (61.7)
Yes	197 (34.1)
Not reported	24 (4.2)
Time from CT to subsequent HCT - no. (%)	

Characteristic	N (%)
<6 months	492 (85.3)
6-12months	50 (8.7)
>12 months	35 (6.1)
Time from initial diagnosis to CT - no. (%)	
0-12 months	118 (20.5)
12-36 months	177 (30.7)
36-60 months	127 (22.0)
>60 months	155 (26.9)
Year of CT - no. (%)	
2017	8 (1.4)
2018	125 (21.7)
2019	173 (30.0)
2020	161 (27.9)
2021	110 (19.1)
Median follow-up of survivors (range), months - median (range)	30.9 (1.1-65.0)

Characteristics of patients with B-cell ALL with HCT in 2015-2021

Characteristic	N (%)
No. of patients	6927
No. of centers	312
Patients with MRD+ - no. (%)	
No	4937 (71.3)
Yes	1990 (28.7)
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	39.2 (0.2-78.4)
<10	594 (8.6)
10-17	671 (9.7)
18-29	1303 (18.8)
30-39	993 (14.3)
40-49	1121 (16.2)
50-59	1224 (17.7)
60-69	899 (13.0)
>=70	122 (1.8)

Characteristic	N (%)
Sex - no. (%)	
Male	3911 (56.5)
Female	3016 (43.5)
Race - no. (%)	
White	4710 (68.0)
Black or African American	304 (4.4)
Asian	501 (7.2)
Native Hawaiian or other Pacific Islander	30 (0.4)
American Indian or Alaska Native	79 (1.1)
More than one race	80 (1.2)
Not reported	1223 (17.7)
Reporting track - no. (%)	
TED	5702 (82.3)
CRF	1225 (17.7)
US or Non-US - no. (%)	
US	4991 (72.1)
Non-US	1936 (27.9)
Karnofsky score prior to HCT - no. (%)	
90-100	4474 (64.6)
< 90	2327 (33.6)
Not reported	126 (1.8)
HCT-CI - no. (%)	
0	2380 (34.4)
1	1054 (15.2)
2	992 (14.3)
3+	2473 (35.7)
TBD, review needed for history of malignancies	17 (0.2)
TBD, inconsistencies between parent and sub-questions	1 (0.0)
Missing	10 (0.1)
Prior CT - no. (%)	
No	6723 (97.1)
Yes	204 (2.9)
Time from prior ct to hct - no. (%)	
<6 months	141 (2.0)
6-12months	44 (0.6)
>12 months	19 (0.3)
Not Reported	6723 (97.1)
Subsequent CT - no. (%)	

Characteristic	N (%)
No	6711 (96.9)
Yes	216 (3.1)
Time from subsequent ct to hct - no. (%)	
<6 months	6 (0.1)
6-12months	47 (0.7)
>12 months	163 (2.4)
Not Reported	6711 (96.9)
Disease Related	
Disease status at time of HCT - no. (%)	
PIF	187 (2.7)
CR1	5901 (85.2)
>=CR3	604 (8.7)
Relapse	230 (3.3)
Not reported	5 (0.1)
Time from diagnosis to HCT - no. (%)	
<6 months	3138 (45.3)
6-12months	2563 (37.0)
>12 months	1226 (17.7)
Transplant Related	
Donor type - no. (%)	
HLA-identical sibling	2021 (29.2)
Other related	1452 (21.0)
Well-matched unrelated (8/8)	2289 (33.0)
Partially-matched unrelated (7/8)	418 (6.0)
Mis-matched unrelated (<= 6/8)	15 (0.2)
Unrelated (matching TBD)	288 (4.2)
Cord blood	444 (6.4)
Donor/recipient CMV serostatus - no. (%)	
+/+	2926 (42.2)
+/-	637 (9.2)
-/+	1607 (23.2)
-/-	1250 (18.0)
CB - recipient +	316 (4.6)
CB - recipient -	123 (1.8)
CB - recipient CMV unknown	5 (0.1)
Not reported	63 (0.9)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
No drugs reported	8 (0.1)

Characteristic	N (%)
MAC	4939 (71.3)
RIC	1330 (19.2)
NMA	517 (7.5)
TBD	129 (1.9)
Not reported	4 (0.1)
Donor/recipient sex match - no. (%)	
M-M	2337 (33.7)
M-F	1631 (23.5)
F-M	1307 (18.9)
F-F	1180 (17.0)
CB - recipient M	256 (3.7)
CB - recipient F	188 (2.7)
Not reported	28 (0.4)
Product type - no. (%)	
BM	1533 (22.1)
PB	4950 (71.5)
UCB	444 (6.4)
ATG/Campath - no. (%)	
ATG + CAMPATH	2 (0.0)
ATG alone	1579 (22.8)
CAMPATH alone	161 (2.3)
No ATG or CAMPATH	5185 (74.9)
GVHD prophylaxis - no. (%)	
None	46 (0.7)
Ex-vivo T-cell depletion	143 (2.1)
CD34 selection	105 (1.5)
PtCy + other(s)	1749 (25.2)
PtCy alone	35 (0.5)
TAC + MMF +- other(s) (except PtCy)	517 (7.5)
TAC + MTX +- other(s) (except MMF, PtCy)	2168 (31.3)
TAC + other(s) (except MMF, MTX, PtCy)	282 (4.1)
TAC alone	125 (1.8)
CSA + MMF +- other(s) (except PtCy,TAC)	366 (5.3)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	1198 (17.3)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	17 (0.2)
CSA alone	105 (1.5)
Other(s)	65 (0.9)
Missing	6 (0.1)

Characteristic	**N (%)**
Year of current transplant - no. (%)	
2015	891 (12.9)
2016	962 (13.9)
2017	1037 (15.0)
2018	1021 (14.7)
2019	1038 (15.0)
2020	959 (13.8)
2021	1019 (14.7)
Median follow-up of survivors (range), months - median (range)	37.3 (0.0-102.6)

Field	Response
Proposal Number	2310-146-MEHTA
Proposal Title	The role of HLA class II mismatched HCT in patients with high-risk acute leukemia
Key Words	High risk leukemia, -DPB1, DRB1, mismatch, relapse, survival, transplantation, HCT
Principal Investigator #1: - First and last name, degree(s)	Rohtesh Mehta, MD MPH MS
Principal Investigator #1: - Email address	rmehta@fredhutch.org
Principal Investigator #1: - Institution name	Fred Hutchinson Cancer Center, Seattle, WA
Principal Investigator #1: - Academic rank	Associate Professor of Medicine
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Annalisa Ruggeri, MD PhD
Principal Investigator #2 (If applicable): - Email address:)	annalisaruggeri80@hotmail.com
Principal Investigator #2 (If applicable): - Institution name:	EBMT Cellular Therapy & Immunobiology Working Party
Principal Investigator #2 (If applicable): - Academic rank:	Chair
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
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:	Rohtesh Mehta
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	PI of IB23-02 co-PI of GV23-01
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Acute Leukemia
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	Yes
If you have already spoken with a scientific director or working committee chair regarding this study, then please specify who:	Dr Kebriaei and Dr Milano
RESEARCH QUESTION:	Among patients with “high-risk” acute leukemia undergoing allogeneic hematopoietic cell transplantation (HCT), do patients with HLA class II (-DRB1 or -DPB1) mismatched HCT have a lower risk of relapse than those with HLA class II matched HCT?

Field	Response
RESEARCH HYPOTHESIS:	HCT with an HLA class II mismatched donor (especially -DRB1 or -DPB1 mismatched) would be associated with a lower risk of relapse in patients with high-risk acute leukemia than HCT with 8/8-HLA matched unrelated donor (MUD) with -DRb1 match.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Two donor categories will be compared: class II HLA-matched [matched related/sibling (MSD) + 8/8-MUD -DPb1 matched] vs class II HLA-mismatched [8/8-MUD -DPb1 mismatched + 7/8-mismatched unrelated donor (MMUD) -DRb1 mismatched]. Because of the anticipated sample size limitation, we propose to use combined datasets from the CIBMTR and the European Society for Blood and Marrow Transplantation (EBMT) registries.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	If our hypothesis stands, it could indicate selecting an HLA class II mismatched donor over a class II matched donor in patients with high-risk acute leukemia, which is currently not the standard practice. P.S. There are additional co-PIs on the proposal as following: 3rd PI Information: PI Name (Last, First, Middle): Milano, Filippo Degree(s): MD Academic Rank: Associate Professor of Medicine Email Address: fmilano@fredhutch.org Institution Name: Fred Hutchinson Cancer Center, Seattle, WA 4th PI Information: PI Name (Last, First, Middle): Kebriaei, Partow Degree(s): MD Academic Rank: Professor of Medicine Email Address: pkebriae@mdanderson.org Institution Name: MD Anderson Cancer Center, Houston, TX

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.	Loss and/or downregulation of surface expression of HLA class II molecules (HLA-DPb1, HLA-DQb1, and HLA-DRb1) on leukemia cells is noted in up to half of the patients who relapse after alloegeneic HCT.1-3 Therefore, it could be postulated that HLA class II mismatched HCT may confer relapse protection, especially in patients who are at high-risk of relapse. In fact, an older CIBMTR study4 that included patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia and myelodysplastic neoplasms (about 75% had low/intermediate risk disease) who were transplanted between 1999 and 2011 showed that HLA-DPb1 mismatches (permissive or nonpermissive) were associated with a lower risk of relapse among patients undergoing 8/8-HLA MUD, with no difference in relapse between the permissive and the nonpermissive cases. Also, the relative risk of relapse was lower for patients with -DRb1 mismatched donors, but the power was limited in this subgroup due to small sample. On the other hand, -DQb1 mismatches were not associated with the risk of relapse among either 8/8-MUD or 7/8-MUD cases.4 To the best of our knowledge, no study has directly compared the outcomes of class II mismatched vs matched donor HCT in patients with high-risk acute leukemia, especially in more recent years. Also, patients who relapse after first allogeneic HCT are at an extremely high risk of relapse after second allogeneic HCT. Several studies compared the outcomes of second allogeneic HCT with either the same or a different donor – either HLA matched or a haploidetical donor.5-14 None of these studies showed a clear advantage of switching to a different donor but no detrimental effect was found either; except one study of AML patients where switching from a matched donor (1st HCT) to a haploidentical donor (2nd HCT) was shown to be associated with a higher risk of non-relapse mortality (NRM) with no differences in relapse.11 In contrast, in one study, changing a donor from a MUD to a different MUD was associated with improved overall survival (HR 1.39; 95% CI 0.99 to 1.96) in patients who did not have any grade III-IV acute GVHD greater or chronic GVHD after first HSCT.5 Most of these studies are historic, did not specify -DPB1 matching, and did not particularly compare class II matched vs mismatched cases. Lastly, preliminary data from an ongoing independent analysis of patients with AML or ALL who underwent 10/10-HLA matched unrelated donor HCT with CNI-based prophylaxis, we assessed the impact of donor age with -DP (mis)matching. In multivariate analysis, -DP matched/older donors had a significantly inferior OS [HR 1.19, 95% CI 1.08-1.33, p=0.001] as

Field	Response
	compared to -DP mismatched/older donors [Figure below]. Further analyses are ongoing to assess outher outcomes and the reason for differences in OS noted in this study. We hypothesize that allogeneic HCT with an unrelated donor that is mismatched at one of the class II loci (-DRb1 or -DPb1) would have a lower risk of relapse and improved disease-free survival as compared to HCT with HLA matched related or unrelated donors without class II mismatches. We are not including haploidentical donors in the analysis as there are multiple HLA and non-HLA factors that determine outcomes in the haploidentical donor HCT setting, which could make our hypothesis challenging to assess. Definition of "high-risk" acute leukemia for the current proposal: 1. Relapsed/refractory disease 2. Active disease pre-HCT 3. Measurable residual disease (MRD) positive disease pre-HCT 4. Complex karyotype 5. tp53 mutation or 17p deletion 6. Hypodiploidy in ALL patients 7. Adverse risk AML per European Leukemia Network classification (if available) 8. Any acute leukemia that relapsed after first allogeneic HCT [to be studied as a separate cohort] STUDY DESIGN: Two broad donor groups will be compared: Class II HLA-matched donors (MSD + 8/8-MUD -DPb1 matched) vs Class II HLA-mismatched donors (8/8-MUD -DPb1 mismatched + 7/8-MMUD -DRb1 mismatched). The analysis will be stratified by first HCT vs second HCT especially if there is a significant statistical interaction between the main effect (donor type) and HCT number (first vs second). If no significant statistical interaction is noted, HCT number (first vs second) may be used as a covariate.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_T7aMqYDAT8fpQEp
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	OS.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	203832
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	1. Donor types: a) MSD b) 8/8-MUD -DPb1 matched c) 8/8-MUD -DPb1 permissive mismatched d) 8/8-MUD -DPb1 nonpermissive mismatched e) 7/8-MMUD (-DRb1 mismatched), regardless of -DPb1 matching 2. Conditioning: myeloablative (MAC) or reduced-intensity (RIC)/non-myeloablative (NMA). 3. Disease type: AML, ALL, or mixed phenotypic acute leukemic (MPAL) 4. Graft: peripheral blood (PB) or bone marrowe (BM) 5. Type of GVHD prophylaxis 6. Both adult and pediatric patients 7. HCT between 2014-2023
Does this study include pediatric patients?	Yes

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	i) Patient-related: •Age at HCT, years • Sex: male vs female • Karnofsky performance score: ≥90% vs. <90% • HCT comorbidity index (HCT-CI) at transplant 0-2 vs >3 • Race/ethnicity: Non-Hispanic White vs. NH-Black vs. Hispanic vs. Asian/pacific islander vs. others • Cytomegalovirus (CMV) status: seropositive vs. seronegative. ii) Disease-related: • Diagnosis • Disease status • Disease-Risk Index • MRD status pre-HCT • Cytogenetics • Extramedullary involvement • Time from diagnosis to HCT • Prior history of malignancy treated with chemotherapy and/or radiation therapy iii) Donor/Transplant-related: • Donor type • Donor age • Graft type: BM vs. PB • Donor/Recipient gender (Female-to-Male vs. other) • Recipient CMV status: seropositive vs. seronegative • HLA -DPb1 match status (for MUD and MMUD): -DPb1 matched vs mismatched • HLA -DRb1 match status (for MUD and MMUD): -DRb1 matched vs mismatched • HLA -DQb1 match status (for MUD and MMUD): -DQb1 matched vs mismatched • In vivo T cell depletion (yes vs no) • Conditioning: MAC vs RIC/NMA • GVHD prophylaxis drugs used • Year of HCT • Follow-up time • For patients undergoing 2nd HCT, following variables will be collected regarding 1st HCT: o donor type o graft source o conditioniong regimen o conditioning intensity (MAC vs RIC/NMA) o GVHD prophylaxis o In vivo TCD o Time to relapse from 1st HCT iv) Outcome related • Primary endpoint: Relapse • Secondary endpoints: o Grade II-IV and grade III-IV acute GVHD o Chronic GVHD: any, and requiring IST o Overall survival o Disease free survival o Causes of death
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 desc	N.A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N.A

Field	Response
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 o	N.A
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.	Because of the anticipated sample size limitation (especially the 2nd HCT recipients), we propose to use combined datasets from the CIBMTR and the European Society for Blood and Marrow Transplantation (EBMT) registries.

REFERENCES:	1. Christopher MJ, Petti AA, Rettig MP, et al: Immune Escape of Relapsed AML Cells after Allogeneic Transplantation. N Engl J Med 379:2330-2341, 2018 2. Toffalori C, Zito L, Gambacorta V, et al: Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nat Med 25:603-611, 2019 3. Vago L: Clonal evolution and immune evasion in posttransplantation relapses. Hematology Am Soc Hematol Educ Program 2019:610-616, 2019 4. Pidala J, Lee SJ, Ahn KW, et al: Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. Blood 124:2596-606, 2014 5. Christopeit M, Kuss O, Finke J, et al: Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. J Clin Oncol 31:3259-71, 2013 6. Eapen M, Giralt SA, Horowitz MM, et al: Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone Marrow Transplant 34:721-7, 2004 7. Gorgeis J, Zhang X, Connor K, et al: T Cell-Replete HLA Haploidentical Donor Transplantation with Post-Transplant Cyclophosphamide Is an Effective Salvage for Patients Relapsing after an HLA-Matched Related or Matched Unrelated Donor Transplantation. Biol Blood Marrow Transplant 22:1861-1866, 2016 8. Kharfan-Dabaja MA, Labopin M, Polge E, et al: Association of Second Allogeneic Hematopoietic Cell Transplant vs Donor Lymphocyte Infusion With Overall Survival in Patients With Acute Myeloid Leukemia Relapse. JAMA Oncol 4:1245-1253, 2018 9. Orti G, Sanz J, Bermudez A, et al: Outcome of Second Allogeneic Hematopoietic Cell Transplantation after Relapse of Myeloid Malignancies following Allogeneic Hematopoietic Cell Transplantation: A Retrospective Cohort on Behalf of the Grupo Espanol de Trasplante Hematopoyetico. Biol Blood Marrow Transplant 22:584-8, 2016 10. Shaw BE, Mufti GJ, Mackinnon S, et al: Outcome of second allogeneic transplants using reduced-intensity conditioning following relapse of haematological malignancy after an initial allogeneic transplant. Bone Marrow Transplant 42:783-9, 2008 11. Shimoni A, Labopin M, Finke J, et al: Donor

Field	Response
	selection for a second allogeneic stem cell transplantation in AML patients relapsing after a first transplant: a study of the Acute Leukemia Working Party of EBMT. Blood Cancer J 9:88, 2019 12. Tischer J, Engel N, Fritsch S, et al: Second haematopoietic SCT using HLA-haploidentical donors in patients with relapse of acute leukaemia after a first allogeneic transplantation. Bone Marrow Transplant 49:895-901, 2014 13. Vrhovac R, Labopin M, Ciceri F, et al: Second reduced intensity conditioning allogeneic transplant as a rescue strategy for acute leukaemia patients who relapse after an initial RIC allogeneic transplantation: analysis of risk factors and treatment outcomes. Bone Marrow Transplant 51:186-93, 2016 14. Yaniv I, Krauss AC, Beohou E, et al: Second Hematopoietic Stem Cell Transplantation for Post-Transplantation Relapsed Acute Leukemia in Children: A Retrospective EBMT-PDWP Study. Biol Blood Marrow Transplant 24:1629-1642, 2018
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	No, I do not have any conflicts of interest pertinent to this proposal

Characteristics of patients with AML and ALL in 2014-2023

Characteristic	N (%)
No. of patients	36518
No. of centers	364
Patient Related	
Age at HCT - no. (%)	
Median (min-max)	51.3 (0.4-82.2)
<10	1884 (5.2)
10-17	2138 (5.9)
18-29	4291 (11.8)
30-39	4081 (11.2)
40-49	5103 (14.0)
50-59	7534 (20.6)
60-69	9031 (24.7)
>=70	2456 (6.7)
Disease Risk - no. (%)	
Low risk	25138 (68.8)
High risk	11380 (31.2)
Donor Types - no. (%)	
MSD/HLA-identical sibling	13776 (37.7)
8/8MUD -DPb1 matched	3211 (8.8)
8/8MUD -DPb1 permissive mismatched	6635 (18.2)
8/8MUD -DPb1 nonpermissive mismatched	3301 (9.0)
7/8-MMUD(-DRb1 mismatched), regardless of -DPb1 matching	308 (0.8)
7/8-MMUD (non-permissively or permissively DPB1 mismatched)	682 (1.9)
8/8-MUD	6200 (17.0)
7/8-MMUD	2405 (6.6)
Sex - no. (%)	
Male	20212 (55.3)
Female	16306 (44.7)
Race - no. (%)	
White	27129 (74.3)
Black or African American	1379 (3.8)
Asian	1871 (5.1)
Native Hawaiian or other Pacific Islander	146 (0.4)
American Indian or Alaska Native	141 (0.4)
More than one race	282 (0.8)
Not reported	5570 (15.3)
Reporting track - no. (%)	
TED	30812 (84.4)

Characteristic	N (%)
CRF	5706 (15.6)
US or Non-US - no. (%)	
US	27568 (75.5)
Non-US	8950 (24.5)
Karnofsky score prior to HCT - no. (%)	
90-100	22216 (60.8)
< 90	13642 (37.4)
Not reported	660 (1.8)
HCT-CI - no. (%)	
0	10316 (28.2)
1	5690 (15.6)
2	5366 (14.7)
3+	14980 (41.0)
TBD, review needed for history of malignancies	126 (0.3)
TBD, inconsistencies between parent and sub-questions	4 (0.0)
Missing	36 (0.1)
Disease Related	
Disease status at time of HCT - no. (%)	
PIF	2684 (7.3)
CR1	25446 (69.7)
CR2	6370 (17.4)
>=CR3	729 (2.0)
Relapse	1235 (3.4)
Not reported	54 (0.1)
Time from diagnosis to HCT - no. (%)	
<6 months	19850 (54.4)
6-12months	9149 (25.1)
>12 months	7519 (20.6)
Transplant Related	
Donor/recipient CMV serostatus - no. (%)	
+/+	14336 (39.3)
+/-	3446 (9.4)
-/+	10791 (29.5)
-/-	7614 (20.8)
Not reported	331 (0.9)
Conditioning regimen intensity (F2400 pre-TED data) - no. (%)	
MAC	23256 (63.7)
RIC	11453 (31.4)
NMA	1809 (5.0)
Donor/recipient sex match - no. (%)	

Characteristic	N (%)
M-M	13164 (36.0)
M-F	9324 (25.5)
F-M	7013 (19.2)
F-F	6947 (19.0)
Not reported	70 (0.2)
Product type - no. (%)	
BM	6519 (17.9)
PB	29999 (82.1)
ATG/Campath - no. (%)	
ATG + CAMPATH	6 (0.0)
ATG alone	9729 (26.6)
CAMPATH alone	948 (2.6)
No ATG or CAMPATH	25835 (70.7)
GVHD prophylaxis - no. (%)	
None	143 (0.4)
Ex-vivo T-cell depletion	251 (0.7)
CD34 selection	296 (0.8)
PtCy + other(s)	5643 (15.5)
PtCy alone	239 (0.7)
TAC + MMF +- other(s) (except PtCy)	2748 (7.5)
TAC + MTX +- other(s) (except MMF, PtCy)	15381 (42.1)
TAC + other(s) (except MMF, MTX, PtCy)	1878 (5.1)
TAC alone	945 (2.6)
CSA + MMF +- other(s) (except PtCy,TAC)	1631 (4.5)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	6482 (17.8)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	20 (0.1)
CSA alone	499 (1.4)
Other(s)	344 (0.9)
Missing	18 (0.0)
Year of current transplant - no. (%)	
2014	3699 (10.1)
2015	3621 (9.9)
2016	3764 (10.3)
2017	3943 (10.8)
2018	4004 (11.0)
2019	4052 (11.1)
2020	3613 (9.9)
2021	3625 (9.9)
2022	3620 (9.9)
2023	2577 (7.1)

Characteristic	N (%)
Median follow-up of survivors (range), months - median (range)	36.5 (0.0-114.4)