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A G E N D A
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Orlando, FL
Thursday, February 20th, 2020, 12:15 - 2:15 PM

Co-Chair:	**Partow Kebriaei, MD; M.D. Anderson Cancer Center, Houston, TX; Telephone: 713- 792-8750; E-mail: pkebriae@mdanderson.org**
Co-Chair:	**Brenda Sandmaier, MD, Fred Hutchinson Cancer Research Center, Seattle, WA; Telephone: 206-667-4961; E-mail: bsandmai@fredhutch.org**
Co-Chair:	**Mark R. Litzow, MD; Mayo Clinic, Rochester, MN; Telephone: 206-667-4961; E-mail: litzow.mark@mayo.edu**
Scientific Director:	**Daniel J. Weisdorf, MD, University of Minnesota Medical Center, Minneapolis, MN; Telephone: 612-624-3101; E-mail: weisd001@umn.edu**
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Statistician:	**Karen Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0834; E-mail: kachen@mcw.edu**

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1. Introduction

a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)
b. Introduction of incoming Co-Chair:
Christopher Hourigan, MD, DPhil
National Heart, Lung, and Blood Institute

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **LK15-02** Yeshurun, M., Weisdorf, D., Rowe, J. M., Tallman, M. S., Zhang, M. J., Wang, H. L., ... Kamble, R. T. (2019). The impact of the graft-versus-leukemia effect on survival in acute lymphoblastic leukemia. *Blood Advances*, 3(4), 670-680.
b. **LK15-01** Ustun, C., Le-Rademacher, J., Wang, H. L., Othus, M., Sun, Z., Major, B., … Artz, A. S. (2019). Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): An alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. *Leukemia,* 33(11), 2599-2609.
c. **LK16-04** Rashidi, A., Hamadani, M., Zhang, M. J., Wang, H. L., Abdel-Azim, H., Aljurf, M., … Saber, W. (2019) Outcomes of haploidentical vs matched sibling transplantation for acute myeloid leukemia in first complete remission. *Blood Advances*, 3(12), 1826-1836.
d. **LK13-02** Lazaryan, A., Dolan, M., Zhang, M. J., Wang, H. L., Kharfan-Dabaja, M. A., Marks, D. I., … Weisdorf, D. (2019). Impact of cytogenetic abnormalities on outcomes of adult Philadelphia-negative acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation: A study by the

Acute Leukemia Working Committee of the Center for International Blood and Marrow Transplant Research. *Haematologica*. Advance online publication.

e. **LK16-01** Reduced Intensity Conditioning (RIC) regimens for Acute Myeloid Leukemia (AML): A comparison of Busulfan (B) and Melphlan (M) based regimens from the CIBMTR database (PI: Z Gul/ G Ahmed/M Khan/G Hilderbrandt/H Alkhateeb/M Damlaj/M Patnaik/R Nath/Z Zhou/J Cerny; MS: Hai-Lin Wang; PhD: Hai-Lin Wang; oversight assignment: Brenda Sandmaier; Sci Dir: Saber) ***Submitted***

f. **LK15-03** Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation (M Wieduwilt/W Stock/D Weisdorf) ***Presented at ASH 2019***

g. **LK16-02** DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes (N Bejanyan/ E Warlick/C Brunstein/D Weisdorf) ***Presented at ASH 2019***

h. **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes (N Callander/L Metheny/M De Lima/A Hall) ***Presented at ASH 2019***

i. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response (M Percival/B Sandmaier/E Estey) ***Presented at ASH 2019***

j. **LK17-02** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia (K Menghrajani/M Tallman) ***Presented at TCT 2020***

4. Studies in progress (Attachment 3)

a. **LK15-03** Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation (M Wieduwilt/W Stock/D Weisdorf) **Manuscript preparation**

b. **LK16-02** DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes (N Bejanyan/ E Warlick/C Brunstein/D Weisdorf) **Manuscript preparation**

c. **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes (N Callander/L Metheny/M De Lima/A Hall) **Manuscript preparation**

d. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response (M Percival/B Sandmaier/E Estey) **Manuscript preparation**

e. **LK17-02** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia (K Menghrajani/M Tallman) **Manuscript preparation**

f. **LK17-03** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia (Z DeFilipp/YB Chen) **Manuscript preparation**

g. **LK18-01** Prognostic Impact of the new European LeukemiaNet Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation (A Jimenez/T Wang/M de Lima/K Komanduri) **Data file preparation**

h. **LK18-02** Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia (M Wieduwilt/L Metheny/M de Lima) **Data file preparation**

i. **LK19-01** Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic

cell neoplasm (H Murthy/M Kharfan-Dabaja) **Protocol development**

j. **LK19-02** Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era (M Krem/R Maziarz) **Protocol development**

k. **LK19-03** Outcomes of allo-HCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (M Boyiadzis/M de Lima) **Protocol development**

5. Future/proposed studies

a. **PROP 1909-01** Comparison of Reduced-Intensity Conditioning Regimens for Older Patients with AML and MDS: A propensity score analysis (S O Ciurea/P Kongtim/M Al Malki/N Bejanyan/B Sandmaier) (Attachment 4)

b. **PROP 1909-02/1910-22/1911-40** Outcomes of second allogeneic hematopoietic stem cell transplantation for patients with relapsed acute leukemia in the modern era (F Yalniz/R Mehta/G Fatobene/P Kebriaei/D Weisdorf /P Imus/E Fuchs/V Rocha) (Attachment 5)

c. **PROP 1910-20** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (H Murthy/M Iqbal/M Kharfan-Dabaja) (Attachment 6)

d. **PROP 1911-18/1911-83/1911-191/1911-224** Acute myeloid leukemia (AML) with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (A Dias/J Yared/A Gomez-Arteaga/R Shallis/M Byrne/B McClune/A Rapoport/A Jakubowski/L Gowda/B Skikne/N Hardy/S Dahiya/T Lin/S Giralt/M Litzow) (Attachment 7)

e. **PROP 1911-73/1911-205** Comparison of outcomes of myeloablative versus reduced-intensity conditioning for allogeneic hematopoietic cell transplant in adults with B-cell acute lymphoblastic leukemia (M Schwartz/M Wieduwilt/M Mei/R Nakamura/I Aldoss) (Attachment 8)

f. **PROP 1911-078** Busulfan based conditioning in ALLO-HCT for acute myeloid leukemia or myelodysplastic syndromes from HLA matched related and unrelated donors (M Sobh/C Bredeson) (Attachment 9)

g. **PROP 1911-162/1911-194/1911-242** Outcomes of second allogeneic hematopoietic cell transplant vs donor lymphocyte infusion in patients with relapsed acute lymphoblastic leukemia relapse after the first allogeneic hematopoietic cell transplant (B Dholaria/A Jimenez/B Wirk/B Savani/K Komanduri/T Wang/M de Lima) (Attachment 10)

h. **PROP 1911-190** Outcomes of allogeneic hematopoietic cell transplantation (HCT) among germline runx1 mutation carriers with acute myeloid leukemia (AML) (P Liu/W Saber/L Cunningham) (Attachment 11)

Proposed studies; not accepted for consideration at this time

a. **PROP 1906-01** Outcomes of allogeneic hematopoietic stem cell transplantation in philadelphia chromosome positive acute myeloid leukemia

b. **PROP 1910-04** Compare outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) in patients with acute lymphoblastic leukemia (ALL) with or without central nervous system disease involvement

c. **PROP 1910-05** Evaluating outcomes of allogeneic hematopoietic cell transplantation in acute myeloid leukemia with central nervous system involvement

d. **PROP 1910-06** Outcomes and predictors of outcomes of adult patients with therapy-related acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation

e. **PROP 1910-08** Impact of donor lymphocyte infusion (DLI) on mixed chimerism and minimal residual disease (MRD) and association with the CD3+ cell dose

f. **PROP 1910-11** Impact of the intensity of the conditioning regimen in adults between 55-65 years diagnosed with high-risk acute myeloid leukemia

g. **PROP 1910-14** Clinical implication of morphologic complete remission following targeted therapy in AML patients undergoing allogeneic hematopoietic stem cell transplantation.
h. **PROP 1910-17** Hematopoietic stem cell transplantation (HCT) for patients with active acute leukemia
i. **PROP 1911-09** Comparison of Flu/2GY TBI vs. Flu/4GY TBI reduced-intensity conditioning regimen in Leukemia/MDS patients undergoing allogeneic HCT
j. **PROP 1911-48** Comparison of post-transplant outcomes for patients with acute myeloid leukemia treated with higher intensity chemotherapy versus lower intensity targeted therapy
k. **PROP 1911-64** Influence of molecular and cytogenetic risk factors in myeloid sarcoma
l. **PROP 1911-82** Transplant outcomes of myeloid/lymphoid neoplasms with 8p11 syndrome (8p11 chromosomal translocation; FGFR1 molecular rearrangement)
m. **PROP 1911-91** The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities
n. **PROP 1911-111** Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia: survival and outcomes in the modern era
o. **PROP 1911-112** Prophylactic CNS therapy after allogenic hematopoietic stem cell transplantation in adult acute lymphoblastic leukemia: A CIBMTR study
p. **PROP 1911-127** Impact of second cell therapy on the outcomes of patients with acute myeloid leukemia or myelodysplastic syndrome relapsed after a first allogeneic hematopoietic cell transplantation
q. **PROP 1911-131** Outcomes of patients with myeloid sarcoma and isolated CNS leukemia post-allogeneic stem cell transplant: a potential trans-Atlantic collaboration with EBMT
r. **PROP 1911-146** Outcomes of allogeneic hematopoietic cell transplantation for early T-precursor acute lymphoblastic leukemia
s. **PROP 1911-161** A new prognostic model for post-transplant AML outcomes
t. **PROP 1911-164** Impact of baseline absolute lymphocyte count on outcomes in patients with acute leukemia who underwent allo-HCT with anti-thymocyte globulin
u. **PROP 1911-179** Clinical outcomes in AML patients carrying isocitrate dehydrogenase (IDH1-2) mutations undergoing allogeneic hematopoietic stem cell transplantation
v. **PROP 1911-184** Allogeneic hematopoietic cell transplant outcomes in adult patients with philadelphia chromosome like acute lymphoblastic leukemia
w. **PROP 1911-217** Comparison of reduced intensity conditioning regimens for allogeneic hematopoietic stem cell transplant with post-transplant cyclophosphamide
x. **PROP 1911-232** Impact of asparaginase containing versus non-asparaginase containing induction regimen on allogeneic transplantation outcomes for acute lymphoblastic leukemia
y. **PROP 1911-243** Comparison of graft failure rate between acute lymphoblastic leukemia vs myeloid neoplasm patients who undergo busulfan-based myeloablative haploidentical stem cell transplant
z. **PROP 1911-246** Exploring the impact of upfront induction therapy intensity in high risk myelodysplastic syndromes and acute myeloid leukemia on post-allogeneic stem cell transplant outcomes in older patients
aa. **PROP 1911-247** Incidence of therapy-related myelodysplastic syndrome and acute myeloid leukemia in the recipients of prior autologous hematopoietic cell transplantation (HCT) and their outcomes after allogeneic HCT
ab. **PROP 1911-263** Impact of systemic immunosuppressive therapy on recurrent malignancy following allogeneic hematopoietic cell transplantation in acute myeloid leukemia
ac. **PROP 1911-271** Mixed chimerism in post hematopoietic stem cell transplant high risk hematologic malignancies: incidence, management and outcomes
ad. **PROP 1912-05** The impact of HLA-B35 expression on the incidence and outcomes of acute myeloid leukemia with IDH2-R140Q mutation

6. Other business

a. Definition of primary induction failure for reporting

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Houston, TX
Friday, February 22nd, 2019, 12:15 – 2:45 pm

Co-Chair:	**Marcos de Lima, MD, University Hospitals Case Medical Center, Cleveland, OH; Telephone: 216-286-6869; E-mail: marcos.delima@uhhospitals.org**
Co-Chair:	**Brenda Sandmaier, MD, Fred Hutchinson Cancer Research Center, Seattle, WA; Telephone: 206-667-4961; E-mail: bsandmai@fredhutch.org**
Co-Chair:	**Mark R. Litzow, MD; Mayo Clinic, Rochester, MN; Telephone: 206-667-4961; E-mail: litzow.mark@mayo.edu**
Scientific Director:	**Daniel J. Weisdorf, MD, University of Minnesota Medical Center, Minneapolis, MN; Telephone: 612-624-3101; E-mail: weisd001@umn.edu**
Assistant Scientific Director:	**Wael Saber, MD, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: wsaber@mcw.edu**
Statistical Director:	**Mei-Jie Zhang, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8375; E-mail: meijie@mcw.edu**

1. Introduction

The CIBMTR Acute Leukemia Working Committee was called to order at 12:15 pm on Friday, February 22rd, 2019, by Dr. Marcos de Lima. Attendees got their name badges scanned for attendance purposes and to maintain committee membership, and to fill out the Working Committee evaluations and voting sheets. The chairs, scientific director and statisticians were presented. Dr. Marcos de Lima introduced the conflict of interest disclosure statement, committee's accomplishments, ongoing studies and metrics for the past year. Dr. Wael Saber made a recognition to our leaving chair Marcos de Lima and Dr. Partow Kebriaei was introduce as incoming chair for the year 2019. Each proposal presentation was limited to 5 minutes to allow for adequate time for discussion (5 minutes).

2. Accrual summary

Dr. Marcos de Lima briefly mentioned that the allo-HCT and auto-HCT accrued summary between 1995 and 2018 were in attachment 2 of the agenda without further details.

3. Presentations published or submitted papers

Publication and presentations were mentioned but not presented.

a. **LK15-02** Impact of GVHD on outcome after allogeneic hematopoietic cell transplantation for acute lymphocytic leukemia: a retrospective registry study (PI: M Yeshurun/ J Rowe/ M Tallman/ V Bachanova; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Sandmaier; Sci Dir: Weisdorf) ***Accepted to Blood Advance 2018.***

b. **LK15-01** AlloHCT vs other consolidation in elderly AML (PI: A Artz/ C Ustun; MS: Hai-Lin Wang; PhD: Jacob Allred; oversight assignment: Weisdorf; Sci Dir: Weisdorf). ***ASH abstract for 2018.Submitted to Leukemia 2019.***

c. **LK16-01** Reduced intensity conditioning regimens for acute myeloid leukemia: A comparison of busulfan and melphalan based regimens from the CIBMTR database (PI: Z Gul/ G Ahmed/ M Khan/ G Hilderbrandt/ H Alkhateeb/ M Damlaj/ M Patnaik/ R Nath/ Z Zhou/ J Cerny; MS: Khalid B.; PhD: Hai-Lin Wang; oversight assignment: Sandmaier; Sci Dir: Saber).***ASH abstract for 2018.***

d. **LK16-04** Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia (Rizwan Romee/ Armin Rashidi/ Mehdi Hamadani/ Wael Saber) ***TCT oral presentation 2019.***

4. Studies in progress

The progress of other ongoing studies during the past year was not presented in order to provide more time for the new proposals' presentation and discussion. A summary of the progress was provided as an attachment to the committee members.

a. **LK13-02** Prognostic significance of cytogenetic abnormalities in patients with Philadelphia - negative acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation in complete remission (A Lazaryan/ V Bachanova/ D Weisdorf) **Manuscript preparation**

b. **LK15-03** Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation (M Wieduwilt/W Stock/ D Weisdorf).
Data File Preparation

c. **LK16-01** Reduced Intensity Conditioning (RIC) regimens for Acute Myeloid Leukemia (AML): A comparison of Busulfan (B) and Melphlan (M) based regimens from the CIBMTR database (Rajneesh Nath/ Zheng Zhou/ Jan Cerny) **Manuscript preparation**

d. **LK16-02** DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes (Nelli Bejanyan/ Erica Warlick/ Claudio Brunstein/ Daniel Weisdorf) **Data File Preparation**

e. **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes (Natalie Callander/ Leland Metheny/ Marcos De Lima/ Aric Hall) **Data File Preparation**

f. **LK16-04** Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia (Rizwan Romee/ Armin Rashidi/ Mehdi Hamadani/ Wael Saber) **Manuscript preparation**

g. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response (Mary-Elizabeth Percival/ Brenda Sandmaier/ Eli Estey) **Data File Preparation**

h. **LK17-02** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia (K Menghrajani/ M Tallman) **Protocol development**

i. **LK17-03** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia (Z DeFilipp/ YB Chen) **Protocol development**

j. **LK18-01** Prognostic Impact of the new European LeukemiaNet Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation (Antonio Jimenez / Trent Wang / Marcos de Lima / Krishna Komanduri; MS: Jonathan Sanchez; PhD: TBD; oversight assignment: Litzow; Sci Dir: Weisdorf. **Protocol development**

k. **LK18-02** Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia (Matthew Wieduwilt / Leland

Metheny / Marcos de Lima; MS: Jonathan Sanchez; PhD: TBD; oversight assignment: de Lima; Sci Dir: Saber) **Protocol development**

5. Future/proposed studies

Drs. Marco de Lima, Brenda Sandmaier and Mark R. Litzow led this session.

a. **PROP 1808-01** Myeloablative or reduced intensity conditioning allogeneic hematopoietic transplantation in acute leukemia: CIBMTR analysis of long-term outcomes (Rammurti Kamble, Parameswaran Hari)
Dr. Rammurti Kamble presented this proposal. There are 35,767 adult patients who underwent first allo-HCT for AML between 2005-2016 and 12,542 adult patients who underwent first allo-HCT for ALL between 2005-2016.
The primary objective of this proposal was to compare TRM, DFS and OS at a 100 days, 1 year and 3 years for allo-HCT for Acute Leukemia base on their Conditioning intensity (MAC vs RIC).
Comments were received to stratify the population between RIC, NMA and MAC. Also, the audience raised comment about the availability of karyotype and MRD information. Also concern regarding not learning anything new beyond what has already been published.

b. **PROP 1810-01** Does the Novel Scoring System (I-CBFit) Predict Outcomes After Allogeneic Hematopoietic Cell Transplantation in Core Binding Factor (CBF) AML with t(8;21)? (Celalettin Ustun)
Dr. Celalettin Ustun presented this proposal. There are 624(TED: n=222; CRF: n=402) patients who underwent first allo-HCT for AML with available data regarding factors for the I-CBFit score. The specific aims of this study if to evaluate if I-CBFit predicts outcomes (Relapse,DFS and OS) after allogeneic HCT in patients with t(8;21) .
Comments were received about MRD data availability.

c. **PROP 1811-23** The influence of FLT3 internal tandem duplication vs flt3 tyrosine kinase domain with or without NPM1 or IDH1/2 on transplant outcome (Shatha Farhan/ Nalini Janakiraman/Edward Peres/Josephine Emole).
Dr. Nalini Janakiraman presented this proposal on behalf of Shatha Farhan. There are 1,339 adult patients receiving First allo-HCT for AML between 2009-2017 with FLT3 ITD, IDH or NMP1 cytogenetic information. The objective of this proposal is to compare overall survival for patients FLT3/IDH dual mutants vs FLT3/IDH dual mutants.
Comments were received about the association between the frequency of FLT3 and IDH. According to the discussion they were not associated. Also, there were comments regarding MRD data availability.

d. **PROP 1811-41** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era (Maxwell Krem, Richard Maziarz)
Dr. Maxwell Krem presented the proposal. There are 959 Ph- and 1,392 adult patients receiving first allo-HCT for ALL between 2001-2015. The primary objective of this study was to compare post-transplant outcomes of Ph-positive ALL patients vs Ph-negative ALL patients undergoing HCT over three time periods: 2001-2005, 2006-2010, 2011-2015.
Comments were received regarding the patients that did not get to transplant it will not bring supporting data for the non-Transplant population. Also, suggestion was made for an internal validation control containing Ph- patients.

e. **PROP 1811-106** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (Michael Boyiadzis, Marcos de Lima)
Dr. Michael Boyiadzis presented the proposal. There are 3,405 adult patients receiving first allo-HCT for AML in CR1 who received 2 or more cycles of induction chemotherapy between 2008-2015.I was hypothesize that the use of multiple cycles of induction chemotherapy causes

undue toxicity, which negatively impacts treatment-related mortality and survival following allo-HCT. The primary objective was to determine treatment-related mortality in patients who underwent allo-HCT in first CR that required 2 or more cycles of induction chemotherapy Comments were made regarding the type of induction and dose, selection bias (patients made to HCT and got to CR) and suggested adjustment for number of consolidations before transplantation. Dr. Saber clarified that the purpose for this study would be to properly classify cases into different risk groups based on number of induction therapy received.

f. **PROP 1811-113** Outcomes of alloHCT for adult acute lymphoblastic leukemia in a second or subsequent complete remission (Lyndsey Runaas, Guru Murthy)
Dr. Lyndsey Runaas presented the proposal. There are 3,733 adult patients receiving first allo-HCT for ALL in CR2 or beyond between 2000-2016, reported to CIBMTR. The proponet hypothesize Outcomes of patients who underwent allogeneic hematopoietic cell transplantation (allo-HCT) for adult acute lymphoblastic leukemia (ALL) beyond first complete remission (CR) have remained historically poor. With the availability of effective salvage therapies, we postulate that the outcomes of these patients transplanted in second CR (CR2) or beyond would have improved over time. The primary objective is to assess the temporal trends in overall survival (OS) of ALL patients undergoing allo-HCT in CR2 or beyond.
Comments were received to restrict to Ph- patients only considering new agents patients seems to have better outcomes and the new agents cohort is relevant to the most recent year which are a small subset of the population.

g. **PROP 1811-137** Outcomes of acute lymphoblastic leukemia arising from a prior hematologic malignancy (Trent Wang, Antonio Jimenez)
Dr. Trent Wang presented this proposal. There are 82 patients a history of malignancy receiving first allo-HCT for S-ALL between 2012-2016, reported to CIBMTR. Dr. Wang hypothesizes that s-ALL is an aggressive leukemia with poor outcomes. Allogeneic stem cell transplantation is employed when possible and can lead to durable remissions in this high-risk population. The primary objective is to evaluate outcomes (relapse, DFS, TRM and OS) for this population.
Comments were made about adding other previous malignancies and expanding proposal to treatment related ALL.

h. **PROP 1811-169** Comparison of outcomes of in vivo T-cell depleted versus T-cell replete donor grafts in reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation for older adults 60 years of age or older with acute myeloid leukemia (AML)
Dr. Marc Schwartz presented this proposal. There are 282 TCD and 446 non-TCD adult older than 60 years receiving first RIC allo-HCT for AML in CR1 between 2000-2017, reported to CIBMTR. The primary objective of this study is to compare OS and Relapse between the following groups: (1) in vivo T cell depletion with Anti-Thymocyte Globulin (ATG), (2) in vivo T cell depletion with alemtuzumab, (3) no in vivo T cell depletion.
Comments were received about the time to ATG, dose of ATG, center effect on TCD, overlap with GVWC ATG dosing study, donor shift in recent years rather than TCD practice change.

i. **PROP 1811-170** Survival Probabilities of Patients with Acute Leukemias, Myelodysplastic Syndromes and Myelofibrosis Undergoing Allogeneic Hematopoietic Cell Transplantation Conditional on Years Already Survived (Sudipto Mukherjee, Ronald Sobecks, Aaron Gerds)
Dr. Sudipto Mukherjee presented this proposal.There are 9,211 Acute Leukemia, 2,676 MDS and 532 MF adult patients receiving first allo-HCT between 2000-2015.The primary objective of this study is to assess 5-year CS in 1-5 year survivors after allogeneic HCT for AL, MDS and MF.

Comments were received about the relevance of providing survival probabilities beyond 4-5 years after HCT given the patient already survived that long. There was suggestion to stratify analysis for patients with or without GVHD and expand to pediatric population.

j. **PROP 1809-02** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm (Hemant Murthy)
Dr. Hemant Murthy presented this proposal. There are 181 allo-HCT and 19 auto-HCT adult patients receiving first HCT for BPDCN between 2000-2017. Dr. Murthy hypothesizes that HCT is associated with durable remissions in patients with BPDCN. The primary objective of the study is to evaluate OS, PFS, NRM and Relapse for this population.
Comments were received about specifying the type of induction received and expand to pediatric patients.

k. **PROP 1811-86 / 1811-96** 10-year survival after allogeneic hematopoietic cell transplantation for AML in adults 60 years and above: frequency and success factors / 10 yr relapse-free survival in Acute myeloid leukemia in patients who underwent HCT in CR1. (Andrew Artz, Celalettin Ustun / Sumithira Vasu).
Sumithira Vasu presented this proposal. There are 21697 patients with 18425 between 18-59 and 3373 older than 60. There are 9536 patients who underwent HCT between 2000-2004 and 12161 underwent HCT between 2005-2009. The primary objective of this study is to evaluate the long-term survival for AML patients after a allo-HCT.
Comments were received about the accuracy of survival data after 10 years.

Proposed studies; not accepted for consideration at this time

These proposals were not discussed during the meeting. Dr. Daniel J. Weisdorf made comments about committee's busy portfolio and common reasons why proposals are not accepted for consideration. Attendees were encouraged to submit ideas again if not feasible at this time.

a. **PROP 1808-01** Myeloablative or reduced intensity conditioning allogeneic hematopoietic transplantation in acute leukemia: CIBMTR analysis of long-term outcomes (Rammurti Kamble, Parameswaran Hari)
b. **PROP 1810-01** Does the Novel Scoring System (I-CBFit) Predict Outcomes After Allogeneic Hematopoietic Cell Transplantation in Core Binding Factor (CBF) AML with t(8;21)? (Celalettin Ustun)
c. **PROP 1811-23** The influence of FLT3 internal tandem duplication vs flt3 tyrosine kinase domain with or without NPM1 or IDH1/2 on transplant outcome (Shatha Farhan/ Nalini Janakiraman/Edward Peres/Josephine Emole)
d. **PROP 1811-113** Outcomes of alloHCT for adult acute lymphoblastic leukemia in a second or subsequent complete remission (Lyndsey Runaas, Guru Murthy)
e. **PROP 1811-137** Outcomes of acute lymphoblastic leukemia arising from a prior hematologic malignancy (Trent Wang, Antonio Jimenez)
f. **PROP 1811-169** Comparison of outcomes of in vivo T-cell depleted versus T-cell replete donor grafts in reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation for older adults 60 years of age or older with acute myeloid leukemia (AML)

6. Other business

- The advisory committee members Bart Scott and Michael Bishop were present during the working committee meting and Bart Scott attended the pre and post meeting deliberations.
- During the post-meeting it was suggested to add MRD information availability in welcoming slides.

- After the new proposals were presented, each participant in the meeting had the opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number or relevant cases and the impact of the study on the field, the following studies will move forward as the committee's research portfolio for the upcoming year:
    - **PROP 1809-02** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm (Hemant Murthy).
        - Include the person who presented this study in previous years as co-author/collaborator: Drs. Rafelson, Ganguly, Deotare, Ahmed and Nishihori
    - **PROP 1811-41** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era (Maxwell Krem, Richard Maziarz)
    - **PROP 1811-106** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (Michael Boyiadzis, Marcos de Lima)

Working Committee Overview Plan for 2019 - 2020

a. **LK15-03:** Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation. Data file preparation underway. (Total hour: 170; Allocated for the fiscal year: 70)

b. **LK16-01** Reduced Intensity Conditioning (RIC) regimens for Acute Myeloid Leukemia (AML): A comparison of Busulfan (B) and Melphlan (M) based regimens from the CIBMTR database. Data file preparation is underway. Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by July 2019. (Total hour: 70; Allocated for the fiscal year: 5)

c. **LK16-02** DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes. Data file preparation underway. The goal is to finalize the protocol and start data file preparation by June 2018 and finish analysis by June 2019. (Total hour: 160; Allocated for the fiscal year: 50)

d. **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes. Protocol development is underway. Data file preparation underway. The goal of the study is to finalize data analysis and manuscript preparation by July 2019. (Total hour: 160; Allocated for the fiscal year: 50)

e. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response. Data file preparation underway. The goal of the study is to finalize data analysis and submit manuscript by July 2019.
(Total hour: 140; Allocated for the fiscal year: 5)

f. **LK17-02** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia. Protocol development is underway. The goal of the study is to finalize data analysis and manuscript preparation by July 2019. (Total hour: 200; Allocated for the fiscal year: 70)

g. **LK17-03** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia. Protocol development is underway. The goal is to finalize the protocol, start data file preparation and analysis by July 2019. (Total hour: 280; Allocated for the fiscal year: 150)

h. **LK18-01** Prognostic impact of ELN risk group in AlloHCT for adult AML in CR1/CR2. Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2019. (Total hour: 280; Allocated for the fiscal year: 150)
i. **LK18-02** Haplo vs RD vs MUD for adult ALL. Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2019. (Total hour: 300; Allocated for the fiscal year: 180)
j. **PROP 1809-02** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm (Hemant Murthy) (Total hour: 330; Allocated for the fiscal year:)
k. **PROP 1811-41** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era (Maxwell Krem, Richard Maziarz) (Total hour: 330; Allocated for the fiscal year:100)
l. **PROP 1811-106** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (Michael Boyiadzis, Marcos de Lima) (Total hour: 330; Allocated for the fiscal year:100)

Oversight Assignments for Working Committee Leadership (March 2019)

Wael Saber	**LK17-02:** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia
Partow Kebriaei	**LK18-02:** Comparison of outcomes of haploidentical hematopoietic cell transplantation (HCT) with matched-related donor or matched-unrelated donor allogeneic HCT for adults with Ph-negative acute lymphoblastic leukemia **LK19-02/PROP 1811-41:** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era
Brenda Sandmaier	**LK16-02:** DRI-guided choice of conditioning intensity for allogeneic hematopoietic cell transplantation in adults with acute myeloid leukemia and myelodysplastic syndromes. **LK16-01:** Reduced intensity conditioning regimens for acute myeloid leukemia: A comparison of busulfan and melphalan based regimens from the CIBMTR database. **LK17-01:** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response **LK19-03/PROP 1811-106:** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy
Mark Litzow	**LK17-03:** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia **LK18-01:** Prognostic Impact of the new European LeukemiaNet (ELN) Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation **LK19-01/PROP 1809-02:** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm

Appendix: Overview Plan

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2018	Hours allocated 7/1/2018-6/30/2019	Total Hours allocated
LK13-02: Prognostic significance of cytogenetic abnormalities in patients with Ph- acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation in complete remission	Submitted	Published - July 2019	10	10	10	0	10
LK15-01: Allogeneic transplants vs other consolidation in elderly AML	Submitted	Published- July 2019	10	10	10	0	10
LK15-02: Impact of GVHD on outcome after allogeneic hematopoietic cell transplantation for acute lymphocytic leukemia: a retrospective registry study	Published	Published- July 2019	0	0	0	0	0
LK15-03: Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation	Data File Preparation	Manuscript Preparation- July 2019	170	100	100	70	170
LK16-01: Reduced intensity conditioning regimens for acute myeloid leukemia: A comparison of busulfan and melphalan based regimens from the CIBMTR database	Manuscript Preparation	Submitted- July 2019	70	70	70	0	70

LK16-02: DRI-guided choice of conditioning intensity for allogeneic hematopoietic cell transplantation in adults with acute myeloid leukemia and myelodysplastic syndromes	Analysis	Manuscript Preparation- July 2019	110	60	60	50	110
LK16-03: Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes	Analysis	Manuscript Preparation- July 2019	150	100	100	50	150
LK16-04: Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia	Submitted	Published- July 2019	10	10	10	0	10
LK17-01: Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response	Data File Preparation	Submitted- July 2019	160	160	160	0	160
LK17-02: Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia	Data File Preparation	Manuscript Preparation- July 2019	200	130	130	70	200
LK17-03: Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia	Protocol Development	Analysis- July 2019	280	130	130	150	280

LK18-01: Prognostic Impact of the new European LeukemiaNet Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation	Protocol Development	Analysis- July 2019	280	130	130	150	280
LK18-02: Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia	Protocol Development	Data File Preparation- July 2019	280	30	30	180	210
LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm	Protocol Pending	Draft Protocol Received- July 2019	330	0	0	100	100
LK19-02: Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era	Protocol Pending	Draft Protocol Received- July 2019	330	0	0	100	100
LK19-03: Outcomes of alloHCT in AML patients who achieved first complete remission after two or more cycles of induction chemotherapty	Protocol Pending	Draft Protocol Received- July 2019	330	0	0	100	100

Accrual Summary for the Acute Leukemia Working Committee

Characteristics of recipients of first allogeneic transplants for AML and ALL reported[a] to the CIBMTR between 1995 and 2019

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Number of patients	22662	11545
Number of centers	419	392
Age in decades		
Median (range)	44 (<1-88)	22 (<1-79)
<10	1935 (9)	2693 (23)
10-17	2152 (9)	2664 (23)
18-29	2587 (11)	2047 (18)
30-39	3019 (13)	1518 (13)
40-49	4133 (18)	1325 (11)
50-59	4848 (21)	895 (8)
60-69	3433 (15)	381 (3)
≥70	555 (2)	22 (<1)
Gender		
Male	12030 (53)	7023 (61)
Female	10631 (47)	4521 (39)
Missing	1 (<1)	1 (<1)
HCT-CI		
0	2817 (12)	1557 (13)
1	1493 (7)	605 (5)
2	1329 (6)	486 (4)
3+	4068 (18)	1162 (10)
N/A, earlier than 2007	12305 (54)	7454 (65)
Missing	650 (3)	281 (2)
Disease status prior to HCT		
Primary induction failure	2975 (13)	392 (3)
CR1	11171 (49)	4936 (43)
CR2	4710 (21)	3900 (34)
≥CR3	420 (2)	983 (9)
Relapse	3320 (15)	1322 (11)
Missing	66 (<1)	12 (<1)
Time from diagnosis to HCT		
Median (range)	6 (<1-352)	11 (1-499)
<6 months	10966 (48)	3284 (28)
6 - 12 months	5489 (24)	2742 (24)
>12 months	6188 (27)	5505 (48)
Missing	19 (<1)	14 (<1)

Accrual Table 1. Allogeneic transplant recipients:	**AML**	**ALL**
Conditioning regimen intensity		
Myeloablative	16185 (71)	10311 (89)
Reduced intensity	3986 (18)	609 (5)
Non-myeloablative	1798 (8)	376 (3)
To be determined	478 (2)	152 (1)
Missing	215 (1)	97 (1)
Graft type		
Bone marrow	7329 (32)	5170 (45)
Peripheral blood	12521 (55)	4312 (37)
Umbilical cord blood	2793 (12)	2049 (18)
Missing	19 (<1)	14 (<1)
Type of donor		
HLA-identical sibling	6973 (31)	3196 (28)
Identical twin	92 (<1)	66 (1)
Other relative	1515 (7)	771 (7)
Unrelated	10667 (47)	5175 (45)
Cord blood	2793 (12)	2049 (18)
Missing	622 (3)	288 (2)
Year of HCT		
1995-1996	1710 (8)	1306 (11)
1997-1998	1516 (7)	1135 (10)
1999-2000	1466 (6)	1068 (9)
2001-2002	1826 (8)	1101 (10)
2003-2004	2171 (10)	1121 (10)
2005-2006	2610 (12)	1250 (11)
2007-2008	2470 (11)	1075 (9)
2009-2010	2148 (9)	638 (6)
2011-2012	904 (4)	430 (4)
2013-2014	2160 (10)	818 (7)
2015-2016	2143 (9)	862 (7)
2017-2018	1406 (6)	656 (6)
2019-current	132 (1)	85 (1)
Median follow-up of survivors (range), months	77 (1-290)	78 (1-290)

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

Characteristics of recipients of first autologous transplants for AML and ALL reported[a] to the CIBMTR between 1995 and 2019

Accrual Table 2. Autologous transplant recipients:	**AML**	**ALL**
Number of patients	998	158
Number of centers	182	60
Age in decades		
Median (range)	44 (<1-78)	30 (1-66)
<10	61 (6)	16 (10)
10-17	68 (7)	25 (16)
18-29	125 (13)	38 (24)
30-39	166 (17)	20 (13)
40-49	189 (19)	28 (18)
50-59	220 (22)	23 (15)
60-69	160 (16)	8 (5)
≥70	9 (1)	0
Gender		
Male	506 (51)	100 (63)
Female	492 (49)	58 (37)
HCT-CI		
0	56 (6)	3 (2)
1	20 (2)	2 (1)
2	14 (1)	4 (3)
3+	44 (4)	3 (2)
N/A, earlier than 2007	862 (86)	146 (92)
Missing	2 (<1)	0
Disease status prior to HCT		
Primary induction failure	10 (1)	2 (1)
CR1	643 (64)	102 (65)
CR2	262 (26)	43 (27)
≥CR3	14 (1)	6 (4)
Relapse	66 (7)	5 (3)
Missing	3 (<1)	0
Time from diagnosis to HCT		
Median (range)	7 (<1-250)	9 (2-153)
<6 months	411 (41)	23 (15)
6 - 12 months	270 (27)	75 (47)
>12 months	316 (32)	60 (38)
Missing	1 (<1)	0
Conditioning regimen intensity		
Myeloablative	800 (80)	148 (94)
Reduced intensity	15 (2)	4 (3)

Accrual Table 2. Autologous transplant recipients:	**AML**	**ALL**
Non-myeloablative	2 (<1)	0
To be determined	173 (17)	2 (1)
Missing	8 (1)	4 (3)
Graft type		
Bone marrow	171 (17)	25 (16)
Peripheral blood	827 (83)	133 (84)
Year of HCT		
1995-1996	266 (27)	55 (35)
1997-1998	221 (22)	45 (28)
1999-2000	107 (11)	16 (10)
2001-2002	89 (9)	12 (8)
2003-2004	65 (7)	5 (3)
2005-2006	87 (9)	9 (6)
2007-2008	103 (10)	10 (6)
2009-2010	20 (2)	1 (1)
2011-2012	6 (1)	0
2013-2014	15 (2)	3 (2)
2015-2016	9 (1)	1 (1)
2017-2018	8 (1)	1 (1)
2019-current	2 (<1)	0
Median follow-up of survivors (range), months	117 (1-281)	145 (2-293)

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

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**19840**	**6243**	**3730**
Source of data			
CRF	10086 (51)	2629 (42)	2054 (55)
TED	9754 (49)	3614 (58)	1676 (45)
Number of centers	234	203	318
Disease at transplant			
AML	13566 (68)	4431 (71)	2418 (65)
ALL	5866 (30)	1674 (27)	1232 (33)
Other acute leukemia	408 (2)	138 (2)	80 (2)
AML Disease status at transplant			
CR1	6997 (52)	2391 (54)	1108 (46)
CR2	2700 (20)	841 (19)	499 (21)
CR3+	259 (2)	73 (2)	53 (2)
Advanced or active disease	3459 (26)	1085 (24)	707 (29)
Missing	147 (1)	41 (1)	47 (2)
ALL Disease status at transplant			
CR1	2842 (48)	871 (52)	516 (42)
CR2	1699 (29)	456 (27)	358 (29)
CR3+	482 (8)	127 (8)	118 (10)
Advanced or active disease	798 (14)	206 (12)	206 (17)
Missing	45 (1)	14 (1)	33 (3)
Recipient age at transplant			
0-9 years	1483 (7)	396 (6)	382 (10)
10-19 years	2015 (10)	546 (9)	493 (13)
20-29 years	2456 (12)	717 (11)	526 (14)
30-39 years	2365 (12)	689 (11)	504 (14)
40-49 years	3046 (15)	938 (15)	562 (15)
50-59 years	3787 (19)	1162 (19)	613 (16)
60-69 years	3880 (20)	1444 (23)	553 (15)
70+ years	808 (4)	351 (6)	97 (3)
Median (Range)	46 (0-84)	48 (0-79)	39 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	16459 (86)	5194 (86)	2708 (84)
African-American, non-Hispanic	746 (4)	226 (4)	149 (5)
Asian, non-Hispanic	479 (3)	203 (3)	138 (4)
Pacific islander, non-Hispanic	25 (<1)	8 (<1)	10 (<1)
Native American, non-Hispanic	77 (<1)	25 (<1)	17 (1)
Hispanic	1330 (7)	370 (6)	195 (6)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Other	18 (<1)	11 (<1)	10 (<1)
Unknown	706 (N/A)	206 (N/A)	503 (N/A)
Recipient sex			
Male	10967 (55)	3463 (55)	2121 (57)
Female	8873 (45)	2780 (45)	1609 (43)
Karnofsky score			
10-80	6977 (35)	2349 (38)	1164 (31)
90-100	12133 (61)	3594 (58)	2279 (61)
Missing	730 (4)	300 (5)	287 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	14 (<1)	23 (<1)	0
4/6	95 (<1)	45 (1)	17 (<1)
5/6	2778 (14)	742 (14)	563 (16)
6/6	16691 (85)	4620 (85)	2925 (83)
Unknown	262 (N/A)	813 (N/A)	225 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	376 (2)	55 (1)	21 (1)
6/8	828 (4)	64 (1)	61 (3)
7/8	3925 (20)	774 (18)	546 (23)
8/8	14038 (73)	3422 (79)	1716 (73)
Unknown	673 (N/A)	1928 (N/A)	1386 (N/A)
HLA-DPB1 Match			
Double allele mismatch	4898 (30)	442 (26)	198 (29)
Single allele mismatch	8797 (53)	840 (50)	361 (53)
Full allele matched	2763 (17)	393 (23)	123 (18)
Unknown	3382 (N/A)	4568 (N/A)	3048 (N/A)
High resolution release score			
No	5274 (27)	6182 (99)	3649 (98)
Yes	14566 (73)	61 (1)	81 (2)
KIR typing available			
No	11326 (57)	6202 (99)	3707 (99)
Yes	8514 (43)	41 (1)	23 (1)
Graft type			
Marrow	6849 (35)	1953 (31)	1531 (41)
PBSC	12970 (65)	4205 (67)	2191 (59)
BM+PBSC	4 (<1)	5 (<1)	1 (<1)
PBSC+UCB	13 (<1)	73 (1)	2 (<1)
Others	4 (<1)	7 (<1)	5 (<1)
Number of cord blood units			
1	6 (100)	0	1 (100)
Conditioning regimen			
Myeloablative	14399 (73)	4267 (68)	2784 (75)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
RIC/Nonmyeloablative	5361 (27)	1960 (31)	893 (24)
TBD	80 (<1)	16 (<1)	53 (1)
Donor age at donation			
To Be Determined/NA	118 (1)	720 (12)	34 (1)
0-9 years	4 (<1)	17 (<1)	1 (<1)
10-19 years	585 (3)	202 (3)	85 (2)
20-29 years	9024 (45)	2566 (41)	1447 (39)
30-39 years	5542 (28)	1586 (25)	1140 (31)
40-49 years	3476 (18)	885 (14)	783 (21)
50+ years	1091 (5)	267 (4)	240 (6)
Median (Range)	30 (0-61)	30 (0-73)	33 (7-67)
Donor/Recipient CMV serostatus			
+/+	5149 (26)	1807 (30)	940 (26)
+/-	2207 (11)	731 (12)	457 (13)
-/+	7025 (36)	2039 (34)	1220 (34)
-/-	5167 (26)	1440 (24)	934 (26)
CB - recipient +	1 (<1)	6 (<1)	0
CB - recipient -	0	2 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Unknown	291 (N/A)	217 (N/A)	179 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	549 (3)	140 (2)	162 (4)
CD34 selection	318 (2)	134 (2)	59 (2)
Post-CY + other(s)	557 (3)	334 (5)	61 (2)
Post-CY alone	53 (<1)	22 (<1)	12 (<1)
Tacrolimus + MMF +- others	2160 (11)	656 (11)	251 (7)
Tacrolimus + MTX +- others (except MMF)	9470 (48)	2994 (48)	1152 (31)
Tacrolimus + others (except MTX, MMF)	1067 (5)	403 (6)	151 (4)
Tacrolimus alone	494 (2)	171 (3)	64 (2)
CSA + MMF +- others (except Tacrolimus)	1036 (5)	266 (4)	246 (7)
CSA + MTX +- others (except Tacrolimus, MMF)	3047 (15)	785 (13)	1167 (31)
CSA + others (except Tacrolimus, MTX, MMF)	320 (2)	106 (2)	125 (3)
CSA alone	221 (1)	69 (1)	149 (4)
Other GVHD prophylaxis	313 (2)	96 (2)	61 (2)
Missing	235 (1)	67 (1)	70 (2)
Donor/Recipient sex match			
Male-Male	7780 (39)	2338 (38)	1403 (38)
Male-Female	5391 (27)	1640 (27)	933 (25)
Female-Male	3117 (16)	1051 (17)	694 (19)
Female-Female	3425 (17)	1060 (17)	654 (18)
CB - recipient M	5 (<1)	38 (1)	0
CB - recipient F	8 (<1)	40 (1)	2 (<1)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	114 (N/A)	76 (N/A)	44 (N/A)
Year of transplant			
1986-1990	119 (1)	17 (<1)	32 (1)
1991-1995	708 (4)	189 (3)	255 (7)
1996-2000	1322 (7)	474 (8)	431 (12)
2001-2005	2476 (12)	516 (8)	738 (20)
2006-2010	4577 (23)	958 (15)	753 (20)
2011-2015	6635 (33)	1835 (29)	926 (25)
2016-2019	4003 (20)	2254 (36)	595 (16)
Follow-up among survivors, Months			
N Eval	8242	2943	1391
Median (Range)	50 (1-338)	26 (1-325)	47 (1-350)

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

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3250**	**756**	**720**
Source of data			
CRF	2419 (74)	569 (75)	484 (67)
TED	831 (26)	187 (25)	236 (33)
Number of centers	137	115	158
Disease at transplant			
AML	2044 (63)	451 (60)	409 (57)
ALL	1121 (34)	287 (38)	289 (40)
Other acute leukemia	85 (3)	18 (2)	22 (3)
AML Disease status at transplant			
CR1	1048 (51)	242 (54)	199 (49)
CR2	569 (28)	114 (25)	116 (28)
CR3+	50 (2)	6 (1)	12 (3)
Advanced or active disease	370 (18)	86 (19)	80 (20)
Missing	7 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	507 (45)	122 (43)	130 (45)
CR2	421 (38)	108 (38)	103 (36)
CR3+	120 (11)	39 (14)	31 (11)
Advanced or active disease	72 (6)	18 (6)	25 (9)
Missing	1 (<1)	0	0
Recipient age at transplant			
0-9 years	724 (22)	228 (30)	189 (26)
10-19 years	477 (15)	112 (15)	130 (18)
20-29 years	376 (12)	60 (8)	69 (10)
30-39 years	363 (11)	80 (11)	83 (12)
40-49 years	372 (11)	76 (10)	75 (10)
50-59 years	470 (14)	92 (12)	89 (12)
60-69 years	410 (13)	94 (12)	79 (11)
70+ years	58 (2)	14 (2)	6 (1)
Median (Range)	31 (0-83)	27 (0-77)	25 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1820 (59)	440 (62)	401 (63)
African-American, non-Hispanic	411 (13)	88 (12)	72 (11)
Asian, non-Hispanic	202 (7)	45 (6)	52 (8)
Pacific islander, non-Hispanic	20 (1)	3 (<1)	7 (1)
Native American, non-Hispanic	18 (1)	3 (<1)	6 (1)
Hispanic	606 (20)	136 (19)	100 (16)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	173 (N/A)	41 (N/A)	82 (N/A)
Recipient sex			
Male	1715 (53)	408 (54)	402 (56)
Female	1535 (47)	348 (46)	318 (44)
Karnofsky score			
10-80	872 (27)	198 (26)	173 (24)
90-100	2313 (71)	526 (70)	515 (72)
Missing	65 (2)	32 (4)	32 (4)
HLA-A B DRB1 groups - low resolution			
<=3/6	45 (1)	24 (4)	6 (1)
4/6	1384 (44)	259 (44)	262 (39)
5/6	1349 (43)	227 (39)	321 (48)
6/6	337 (11)	73 (13)	78 (12)
Unknown	135 (N/A)	173 (N/A)	53 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	1601 (59)	258 (60)	299 (55)
6/8	650 (24)	97 (23)	136 (25)
7/8	330 (12)	43 (10)	79 (15)
8/8	150 (5)	29 (7)	29 (5)
Unknown	519 (N/A)	329 (N/A)	177 (N/A)
HLA-DPB1 Match			
Double allele mismatch	425 (39)	38 (47)	36 (40)
Single allele mismatch	559 (52)	35 (43)	43 (48)
Full allele matched	99 (9)	8 (10)	11 (12)
Unknown	2167 (N/A)	675 (N/A)	630 (N/A)
High resolution release score			
No	2436 (75)	724 (96)	714 (99)
Yes	814 (25)	32 (4)	6 (1)
KIR typing available			
No	2566 (79)	751 (99)	715 (99)
Yes	684 (21)	5 (1)	5 (1)
Number of cord blood units			
1	2665 (82)	0	587 (82)
2	584 (18)	0	133 (18)
3	1 (<1)	0	0
Unknown	0 (N/A)	756 (N/A)	0 (N/A)
Graft type			
UCB	3070 (94)	683 (90)	675 (94)
PBSC+UCB	161 (5)	73 (10)	39 (5)
Others	19 (1)	0	6 (1)
Conditioning regimen			
Myeloablative	2301 (71)	542 (72)	498 (69)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
RIC/Nonmyeloablative	943 (29)	212 (28)	221 (31)
TBD	6 (<1)	2 (<1)	1 (<1)
Donor age at donation			
To Be Determined/NA	99 (3)	41 (5)	41 (6)
0-9 years	2899 (89)	587 (78)	620 (86)
10-19 years	147 (5)	67 (9)	29 (4)
20-29 years	32 (1)	20 (3)	6 (1)
30-39 years	32 (1)	22 (3)	12 (2)
40-49 years	17 (1)	9 (1)	4 (1)
50+ years	24 (1)	10 (1)	8 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-72)
Donor/Recipient CMV serostatus			
+/+	838 (26)	167 (22)	155 (22)
+/-	292 (9)	76 (10)	56 (8)
-/+	644 (20)	142 (19)	148 (21)
-/-	378 (12)	78 (10)	97 (13)
CB - recipient +	707 (22)	181 (24)	146 (20)
CB - recipient -	352 (11)	90 (12)	101 (14)
CB - recipient CMV unknown	39 (1)	22 (3)	17 (2)
GvHD Prophylaxis			
Ex vivo T-cell depletion	21 (1)	6 (1)	2 (<1)
CD34 selection	133 (4)	57 (8)	34 (5)
Post-CY + other(s)	3 (<1)	3 (<1)	0
Tacrolimus + MMF +- others	905 (28)	196 (26)	115 (16)
Tacrolimus + MTX +- others (except MMF)	127 (4)	36 (5)	37 (5)
Tacrolimus + others (except MTX, MMF)	107 (3)	29 (4)	18 (3)
Tacrolimus alone	73 (2)	20 (3)	10 (1)
CSA + MMF +- others (except Tacrolimus)	1596 (49)	328 (43)	385 (53)
CSA + MTX +- others (except Tacrolimus, MMF)	53 (2)	13 (2)	18 (3)
CSA + others (except Tacrolimus, MTX, MMF)	123 (4)	46 (6)	60 (8)
CSA alone	30 (1)	9 (1)	27 (4)
Other GVHD prophylaxis	64 (2)	5 (1)	11 (2)
Missing	15 (<1)	8 (1)	3 (<1)
Donor/Recipient sex match			
CB - recipient M	1715 (53)	408 (54)	400 (56)
CB - recipient F	1535 (47)	348 (46)	318 (44)
CB - recipient sex unknown	0	0	2 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	51 (2)	53 (7)	15 (2)
2006-2010	1016 (31)	224 (30)	222 (31)
2011-2015	1528 (47)	268 (35)	344 (48)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2016-2019	655 (20)	210 (28)	136 (19)
Follow-up among survivors, Months			
N Eval	1494	381	330
Median (Range)	52 (2-168)	44 (3-192)	48 (1-176)

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

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and donor only samples

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3840**	**598**	**226**
Source of data			
CRF	1224 (32)	145 (24)	83 (37)
TED	2616 (68)	453 (76)	143 (63)
Number of centers	80	60	42
Disease at transplant			
AML	2519 (66)	367 (61)	140 (62)
ALL	1219 (32)	215 (36)	83 (37)
Other acute leukemia	102 (3)	16 (3)	3 (1)
AML Disease status at transplant			
CR1	1570 (62)	243 (66)	86 (61)
CR2	391 (16)	42 (11)	15 (11)
CR3+	28 (1)	6 (2)	1 (1)
Advanced or active disease	520 (21)	73 (20)	36 (26)
Missing	10 (<1)	3 (1)	2 (1)
ALL Disease status at transplant			
CR1	765 (63)	136 (63)	56 (67)
CR2	326 (27)	49 (23)	16 (19)
CR3+	62 (5)	9 (4)	6 (7)
Advanced or active disease	66 (5)	20 (9)	5 (6)
Missing	0	1 (<1)	0
Recipient age at transplant			
0-9 years	257 (7)	29 (5)	10 (4)
10-19 years	408 (11)	43 (7)	23 (10)
20-29 years	381 (10)	76 (13)	27 (12)
30-39 years	385 (10)	61 (10)	24 (11)
40-49 years	566 (15)	101 (17)	33 (15)
50-59 years	875 (23)	135 (23)	44 (19)
60-69 years	838 (22)	132 (22)	57 (25)
70+ years	130 (3)	21 (4)	8 (4)
Median (Range)	49 (1-78)	49 (1-76)	49 (2-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	2475 (68)	317 (57)	148 (69)
African-American, non-Hispanic	344 (9)	45 (8)	11 (5)
Asian, non-Hispanic	170 (5)	58 (10)	11 (5)
Pacific islander, non-Hispanic	11 (<1)	1 (<1)	1 (<1)
Native American, non-Hispanic	16 (<1)	1 (<1)	0
Hispanic	634 (17)	136 (24)	42 (20)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	190 (N/A)	40 (N/A)	13 (N/A)
Recipient sex			
Male	2178 (57)	339 (57)	126 (56)
Female	1662 (43)	259 (43)	100 (44)
Karnofsky score			
10-80	1429 (37)	274 (46)	93 (41)
90-100	2332 (61)	314 (53)	124 (55)
Missing	79 (2)	10 (2)	9 (4)
Graft type			
Marrow	973 (25)	115 (19)	63 (28)
PBSC	2853 (74)	476 (80)	159 (70)
BM+PBSC	2 (<1)	3 (1)	0
BM+UCB	4 (<1)	1 (<1)	0
PBSC+UCB	0	0	3 (1)
Others	8 (<1)	3 (1)	1 (<1)
Conditioning regimen			
Myeloablative	2704 (70)	408 (68)	156 (69)
RIC/Nonmyeloablative	1130 (29)	188 (31)	68 (30)
TBD	6 (<1)	2 (<1)	2 (1)
Donor age at donation			
To Be Determined/NA	8 (<1)	1 (<1)	0
0-9 years	182 (5)	18 (3)	11 (5)
10-19 years	353 (9)	50 (8)	17 (8)
20-29 years	555 (14)	96 (16)	29 (13)
30-39 years	567 (15)	108 (18)	40 (18)
40-49 years	624 (16)	106 (18)	31 (14)
50+ years	1551 (40)	219 (37)	98 (43)
Median (Range)	44 (0-80)	43 (0-79)	45 (3-76)
Donor/Recipient CMV serostatus			
+/+	1259 (42)	252 (53)	89 (51)
+/-	286 (10)	31 (7)	15 (9)
-/+	862 (29)	118 (25)	45 (26)
-/-	558 (19)	75 (16)	27 (15)
Unknown	42 (N/A)	5 (N/A)	5 (N/A)
GvHD Prophylaxis			
Ex-vivo T-cell depletion	56 (1)	16 (3)	4 (2)
CD34 selection	59 (2)	14 (2)	6 (3)
Post-CY + other(s)	848 (22)	126 (21)	53 (23)
Post-CY alone	24 (1)	7 (1)	3 (1)
TAC + MMF +- other(s) (except post-CY)	350 (9)	32 (5)	16 (7)
TAC + MTX +- other(s) (except MMF, post-CY)	1683 (44)	194 (32)	96 (42)
TAC + other(s) (except MMF, MTX, post-CY)	341 (9)	150 (25)	22 (10)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
TAC alone	21 (1)	1 (<1)	2 (1)
CSA + MMF +- other(s) (except post-CY)	54 (1)	7 (1)	3 (1)
CSA + MTX +- other(s) (except MMF, post-CY)	280 (7)	29 (5)	15 (7)
CSA + others (except TAC, MTX, MMF, post-CY)	0	1 (<1)	0
CSA alone	31 (1)	6 (1)	0
Other(s)	38 (1)	7 (1)	3 (1)
Missing	55 (1)	8 (1)	3 (1)
Donor/Recipient sex match			
Male-Male	1225 (32)	215 (36)	67 (30)
Male-Female	866 (23)	132 (22)	52 (23)
Female-Male	950 (25)	122 (20)	57 (25)
Female-Female	795 (21)	125 (21)	46 (20)
CB - recipient M	3 (<1)	2 (<1)	2 (1)
CB - recipient F	1 (<1)	2 (<1)	2 (1)
Year of transplant			
2006-2010	249 (6)	26 (4)	19 (8)
2011-2015	1757 (46)	254 (42)	86 (38)
2016-2019	1834 (48)	318 (53)	121 (54)
Follow-up among survivors, Months			
N Eval	2318	355	135
Median (Range)	25 (2-124)	24 (3-101)	25 (3-120)

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

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

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TO: Acute Leukemia Working Committee Members

FROM: Daniel J. Weisdorf, MD; Scientific Director and Wael Saber, MD, MS; Assistant Scientific Director for the Acute Leukemia Working Committee

RE: Studies in Progress Summary

LK15-03: Comparison of outcomes of older adolescents and young adults with Philadelphia-chromosome/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation (M Wieduwilt / W Stock; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Brenda Sandmaier; Sci Dir: Weisdorf)
The purpose of this study is:
(1) To compare overall survival, relapse-free survival, relapse, and non-relapse mortality between older adolescent and young adults aged 16-39 years with Ph/BCR-ABL1-negative acute lymphoblastic leukemia in first complete remission receiving consolidation therapy with pediatric-inspired chemotherapy on CALGB 10403 to myeloablative allogeneic hematopoietic cell transplantation.
(2) To compare outcomes of CALGB 10403 to allogeneic HCT using fully matched related or unrelated donors in patients who attained CR1 in <8 weeks.
(3) To compare outcomes of obese and non-obese ALL patients between cohorts
(4) To compare CNS relapse rates in the two cohorts.
(5) To determine patient and disease factors influencing outcomes of consolidation with pediatric-inspired chemotherapy versus allogeneic hematopoietic cell transplantation.
Draft manuscript has been received for review by LKWC leadership. The goal is to have the manuscript finalized and submitted by July 2020.

LK16-02: DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes (N Bejanyan / E Warlick / C Brunstein / D Weisdorf; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Brenda Sandmaier; Sci Dir: Weisdorf)
The purpose of this study is:
(1) To study the effect of conditioning intensity on overall survival (OS) of adult allograft recipients with AML and MDS based on DRI assignment.
(2) To study neutrophil recovery, platelet recovery, acute and chronic GVHD, treatment-related mortality (TRM), malignancy relapse and leukemia-free survival (LFS).
Draft manuscript is being reviewed by LKWC leadership. The goal is to have the manuscript finalized and submitted by July 2020.

LK16-03: Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes (N Callander / L Metheny / M De Lima / A Hall; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Partow Kebriaei; Sci Dir: Weisdorf)
The purpose of this study is:

(1) To evaluate overall survival of adult allogeneic HCT patients with therapy related AML and MDS (t-AML and t-MDS).
(2) To assess day-30 mortality, day-100 mortality, leukemia-free-survival (LFS), treatment- related mortality (TRM), non-relapse mortality (NRM), relapse rate (REL), acute and chronic GVHD
(3) To evaluate overall survival of adult allogeneic HCT patients with t-AML/ t-MDS secondary to autologous transplant.
(4) To assess the effect of preparative regimen intensity on outcomes.
(5) To identify patient, disease and transplant related prognostic factors for outcome after allogeneic hematopoietic stem cell transplantation.
Draft manuscript is being reviewed by LKWC leadership. The goal is to have the manuscript finalized and submitted by July 2020.

LK17-01: Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response (M Percival / B Sandmaier / E Estey; MS: Hai-Lin Wang; PhD: Hai-Lin Wang; oversight assignment: Brenda Sandmaier; Sci Dir: Weisdorf)
The purpose of this study is:
(1) To compare overall survival in AML patients undergoing HCT in CR1 who have CR vs. a response less than complete remission.
(2) To evaluate event-free survival and treatment-related mortality in AML patients undergoing HCT in CR1 who have CR vs. a response less than complete remission.
Manuscript has been circulated to Writing Committee and comments are under review by study team. The goal is to have the manuscript finalized and submitted by July 2020.

LK17-02: Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia (K Menghrajani / M Tallman; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Saber; Sci Dir: Saber)
The purpose of this study is to:
(1) Retrospectively evaluate the overall survival, leukemia-free survival, relapse incidence, and non-relapse mortality of adult AML patients with MLL-rearranged acute myeloid leukemia who underwent an allogeneic bone marrow transplant in CR1.
(2) Evaluate whether or not the type of MLL rearrangement (e.g.11q- or any balanced 11q23 abnormality) allows for stratification of the above outcomes.
(3) Understand how outcomes differ for patients who undergo allogeneic transplant for MLL-rearranged leukemia as compared to AML with other intermediate- or adverse-risk features.
TCT abstract was submitted and draft manuscript is in progress. The goal is to have the manuscript finalized and submitted by July 2020.

LK17-03: Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia (Z DeFilipp / Y Chen; MS: Hai-Lin Wang; PhD: Mei-Jie Zhang; oversight assignment: Mark Litzow; Sci Dir: Saber)
The purpose of this study is to:
(1) Describe DFS (at 1- and 3-years post-transplant) of patients with Ph+ ALL undergoing allogeneic HCT in CR1 who received maintenance TKI therapy and compare to controls (no maintenance therapy).
(2) Compare the OS (at 1- and 3-years post-transplant) between the same two groups (maintenance versus no maintenance).
Analysis was finished in January 2020 and draft manuscript is in progress. The goal is to have the manuscript finalized and submitted by July 2020.

LK18-01: Prognostic Impact of the new European LeukemiaNet Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation (A Jimenez / T Wang; MS: Karen Chen; PhD: Mei-Jie Zhang; oversight assignment: Mark Litzow; Sci Dir: Weisdorf)
The purpose of this study is:
(1) To identify differences in specific transplant outcomes (overall survival, leukemia-free survival, cumulative incidence of transplant-related mortality, and cumulative incidence of relapse) amongst patients categorized into ELN genetic groups.
(2) To evaluate differences in transplant outcomes (overall survival, leukemia-free survival, cumulative incidence of transplant-related mortality, and cumulative incidence of relapse) between age cohorts as previously described by ELN.
(3) To evaluate differences in transplant outcomes among genetic subsets within high-risk patients.
Writing Committee comments on the draft protocol are under review and data file preparation is underway. The goal is to finish preparing the data file, perform the analysis, and start manuscript preparation by July 2020.

LK18-02: Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia (M Wieduwilt / L Metheny / M de Lima; MS: Noel Estrada; PhD: Mei-Jie Zhang; oversight assignment: Partow Kebriaei; Sci Dir: Saber)
The purpose of this study is:
(1) To compare the overall survival between haploidentical HCT, matched-related donor allogeneic HCT, and matched-unrelated donor HCT.
(2) To compare the relapse-free survival, relapse, and non-relapse mortality between the groups.
(3) To compare Grade 2-4 and Grade 3-4 acute GVHD rates between the groups.
(4) To compare chronic GVHD rates between the three groups.
(5) To compare causes of death between the three groups.
Writing Committee comments on the draft protocol are under review and data file preparation is underway. The goal is to finish preparing the data file, perform the analysis, and start manuscript preparation by July 2020.

LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm (H Murthy / M Kharfan-Dabaja; MS: Karen Chen; PhD: Mei-Jie Zhang; oversight assignment: Mark Litzow; Sci Dir: Saber)
The purpose of the study is:
(1) To describe clinical outcomes of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) undergoing allogeneic HCT.
(2) To describe clinical outcomes of patients with BPDCN undergoing autologous HCT.
(3) To identify the impact of patient-, disease-, and transplant-related factors on progression-free survival, overall survival, relapse and non-relapse mortality for both autologous and allogeneic HCT.
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020.

LK19-02: Evolving significance of Ph-positive status on ALL post-transplant outcomes in the TKI era (M Krem / R Maziarz; MS: Karen Chen; PhD: Mei-Jie Zhang; oversight assignment: Partow Kebriaei; Sci Dir: Saber)
The purpose of the study is:

(1) To compare post-transplant outcomes of Ph-positive ALL patients vs Ph-negative ALL patients undergoing HCT over three time periods: 2001-2005, 2006-2010, 2011-2015.
(2) To compare overall survival, disease relapse, GVHD incidence, and NRM by Ph-chromosome status in ALL patients undergoing allo-HCT in CR1.
(3) To evaluate the impact of conditioning regimen intensity, MRD status, TKI use, and additional cytogenetic abnormalities on post-transplant outcomes of Ph-positive ALL patients.
(4) To evaluate changes in post-allo-HCT outcomes over time periods corresponding to advancements in TKI therapy.
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020.

LK19-03: Outcomes of allo-HCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy (M Boyiadzis / M de Lima; MS: Karen Chen; PhD: Mei-Jie Zhang; oversight assignment: Brenda Sandmaier; Sci Dir: Weisdorf)
The purpose of this study is:
(1) To determine treatment-related mortality in patients who underwent allo-HCT in first CR that required 2 or more cycles of induction chemotherapy.
(2) To determine overall survival in patients who underwent allo-HCT in first CR that required 2 or more cycles of induction chemotherapy.
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020.

Proposal: 1909-01

Title:
Comparison of Reduced-Intensity Conditioning Regimens for Older Patients with AML and MDS: A propensity score analysis

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Hypothesis:
Allogeneic hematopoietic cell transplantation (AHCT) using a reduced-intensity conditioning (RIC) fludarabine and melphalan 100mg/m^2 (FM100) is associated with better long-term survival and acceptable toxicity in elderly patients with AML and MDS.

Specific objectives:
Primary objective: To compare 3-year progression-free survival (PFS) of elderly patients with AML and MDS receiving AHCT using FM100 conditioning with other RIC or non-myeloablative (NMA) conditioning regimens.

Secondary objectives:
Compare:
- Cumulative incidence of grades II-IV and III-IV acute GVHD
- Cumulative incidence extensive chronic GVHD
- Cumulative incidence of relapse
- Cumulative incidence of non-relapse mortality (NRM)
- Overall survival (OS)
- GVHD-free, relapse-free survival (GRFS)

Scientific justification:
Allogeneic hematopoietic stem cell transplant (AHCT) is a potential curative treatment for patients with AML and MDS. However, this treatment modality has been traditionally limited to younger individuals and those without significant comorbidities because of higher regimen-related toxicity associated with myeloablative conditioning. Given that median age of patients with AML and MDS is >60 years, most patients with these diseases are not eligible for conventional AHCT.
In an attempt to extend this therapy to older and unfit patients, a major step forward was the introduction of reduced-intensity conditioning (RIC) regimens (1, 2), for which tumor eradication relies primarily on the graft-versus-tumor (GVT) effect (3, 4) instead of myeloablation with high intensity conditioning. During the last several years, a variety of RIC regimens have been developed that usually include a combination of a purine analog (primarily fludarabine) with an alkylating agent (usually melphalan or busulfan) and/or low dose TBI. These regimens convey different degree of myelosuppression and have been successfully used in elderly or unfit patients with AML and MDS with reported long-term survival rates ranging between 30% and 60%.(5-14)
Results from a prospective multicenter phase II study evaluating the efficacy of fludarabine and busulfan (FB) RIC regimen for elderly patients with AML in first complete remission showed promising outcomes

with 42% disease-free survival (DFS) and NRM of only 15%.(15) Similarly, a group from Dana-Farber Cancer Institute reported encouraging AHCT outcomes in elderly AML patients using FB RIC regimen with busulfan total dose of either 3.2 or 6.4 mg/kg. In this study, PFS was comparable (40% vs. 39%, respectively) and NRM was less than 10% in both busulfan dose groups.(16) Adding rabbit ATG to the FB RIC regimen, the French group has shown a reduction of GVHD incidence without an increased risk of relapse.(17)

RIC regimens using-low dose TBI have also been commonly used.(18-20) Results with HLA-identical sibling grafts in elderly or medically infirm patients with hematological malignancies using low-dose TBI have been encouraging, and remissions, including molecular remissions, have been accomplished.(18, 19) In a study by Niederwieser et al. evaluating outcomes of 52 elderly or medically unfit patients with hematological diseases who received AHCT using fludarabine in combination with 2 Gy TBI, the OS was 44% with only 11% regimen-related mortality at 100 days.(19)

The combination of melphalan with a purine nucleotide analog (fludarabine or cladribine) as conditioning regimens for AHCT in patients with hematological malignancies (including AML and MDS) has been developed at MDACC (21-24). Several studies have reported favorable outcomes of fludarabine and melphalan (FM) 140-180 mg/m^2 conditioning regimen.(6, 22, 23, 25, 26) Results from a retrospective study in patients $\geq$ 55 years of age with AML and MDS from MDACC showed that the combination of fludarabine 100-150 mg/m^2 and melphalan 140-180 mg/m^2 RIC regimen provides better disease control than a truly non-myeloablative (NMA) regimen (120 mg/m^2 fludarabine, 4 g/m^2 cytarabine, and 36 mg/m^2 idarubicin [FAI]); however, at a cost of increased NRM and risk of GVHD.(6) However, another report by investigators from the City of Hope showed that this regimen could be used safely in patients older than 70 years as rate of GVHD and NRM did not differ from those expected in younger patients treated with RIC regimens.(27)

Several studies also compared RIC FM and FB regimens for AHCT in patients with AML and MDS and reported significantly lower risk of relapse with use of FM.(28-31) While overall survival was similar between the FM and FB regimens in most prior reported studies, mainly due to relapse benefit being offset by increased NRM(28-30), the CIBMTR registry study in 1258 AML and 951 MDS patients demonstrated significantly better OS and relapse-free survival benefit with FM as compared to RIC FB.(31) The total dose of melphalan used in FM conditioning in these reports was mostly 140 mg/m^2, including in 82% of patients in CIBMTR study.

To further reduce toxicity, melphalan 100 mg/m^2 in combination with fludarabine (FM100) has been studied. Our group reported long-term outcomes of 36 patients with AML in complete remission who received AHCT from HLA-related and unrelated donor using fludarabine-melphalan RIC regimen, of which 21/36 patients received FM100 regimen. With a median follow-up of 52 months, OS and PFS rates at 4 years were 71% and 68%, respectively. The cumulative incidence of NRM at 4 years was 20% and relapse-related mortality was only 8%.(23) Encouraging outcomes of fludarabine and melphalan 100 mg/m^2 or 140 mg/m^2 have also been reported in alternative donor AHCT in various hematologic malignancies.(32)

To determine whether using the FM100 regimen would provide better disease control without the risk of an increase mortality in elderly patients with AML, the MDACC group recently evaluated the effect of RIC regimen type on 404 patients with AML $\geq$ 60 years receiving AHCT between 01/2005-08/2018. Conditioning regimens examined included: 1) fludarabine + melphalan 100mg/m^2 (FM100, N=78), 2) fludarabine + melphalan 140mg/m2 (FM140, N=89), 3) fludarabine + IV busulfan x 4 days with Bu AUC$\geq$5,000/day (equivalent dose 130mg/m^2/day) (Bu$\geq$5,000, N=131), 4) fludarabine + IV busulfan x 4 days with Bu AUC 4,000/day (equivalent dose 110mg/m^2/day) (Bu4,000, N=106). To adjust for potential selection bias in choices of conditioning regimen, propensity score was calculated and used as a stratifying variable in a multivariable Cox regression model. Results from this analysis showed that older patients with AML benefitted from a RIC with FM100 conditioning regimen, which was associated with

significantly better survival compared with other more intense conditioning regimens evaluated (Figure 1), despite the fact that patients who could not receive more intense conditioning preferentially received FM100 regimen (*data will be presented at ASH 2019*).

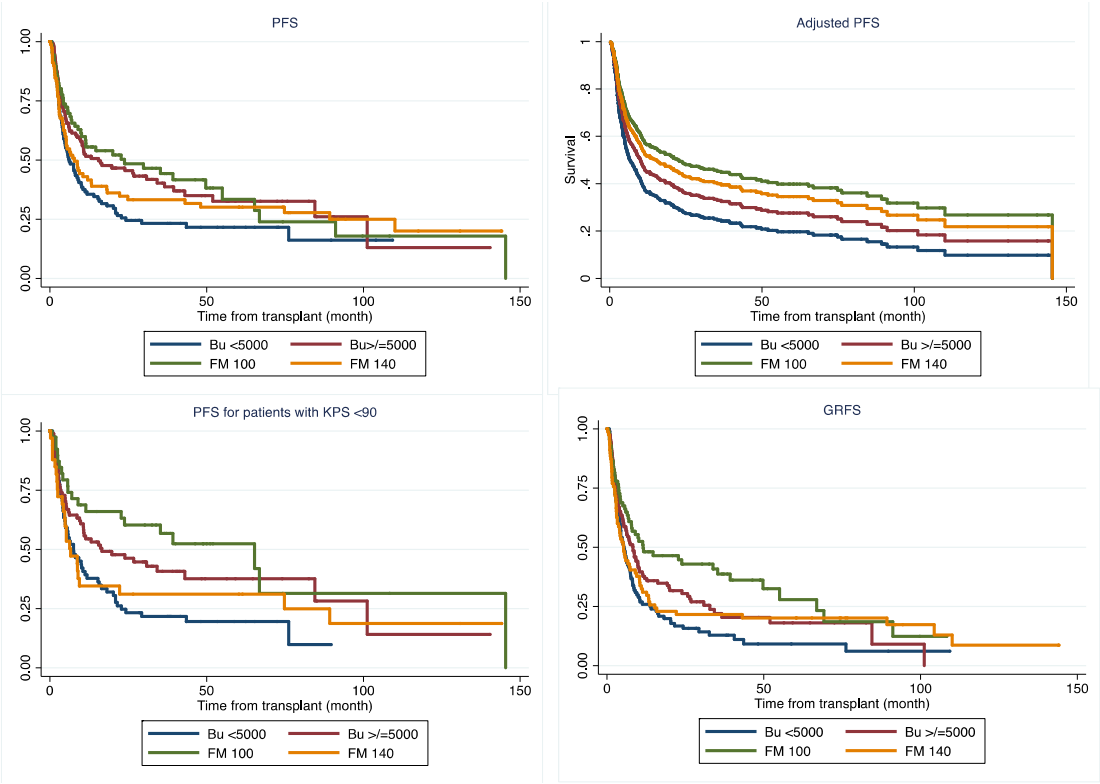

Figure 1. PFS, propensity score-adjusted PFS, PFS for patients with KPS<90% and GRFS

To further confirm our findings and determine the preferred RIC/NMA regimen for AHCT in a larger cohort of elderly patients with AML and MDS, we propose to compare clinical outcomes after commonly used RIC or NMA conditioning regimens in older patients with AML and MDS reported to the CIBMTR. Results from this proposed study could help to determine the preferred conditioning regimen for AHCT and to select a more personalized transplant procedure for older and unfit patients with AML and MDS.

Patient eligibility population:

Inclusion criteria:

- Patients with AML and MDS who underwent 1st AHCT from January 2008 to December 2018
- Age 60 years or older
- Patients in complete remission or with active disease at transplant
- Patients who received AHCT using stem cell from HLA-matched related, HLA-matched unrelated, HLA-mismatched related, HLA-mismatched unrelated and unmanipulated haploidentical donor
- Patients who received RIC/NMA conditioning regimens according to the previously defined guidelines(1, 33)
- Patients who received stem cell products from bone marrow or peripheral blood

Exclusion criteria:

- Patients with a diagnosis of acute promyelocytic leukemia

Data requirements:
The study will use data collected from CIBMTR. No additional data are required.

Sample requirements:
No clinical samples are required.

Study design:
This is a retrospective cohort analysis to evaluate the impact of various RIC/NMA regimens on outcomes of elderly AML and MDS patients.

Eligible patients will be categorized into subgroups based on type of conditioning regimen as the following:

- Patients who received busulfan-based vs. melphalan-based vs. low dose TBI-based
- Patients who received FM100 regimen vs. other RIC/NMA regimens
- Patients who received FM100 regimen vs. FM140 regimen

Transplant outcomes of patients in these subgroups will be compared:

- Primary outcome: PFS at 3 years after transplant
- Secondary outcome measures include the following:
    - OS at 3 years after transplant
    - GRFS at 3, 5 years after transplant
    - 100-day-cumulative incidence of acute grades II-IV and III-IV GVHD
    - 3-year-cumulative incidence of extensive chronic GVHD
    - Cumulative incidence of NRM at 1 and 3 year after transplantation
    - Cumulative incidence of relapse at 3 year after transplantation

Variables to be analyzed are:
Patient related characteristics:

- Age of recipient
- Gender (male or female)
- Karnofsky performance status
- HCT-CI

Disease related characteristics:

- Percentage of blast count in bone marrow at diagnosis
- IPSS and revised-IPSS for MDS
- Cytogenetic risk at diagnosis and at transplant for AML
- ELN 2017 genetic risk at diagnosis and at transplant for AML (if available)
- Disease risk index according to the previous described criteria(34)
- Disease status at time of transplant (active disease, 1st CR, > 1st CR)
- MRD status at transplant (if available)

Transplant related characteristics:

- Year of transplant
- Transplant center
- Type of donor

- Conditioning regimen (main effect)
- Graft source (peripheral blood, bone marrow)
- GVHD prophylaxis regimen
- Serotherapy (ATG/Alemtuzumab) use
- Donor/recipient CMV status
- Donor-recipient gender match

Endpoint definitions and statistical analysis:
The Chi-square or Fisher's exact test will be used for categorical variables and the Wilcoxon rank-sum or Kruskal–Wallis test for continuous variables to compare patient, disease, and transplant related characteristics between subgroups of interest. Primary outcome is PFS, while overall survival (OS), GVHD-free, relapse-free survival (GRFS), non-relapse mortality (NRM) and relapse incidence will be assessed as secondary outcomes. PFS is computed from date of AHSCT to date of disease progression, death or the last evaluation date. Patients who were alive and did not experience progression of disease at the last follow-up date will be censored. OS and NRM will be computed from date of AHCT to last known vital sign. Patients alive at the last follow-up date will be censored. GRFS is defined as the first event among acute GVHD grades 3-4, extensive chronic GVHD, relapse, and death.(35) Those patients who did not experience an event will be censored. The Kaplan-Meier method will be used to estimate all survival measures. Differences in survival between different conditioning regimen groups will be assessed using the log-rank test. Associations between survival outcomes (PFS, OS and GRFS) and potential prognostic factors will be determined using univariable and multivariable Cox proportional hazards regression models. All variables of interest will be tested for the proportional hazard assumption and interaction terms.
The cumulative incidence function with the competing risks method will be used to estimate the endpoints of relapse, NRM, acute GVHD, and chronic GVHD. The competing risk will be included for NRM is relapse, and the competing risk included for relapse is death. For GVHD, the competing risks included are relapse and death. Differences in cumulative incidence between subgroups will be assessed using Fine and Gray's test.(36) The univariable and multivariable Fine and Gray's subdistribution hazard regression will be used to assess the impact of variables of interest on cumulative incidence outcomes.
The propensity score adjusted analysis will be used, in order to adjust for any potential bias derived from imbalanced pre-transplant factors between different conditioning regimen types. Initially, logistic regression model will be used for propensity score calculation from baseline patient characteristics associated with decision on choosing type of conditioning regimen. The following independent pre-transplant factors will be included in the binary logistic regression model for calculation of propensity score: age, remission status, diagnosis, disease risk index(34), performance status, stem cell source, transplant center and year of transplant. The propensity score will be used as an adjusted variable in a univariable and multivariable regression model to calculate the true impact of type of conditioning regimen on outcomes of interest. A P value of less than 0.05 is considered for statistical significance.
We would be happy to do the analysis to save statistician time for CIBMTR.
Non-CIBMTR Data Source: If not enough patients will be in the CIBMTR database, a combined proposal with MDACC data and/or EBMT data will be considered.

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Characteristics of patient over 60 years old receiving first allo-HCT for AML/MDS with RIC/NMA between 2008-2018, as reported to the CIBMTR

Characteristic	FM100*	Other regimen
No. of patients	89	3560
No. of centers	22	161
Age at HCT		
Median (min-max)	68.15 (60.21-76.67)	66.8 (60.01-83.42)
60-69	65 (73)	2798 (78.6)
≥70	24 (27)	762 (21.4)
Gender		
Male	66 (74.2)	2282 (64.1)
Female	23 (25.8)	1278 (35.9)
Disease		
AML	31 (34.8)	1331 (37.4)
MDS	58 (65.2)	2229 (62.6)
Karnofsky score		
<90	35 (39.3)	1793 (50.4)
≥90	53 (59.6)	1726 (48.5)
Missing	1 (1.1)	41 (1.2)
HCT-CI		
0	15 (16.9)	567 (15.9)
1	17 (19.1)	432 (12.1)
2	11 (12.4)	440 (12.4)
3+	44 (49.4)	1978 (55.6)
TBD, review needed for history of malignancies	0	3 (0.1)
TBD, inconsistencies between parent and sub-questions	2 (2.2)	102 (2.9)
NA, f2400 (pre-TED) not completed	0	17 (0.5)
Missing	0	21 (0.6)
Donor type		
HLA-identical sibling	34 (38.2)	1011 (28.4)
Other related	3 (3.4)	685 (19.2)
Well-matched unrelated (8/8)	40 (44.9)	1500 (42.1)
Partially-matched unrelated (7/8)	12 (13.5)	280 (7.9)
Mis-matched unrelated (≤ 6/8)	0	20 (0.6)
Multi-donor	0	21 (0.6)
Unrelated (matching TBD)	0	40 (1.1)
Missing	0	3 (0.1)
Graft type		
Bone marrow	7 (7.9)	425 (11.9)
Peripheral blood	82 (92.1)	3135 (88.1)

Characteristic	FM100*	Other regimen
Conditioning regimen		
RIC		
TBI/Cy/Flu	0	30 (0.8)
TBI/VP	0	1 (0)
TBI/Mel	0	77 (2.2)
TBI/Flu	0	291 (8.2)
TBI/other(s)	0	21 (0.6)
Flu/Bu	0	1298 (36.5)
Flu/Mel	89	968 (27.2)
BEAM	0	1 (0)
Other(s)	0	1 (0)
NMA		
TBI/Cy/Flu	0	568 (16)
TBI/Flu	0	167 (4.7)
Cy/Flu	0	60 (1.7)
Cy alone	0	2 (0.1)
TLI	0	73 (2.1)
Other(s)	0	2 (0.1)
GVHD prophylaxis		
No GVHD prophylaxis	2 (2.2)	46 (1.3)
Ex-vivo T-cell depletion	0	12 (0.3)
CD34 selection	0	7 (0.2)
Post-CY + other(s)	5 (5.6)	640 (18)
Post-CY alone	0	2 (0.1)
TAC + MMF ± other(s) (except post-CY)	16 (18)	716 (20.1)
TAC + MTX ± other(s) (except MMF, post-CY)	50 (56.2)	1212 (34)
TAC + other(s) (except MMF, MTX, post-CY)	5 (5.6)	230 (6.5)
TAC alone	1 (1.1)	93 (2.6)
CSA + MMF ± other(s) (except post-CY)	7 (7.9)	348 (9.8)
CSA + MTX ± other(s) (except MMF, post-CY)	2 (2.2)	148 (4.2)
CSA + other(s) (except MMF, MTX, post-CY)	0	15 (0.4)
CSA alone	1 (1.1)	19 (0.5)
Other(s)	0	50 (1.4)
Missing	0	22 (0.6)
Year of HCT		
2008	3 (3.4)	247 (6.9)
2009	4 (4.5)	194 (5.4)
2010	2 (2.2)	48 (1.3)
2011	1 (1.1)	185 (5.2)
2012	7 (7.9)	241 (6.8)
2013	9 (10.1)	401 (11.3)

Characteristic	FM100*	Other regimen
2014	11 (12.4)	460 (12.9)
2015	18 (20.2)	493 (13.8)
2016	12 (13.5)	449 (12.6)
2017	12 (13.5)	450 (12.6)
2018	10 (11.2)	392 (11)
Median follow-up of survivors (range), months	47.63 (5.99-76.68)	59.84 (2.07-126.12)

* Melphalan dose: 90-110 mg/m^2, based on adjusted body weight

Combined Proposal: 1909-02/1910-22/1911-40

Title:
Outcomes of second allogeneic hematopoietic stem cell transplantation for patients with relapsed acute leukemia in the modern era

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Research hypothesis:
Outcomes for second allogeneic hematopoietic stem cell transplantation (allo-HCT2) in patients with relapsed acute leukemia may be improved in the modern era with availability of alternative donors and maintenance treatments.

Specific aims:
- Primary aim is to assess the outcomes of adult patients who underwent allo-HCT2 for relapsed acute leukemia / myelodysplastic syndrome and to identify the risk factors for associated with survival
- Secondary aim is to establish the impact of using haploidentical donors for allo-HCT2 in patients with relapsed acute leukemia after allo-HCT1.
- Primary outcome is overall survival (OS)
- Secondary outcomes include relapse incidence (RI), non-relapse mortality (NRM), disease free survival (DFS) and incidence of acute or chronic graft-versus-host disease (GVHD).
- Subset analyses of the above outcomes in 1) novel haplotype vs. non-novel haplotype at allo-HCT2, 2) Haploidentical donor vs. MUD vs. MRD at HCT2, and 3) same vs. different donor at HCT2.

Scientific impact:
Disease relapse is the leading cause of treatment failure after an allo-HCT1 for acute leukemia and the outcomes following relapse after allo-HCT1 is poor [1, 2]. Allo-HCT2 is a potentially curative option in a subset of patients [3]. However, given the high non-relapse mortality and the relapse following allo-HCT2, it is important to determine the predictive factors associated with outcomes. We believe this study, by further identifying the predictive factors for outcomes, would help clinicians to assist in the clinical decision of whether to perform an allo-HCT2 in patients with relapsed acute leukemia after allo-HCT1 in the modern era.

Scientific justification:
Allo-HCT is an effective treatment for acute leukemia. Although patients can achieve long term disease-free remissions after allo-HCT, disease relapse remains a major cause of failure[4]. Relapse after allo-

HCT generally leads to poor survival with only 10-20% of patients surviving beyond two years [5]. A second allo-HCT can achieve durable remissions in a subset of patients with relapsed leukemia [1, 6]. It is important to determine the predictive factors associated with outcomes of allo-HCT2 given the risk of relapse and high non-relapse mortality.

There are published reports on outcomes after allo-HCT2 in patients with relapsed leukemia. In the earlier CIBMTR analysis time from allo-HCT1 to relapse, age and conditioning intensity identified as important determinants of outcomes. This analysis was limited to patients who received allo-HCT2 from HLA-identical siblings between 1990 and 2010 [7]. In a more recent CIBMTR analysis, the study concluded that remission status before allo-HCT2 as the most important determinant of outcome. The analysis was limited to children and young adolescents [8]. The European Society for Blood and Marrow Transplantation (EBMT) has recently conducted a retrospective non-planned subgroup analysis of European acute lymphoblastic leukemia (ALL) patients who received a second allo-HCT for relapsed ALL between 2000 and 2017. They identified age, time from allo-HCT1 to relapse, conditioning for allo-HCT1, Karnofsky score at allo-HCT2 and donor for allo-HCT-2 as prognostic factors for survival. However, the analysis was limited to ALL patients with a history of allo-HCT1 in first CR and allo-HCT2 from a matched sibling donor [9].

Over the last decade, donor choice has evolved with the introduction of HLA-haploidentical donors and outcomes following transplantation improved with the utility of maintenance options. Furthermore recent data showed evidence of benefit of using HLA-haploidentical donors in patients with relapsed leukemia after a first allo-HCT [10, 11]. Therefore identifying prognostic factors associated with relapse and leukemia free survival in the modern era would provide important information.

Patient eligibility population:

Inclusion criteria:

- Adult patients (age ≥18 years old) at time of allo-HCT2 between the years of 2000-2018 (in order to allow at least 1-year follow-up)
- Patients who received allo-HCT1 for acute myeloid leukemia (AML), myelodysplastic syndrome or acute lymphoid leukemia (ALL), and allo-HCT2 for relapsed disease

Exclusion criteria:

- Patients who did not consent to research
- Patients who received transplants from cord blood donors
- More than one previous allogenic stem cell transplant;
- Haploidentical transplantation with any other GVHD prophylaxis except for posttransplant cyclophosphamide;

Data requirements:

We will collect data from standard CIBMTR forms including the following:

- Recipient baseline data
- Disease, donor and transplant related variables for allo-HCT1 and allo-HCT2
- Outcome data for allo-HCT1 and allo-HCT2

Sample requirements:

Not applicable

Study design:

This will be a retrospective observational study of patients reported to CIBMTR with completed follow-up. Eligibility criteria entailed adults (age ≥18 years) who received an allo-HCT2 for relapsed acute leukemia and myelodysplastic syndrome (MDS) (morphologic, cytogenetic and molecular) after their allo-HCT1 for ALL, AML or MDS. Recipients of myeloablative and reduced intensity/non-myeloablative conditioning regimens planned to be included. All allo-HCT2's should be performed between 2000 and 2018.

The primary end point is overall survival (OS). Secondary end points included relapse incidence (RI), non-relapse mortality (NRM), disease free survival (DFS) and incidence of acute and chronic graft-versus host disease (GVHD). DFS is defined as survival without evidence of relapse or progression and RI is defined as leukemia recurrence. As the exact date of progression for patients who received the allo-HCT2 in the active disease and never achieved a complete remission (CR) will not be available, DFS and RI are to be evaluated only in patients known to be in CR. OS is defined as time from second allo-HCT to death, regardless of cause. NRM is defined as death without evidence of relapse or progression. All surviving patients should be censored at the time of last contact. Results will be reported for all patients overall and as subgroups (AML/MDS vs ALL). Our secondary aim is to establish the impact of using haploidentical donors for allo-HCT2. Since most of the haploidentical transplants are after 2013, results will also be reported by allo-HCT2 years (Allo-HCT2 between 2000-2006 vs 2007-2012 vs 2013-2018). Probabilities of OS and DFS (patients in CR) planned to be calculated using the Kaplan-Meier method.

<u>Variables need to be included for the analysis as follows:</u>

- Age at allo-HCT1
- Gender
- Remission status at allo-HCT1 (remission versus active disease)
- Donor source at allo-HCT1 (related vs unrelated vs haploidentical)
- Cell source at allo-HCT1 (bone marrow vs peripheral blood)
- Donor gender at allo-HCT1
- Performance score, Karnofsky / HCT-CI at allo-HCT1
- Conditioning regimen used for allo-HCT1 (myeloablative vs reduced intensity / non-myeloablative)
- Graft versus host disease (GVHD) prophylaxis used for allo-HCT1
- Maintenance treatment following allo-HCT1
    - If yes;
        - Date of maintenance initiation
        - Date of last maintenance
- Date of disease relapse
- Time from allo-HCT1 and relapse
- Time from relapse to allo-HCT2
- Grade 2-4 GVHD before allo-HCT2
- Chronic GVHD before allo-HCT2
- Remission status at allo-HCT2 (remission versus active disease)
- Donor source at allo-HCT2 (related vs unrelated vs haploidentical)
- Same vs different donor for first and second allo-HCT
- Cell source at allo-HCT2 (bone marrow vs peripheral blood)
- Donor gender at allo-HCT2
- Performance score, Karnofsky / HCT-CI at allo-HCT2
- Conditioning regimen used for allo-HCT2 (myeloablative vs reduced intensity / non-myeloablative)
- T-cell depletion at allo-HCT2: ATG vs. ex-vivo vs. no
- Maintenance treatment following allo-HCT2
    - If yes;

    - Date of maintenance initiation
    - Date of last maintenance
- Grade 2-4 acute GVHD following allo-HCT2
- Chronic GVHD following allo-HCT2
- Relapse (if applicable) following allo-HCT2 (yes vs no)
    - Date of relapse
- Death vs Alive
    - Date of death
    - Reason for death
- Date of last follow-up
- Disease status at last follow-up (remission vs active disease)

Non-CIBMTR data source:
Not applicable.

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Table 1. Characteristics of adult patients receiving second allo-HCT for relapsed AML, ALL, or MDS between 2000-2018 at time of first allo-HCT

Characteristic	N (%)
No. of patients	790
No. of centers	152
Age at HCT	
Median (min-max)	45.44 (13.66-74.01)
10-17	24 (3)
18-29	163 (20.6)
30-39	131 (16.6)
40-49	168 (21.3)
50-59	191 (24.2)
60-69	101 (12.8)
≥70	12 (1.5)
Gender	
Male	424 (53.7)
Female	366 (46.3)
Disease	
AML	511 (64.7)
ALL	145 (18.4)
MDS	134 (17)
Karnofsky score	
<90	246 (31.1)
≥90	495 (62.7)
Missing	49 (6.2)
HCT-CI	
0	94 (11.9)
1	41 (5.2)
2	42 (5.3)
3+	101 (12.8)
TBD, inconsistencies between parent and sub-questions	16 (2)
NA, f2400 (pre-TED) not completed	482 (61)
Missing	14 (1.8)
Donor type	
HLA-identical sibling	337 (42.7)
Other relative	10 (1.3)
Haploidentical	23 (2.9)
Well-matched unrelated (8/8)	304 (38.5)
Partially-matched unrelated (7/8)	83 (10.5)
Mis-matched unrelated (≤6/8)	22 (2.8)
Multi-donor	2 (0.3)

Characteristic	N (%)
Unrelated (matching TBD)	9 (1.1)
Graft type	
Bone marrow	238 (30.1)
Peripheral blood	552 (69.9)
GVHD prophylaxis	
No GVHD prophylaxis	4 (0.5)
Ex-vivo T-cell depletion	16 (2)
CD34 selection	23 (2.9)
Post-CY + other(s)	32 (4.1)
TAC + MMF ± other(s) (except post-CY)	76 (9.6)
TAC + MTX ± other(s) (except MMF, post-CY)	305 (38.6)
TAC + other(s) (except MMF, MTX, post-CY)	27 (3.4)
TAC alone	30 (3.8)
CSA + MMF ± other(s) (except post-CY)	35 (4.4)
CSA + MTX ± other(s) (except MMF, post-CY)	175 (22.2)
CSA + other(s) (except MMF, MTX, post-CY)	16 (2)
CSA alone	23 (2.9)
Other(s)	4 (0.5)
Missing	24 (3)
Conditioning regimen intensity	
MAC	514 (65.1)
RIC	182 (23)
NMA	52 (6.6)
TBD	14 (1.8)
Missing	28 (3.5)
Year of HCT	
1992	1 (0.1)
1993	2 (0.3)
1994	1 (0.1)
1995	1 (0.1)
1996	5 (0.6)
1997	1 (0.1)
1998	12 (1.5)
1999	41 (5.2)
2000	42 (5.3)
2001	41 (5.2)
2002	58 (7.3)
2003	47 (5.9)
2004	52 (6.6)
2005	62 (7.8)
2006	68 (8.6)

Characteristic	N (%)
2007	57 (7.2)
2008	50 (6.3)
2009	50 (6.3)
2010	32 (4.1)
2011	16 (2)
2012	17 (2.2)
2013	40 (5.1)
2014	29 (3.7)
2015	30 (3.8)
2016	19 (2.4)
2017	12 (1.5)
2018	4 (0.5)
Median follow-up of survivors (range), months	136.58 (5.3-250.76)

Table 2. Characteristics of adult patients receiving second allo-HCT for relapsed AML, ALL, or MDS between 2000-2018 at time of second allo-HCT

Characteristic	N (%)
No. of patients	790
No. of centers	152
Age at HCT	
Median (min-max)	47 (18.12-75.72)
18-29	152 (19.2)
30-39	130 (16.5)
40-49	161 (20.4)
50-59	197 (24.9)
60-69	130 (16.5)
≥70	20 (2.5)
Gender	
Male	424 (53.7)
Female	366 (46.3)
Disease	
AML	544 (68.9)
ALL	144 (18.2)
MDS	102 (12.9)
Karnofsky score	
<90	393 (49.7)
≥90	311 (39.4)
Missing	86 (10.9)
HCT-CI	
0	39 (4.9)
1	25 (3.2)
2	27 (3.4)
3+	111 (14.1)
TBD, inconsistencies between parent and sub-questions	3 (0.4)
NA, f2400 (pre-TED) not completed	580 (73.4)
Missing	5 (0.6)
Donor type	
HLA-identical sibling	203 (25.7)
Other relative	21 (2.7)
Haploidentical	42 (5.3)
Well-matched unrelated (8/8)	244 (30.9)
Partially-matched unrelated (7/8)	69 (8.7)
Mis-matched unrelated (≤6/8)	10 (1.3)
Multi-donor	5 (0.6)
Unrelated (matching TBD)	137 (17.3)

Characteristic	N (%)
Missing	59 (7.5)
Graft type	
Bone marrow	67 (8.5)
Peripheral blood	723 (91.5)
GVHD prophylaxis	
No GVHD prophylaxis	133 (16.8)
Ex-vivo T-cell depletion	9 (1.1)
CD34 selection	13 (1.6)
Post-CY + other(s)	30 (3.8)
TAC + MMF ± other(s) (except post-CY)	93 (11.8)
TAC + MTX ± other(s) (except MMF, post-CY)	182 (23)
TAC + other(s) (except MMF, MTX, post-CY)	38 (4.8)
TAC alone	47 (5.9)
CSA + MMF ± other(s) (except post-CY)	37 (4.7)
CSA + MTX ± other(s) (except MMF, post-CY)	52 (6.6)
CSA + other(s) (except MMF, MTX, post-CY)	20 (2.5)
CSA alone	33 (4.2)
Other(s)	37 (4.7)
Missing	66 (8.4)
Conditioning regimen intensity	
MAC	200 (25.3)
RIC	214 (27.1)
NMA	54 (6.8)
TBD	144 (18.2)
Missing	178 (22.5)
Year of HCT	
2000	40 (5.1)
2001	29 (3.7)
2002	55 (7)
2003	50 (6.3)
2004	36 (4.6)
2005	46 (5.8)
2006	57 (7.2)
2007	54 (6.8)
2008	46 (5.8)
2009	53 (6.7)
2010	48 (6.1)
2011	40 (5.1)
2012	35 (4.4)
2013	19 (2.4)
2014	39 (4.9)

Characteristic	N (%)
2015	34 (4.3)
2016	38 (4.8)
2017	35 (4.4)
2018	36 (4.6)
Median follow-up of survivors (range), months	73.45 (0.03-194.57)

Proposal: 1910-20

Title:
Evaluating Outcomes of Allogeneic Hematopoietic Cell Transplantation in T-cell Acute Lymphoblastic Leukemia

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Hypothesis:
Allogeneic hematopoietic cell transplantation (allo-HCT) is associated with durable remissions in patients with T-cell acute lymphoblastic leukemia (T-ALL)

Study objectives:
- To describe clinical outcomes of patients with T-cell acute lymphoblastic leukemia (T-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
- To identify the impact of patient-, disease-, and transplant-related factors on the outcomes of PFS, OS, relapse and NRM for allogeneic hematopoietic cell transplantation.

Scientific justification:
T-ALL is a rare aggressive malignant neoplasm accounting for nearly 20% of all ALL and is more common in adults in contrast to its counterpart B-cell ALL(B-ALL) (1). Our understanding of T-ALL remains relatively limited secondary to its rarity and underlying heterogeneity (2).Prognosis for adult patients with ALL remain poor with the exception of improvement in outcomes seen in recent years for adolescents and young adults (AYAs) treated with pediatric-intensive chemotherapy regimens(3,4).
Allo-HCT is frequently considered in adult patients with T-ALL given the poor prognosis and high risk of relapse. A recent retrospective multicenter study reported outcomes for 208 patients with T-ALL with 5-yr OS at 34% with corresponding NRM and RR at 27% and 41% respectively. Factors adversely impacting outcomes were age greater than 35, lack of complete remission (CR) at the time of allo-HCT whereas the use of TBI positively impacted outcomes (5). Another study reported outcomes of allo-HCT in 53 patients with T-ALL where patients who underwent allo-HCT in CR1 had improved 5-yr OS at 53.5% compared to 31.9% in patients who underwent allo-HCT in CR $\geq$2 (6). Similar observation was made in another study where 3-yr OS was reported at 62% in patients undergoing allo-HCT in CR1 versus 24% for those transplanted in CR$\geq$2(7). A larger series of 886 patients reported from the EBMT registry reported outcomes for allo-HCT after myeloablative conditioning in T-ALL with 4-yr OS and DFS at 58% and 55% respectively. Advanced age adversely affected outcomes whereas the use of TBI was again seen to have positively impacted outcomes (8).
No randomized controlled trials (RCTs) exist comparing the efficacy of allo-HCT to chemotherapy alone. Due to the rare nature of T-cell ALL, it is unlikely that a RCT will ever be conducted. Also, it is becoming a standard practice to offer an allo-HCT early in their treatment course. We believe that there is an unmet need for larger observational studies to better inform and guide clinical decision making regarding the

role of allo-HCT in T-cell ALL. The most feasible approach to evaluate transplant outcomes in these rare presentations is by using registry data. Thus we propose to utilize the Center for International Blood and Marrow Transplantation Research (CIBMTR) database to evaluate outcomes of allo- HCT recipients with T-ALL.

Patient eligibility:

Inclusion criteria:

- Diagnosis of T-Acute lymphoblastic leukemia of or T-Lymphoblastic leukemia
- First Allo- HCT between 2000-2017

Exclusion criteria:

- Autologous HCT recipient
- Allo-HCT for any other etiology aside from T-ALL

Outcomes:

Primary outcomes:

- OS: Time to death. Death from any cause will be considered an event. Surviving patients will be censored at the time of last follow up.

Secondary outcomes:

- PFS: Survival following HCT without relapse or progression. Relapse or progression of disease are considered events
- Relapse/progression: Progressive disease or recurrences of disease would be counted as events. Treatment related death, defined as death without relapse or progression, is the competing event. Those who survive without recurrence or progression would be censored at the time of last contact
- NRM: Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse and progression are competing events.
- Incidence of acute and chronic GVHD (Allo-HCT only): Cumulative incidence of grade II-IV and grade III-IV acute GVHD per CIBMTR consensus criteria(9), with death as competing risk. Cumulative incidence of chronic GVHD by 2014 NIH consensus criteria (10), with death as competing risk.
- Cause of death: Descriptive only

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
- Induction therapy: Hyper CVAD induction vs pediatric style induction vs other induction strategies
- Pre-transplant exposure to nelarabine (yes/no)
- BM involvement: (yes/no)

- Cytogenetic abnormalities at diagnosis

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

Study design:

A retrospective multicenter study will be conducted utilizing CIBMTR dataset. Patients will be eligible if they satisfied the criteria detailed in the "Patient Eligibility" section. Patients will be stratified by conditioning intensity (myeloablative vs. reduced intensity) according to established definitions (11) such that subsequent analysis will compare these approaches and their effects on HCT outcomes. Descriptive tables of patient, disease-, and transplant-related factors will be created. The tables will list median and range for continuous variables and proportions for categorical variables. Cumulative incidence of chronic GVHD, relapse/progression, and NRM will be calculated while accounting for competing events. Probabilities of OS will be calculated using the Kaplan-Meier estimator. If Sample size and number of events allow, multivariate analysis will be performed using Cox proportional hazards models for outcomes for chronic GVHD, relapse/progression, NRM, PFS, and OS and logistic regression for acute GVHD. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. The proportional hazards assumption will be checked for the Cox model. If violated, it will be added as time-dependent covariates.

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Characteristics of patients receiving first allo-HCT for T-cell ALL between 2000-2017, as reported to the CIBMTR

Characteristic	N (%)
No. of patients	1144
No. of centers	227
Age at HCT	
Median (min-max)	21.76 (1.21-78.58)
<10	224 (19.6)
10-17	228 (19.9)
18-29	326 (28.5)
30-39	160 (14)
40-49	124 (10.8)
50-59	53 (4.6)
60-69	26 (2.3)
≥70	3 (0.3)
Gender	
Male	835 (73)
Female	308 (26.9)
Missing	1 (0.1)
Disease status prior to HCT	
Primary induction failure	49 (4.3)
CR1	489 (42.7)
CR2	417 (36.5)
≥CR3	35 (3.1)
Relapse	117 (10.2)
Missing	37 (3.2)
Karnofsky score	
<90	301 (26.3)
≥90	778 (68)
Missing	65 (5.7)
HCT-CI	
0	223 (19.5)
1	68 (5.9)
2	53 (4.6)
3+	130 (11.4)
TBD, inconsistencies between parent and sub-questions	22 (1.9)
NA, f2400 (pre-TED) not completed	638 (55.8)
Missing	10 (0.9)
Donor type	
HLA-identical sibling	333 (29.1)
Other related	76 (6.6)

Characteristic	N (%)
Well-matched unrelated (8/8)	286 (25)
Partially-matched unrelated (7/8)	128 (11.2)
Mis-matched unrelated (≤6/8)	50 (4.4)
Unrelated (matching TBD)	15 (1.3)
Cord blood	256 (22.4)
Graft type	
Bone marrow	349 (30.5)
Peripheral blood	539 (47.1)
Cord blood	255 (22.3)
UCB + other	1 (0.1)
Conditioning regimen intensity	
MAC	1008 (88.1)
RIC	59 (5.2)
NMA	31 (2.7)
TBD	18 (1.6)
Missing	28 (2.4)
GVHD prophylaxis	
No GVHD prophylaxis	11 (1)
Ex-vivo T-cell depletion	61 (5.3)
CD34 selection	18 (1.6)
Post-CY + other(s)	42 (3.7)
TAC + MMF ± other(s) (except post-CY)	97 (8.5)
TAC + MTX ± other(s) (except MMF, post-CY)	250 (21.9)
TAC + other(s) (except MMF, MTX, post-CY)	42 (3.7)
TAC alone	18 (1.6)
CSA + MMF ± other(s) (except post-CY)	130 (11.4)
CSA + MTX ± other(s) (except MMF, post-CY)	344 (30.1)
CSA + other(s) (except MMF, MTX, post-CY)	66 (5.8)
CSA alone	27 (2.4)
Other(s)	15 (1.3)
Missing	23 (2)
Year of HCT	
2000	64 (5.6)
2001	76 (6.6)
2002	83 (7.3)
2003	70 (6.1)
2004	75 (6.6)
2005	102 (8.9)
2006	99 (8.7)
2007	80 (7)

Characteristic	N (%)
2008	83 (7.3)
2009	56 (4.9)
2010	44 (3.8)
2011	39 (3.4)
2012	43 (3.8)
2013	42 (3.7)
2014	60 (5.2)
2015	46 (4)
2016	40 (3.5)
2017	42 (3.7)
Median follow-up of survivors (range), months	75.53 (1.55-216.25)

Combined Proposal: 1911-18/1911-83/1911-191/1911-224

Title:
Acute Myeloid Leukemia (AML) with chromosome 17 abnormalities with or without *TP53* abnormalities and outcomes after hematopoietic stem cell transplantation

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Hypothesis:
The cytogenetic and genomic profile of an individual patient's AML at diagnosis predicts outcomes to initial therapy and long-term survival. Chromosome 17 abnormalities especially loss of the 17p region and *TP53* gene mutations result in marked chemo-refractoriness and very low rate of cure for patients treated with conventional chemotherapy. Even with an allogeneic stem cell transplantation (HCT) the outcomes remain poor with a dismal 24% estimated two-year leukemia free survival (LFS)[1]. We hypothesize that use of myeloablative conditioning improves overall survival (OS) for patients transplanted with chromosome 17 abnormalities with or without *TP53* mutations compared to the use of reduced intensity conditioning. Our aim is to identify patient-/disease-/transplant-related variables that can be predictors of *TP53*-mutated AML outcomes and find characteristics that are more likely to yield durable remission of *TP53*-mutated AML after allo-HCT. We also aim to assess the measurable disease prior to transplant and determine its impact on post-allo-HCT outcomes.

Specific aims:
- Determine the incidence of chromosome 17 abnormalities including 17p loss and other chromosome 17 abnormalities in patients with AML reported to CIBMTR
- To determine the effect of myeloablative conditioning vs. reduced-intensity conditioning for patients with abnormal *17p (TP53)*-related AML on OS, CIR and NRM and identify patient-, disease- and transplant-related characteristics or factors that might be predictive of improved LFS and OS in TP53-mutated AML
- To evaluate the effect of the disease status prior to transplant on transplantation outcomes in

abnormal *17p (TP53)*-related AML

- To identify the subgroup of patients with abnormal *17p* (*TP53*)-related AML who most benefit from an allogeneic stem cell transplantation and develop a prognostic risk scoring system that is predictive of outcome following allo-HCT for this patient subgroup.

Scientific impact:

Transplant centers across the United States use different criteria when selecting patients with chromosome 17 abnormalities for an allo-HCT. Despite poor outcomes mainly related to high cumulative incidence of relapse, allo-HCT remains the only potential curative option for patients that achieve an initial response to induction treatment, and the question of optimal transplant strategy remains at the forefront of active discussions within the transplant community. For patients with *TP53*-mutated AML, development of a prognostic scoring system predictive of transplant outcome would enhance the identification and stratification of patients into prognostic subgroups and ultimately help guide their optimal treatment. In addition, there is currently no clear understanding of the role of the intensity of the conditioning, donor selection and role of post-transplant strategies for AML patients with *17p* abnormalities and *TP53* mutations. In this context, the use of large registry data constitutes an essential means of identifying subsets of patients that achieve the most benefit from an allo-HCT. We are proposing to evaluate all AML patients with *17p* abnormalities including cytogenetic data and molecular data where available.

Scientific justification:

Background:

Allogeneic stem cell transplantation (allo-HCT) is now the standard approach recommended for patients with high risk acute myeloid leukemia (AML) in complete remission(CR)[2,3]. Adverse-risk AML is mainly defined by the presence of poor-risk cytogenetic abnormalities and/ or mutational abnormalities at diagnosis[4-7]. In general, conventional post-remission high-dose chemotherapy (-consolidation therapy) is not sufficient to eradicate chemotherapy- resistant, leukemia initiating cells of high-risk AML[8], and only the potent graft-versus-leukemia affect arising after allo-HCT may overcome the poor prognosis of these high-risk AML subtypes[9]. Indeed, several reports have confirmed the significant advantage of allo-HCT in high-risk AML, especially when performed early in the course of the disease[10-12]. Among the heterogeneous group of high-risk AML, prognosis can be further stratified based on specific genetic abnormalities, and the potential benefit of allo-HCT differs between these diverse AML subtypes[13-17]. It is still questionable if distinct genetic abnormalities like complex karyotype (CK) and monosomal karyotype (MK) which independently predict inferior AML patient overall survival, will similarly respond favorably to allo-HCT[18].

The frequency of chromosome 17 abnormalities in AML varies between 5-8% in de-novo AML and is close to 40% among patients with therapy related AML[19]. *TP53* is located in the 17p13 chromosomal region and is one of the major tumor suppressor genes, often inactivated by deletion and/or mutation in many tumors[20]. In AML, *TP53* inactivation is associated with a significantly lower response to intensive chemotherapy, translating into poorer outcome[21]. Although *TP53* mutations/deletions show a high correlation with complex karyotype in AML[22-24], *TP53* mutations and/or loss have emerged as strong and independent prognostic markers of very poor outcomes regardless of associated cytogenetic abnormalities[25,26]. Thus, long-term disease control is observed in < 5% of patients harboring *TP53* mutations with conventional chemotherapy[26,27]. Molecular screening for *TP53* mutations is not routinely performed, and loss or disruption of 17p13 is usually identified by karyotyping and /or FISH analysis[28]. In this context, the potential capability of allo-SCT to overcome the dismal prognosis of abnormal (17p) AML is of great interest. An early report described the outcome of 47 allografted patients with 17p deletion and showed no difference in outcomes compared to non-transplanted patients, suggesting a

lack of sensitivity of this entity to the graft-versus-leukemia effect[29]. The detrimental effect of abnormal (17p) on allo-SCT outcomes was confirmed in another report where an event-free survival (EFS) of only 11% was reported due to a very high incidence of relapse[18]. More recently, published data from 201 patients with abnormal (17p) AML transplanted in the past decade, showed an EFS of only 12%, with only a slightly better outcome among the 84 patients allografted in first CR (3-year EFS 18 vs. 7%; $p < 0.001$)[30]. A recently published European Society of Blood and Marrow Transplantation (EBMT) of 139 patients who underwent an allogeneic transplant in first CR showed a 2-year OS of 28% and LFS of 24%. The 2 year non relapse mortality (NRM) was 15% and 2- year relapse incidence (RI) was 61%[1]. This wide variability in survival outcomes needs further investigation to better define post allo-HCT in this subset of patients.

Besides chromosome 17p deletions, chromosome 17 abnormalities also include translocations, monosomy 17 and trisomy 17, which may affect alterations in the *TP53* allelic state and critically alter the *TP53* pathway[31,32]. Additionally, with current NGS testing it is evident that not all *TP53* mutations are the same and may vary significantly within the same gene, e.g. point mutations vs. frame- shift mutations. The specific gene mutations involving TP53 may have a bearing on the response to treatment as well as on relapse and OS.

Importance:

The above information suggests poor overall outcome in patients with chromosome 17 abnormalities with or without chromosomal loss or mutated *TP53*. We plan to explore the incidence and composition of concomitant *TP53* mutations in addition to chromosome 17 abnormalities that could contribute to poor outcomes. In this retrospective data collection and analysis, we would like to evaluate the occurrence and impact of chromosome 17 abnormalities and *TP53* mutations in de-novo and secondary AML patients as well as their treatment outcomes with allo-HCT. We hope that exploration of this data could help guide optimal treatment for this subset of unfortunate patients.

Study population:

Inclusion:

- Subjects age 18 or older
- Diagnosis of de novo or secondary AML with any chromosome 17 abnormality.
- Allo –HCT between 2007-2018 for AML with chromosome 17 abnormalities with or without TP53 mutation
- All allo-HCT types (MRD, MUD, MMUD, UCB, Haplo-identical, Haplo/UCB), and any stem cell product type

Exclusion:

- Patients who have had a prior allo- HCT
- Patients with chromosome 17 abnormalities involving the long arm (‘q’arm)

Data requirements:

Data will primarily come from CIBMTR data collections forms.

Baseline patient-, disease-, and transplant- related data and characteristics. This will also include post - HCT data and case report information form at day 100, 6 months, 1 year.

Measures:

Data will be analyzed systematically. Key variables from the database include:

Patient specific variables:

- Age: in decades (<20, 21-30, 31-40,41-50,51-60, 61-70 and >71)
- Gender: Male vs. Female
- Race: White, Hispanic, Black, Asian, others
- Performance status: KPS/ ECOG at transplant (<90 or >90 / 0 or >1)
- HCT-CI

Disease related:

- Type of AML- denovo vs. secondary
- Cause of secondary AML- evolved from MDS/MPN/ prior chemotherapy/ exposure to RT/ exposure to chemicals
- Cytogenetics: chromosome 17 abnormality, isochromosome i(17)(q10), deletion del(17)(pvar(variable)), unbalanced translocations der(var)t(var;17)(var;qvar), -17 or der(var)t(var;17)(var;pvar), -17 or der(17)t(17;var)(pvar;var), balanced translocation t(12;17)(p11;p13); additive material: add(17)(pvar), dicentric chromosome dic(var;17)(var;pvar), ring chromosome r(17)(pvarqvar).
- FISH for TP 53 mutations: positive/ negative
- Other molecular markers: Any TP53 mutation by NGS regardless of VAF or number of mutations that is available
- Other associated cytogenetic abnormalities including: complex karyotype (CK), monosomal karyotype (MK), presence of monosomy 7, presence of loss of 5q and /or presence of inversion of chromosome 3 (inv (3)).
- Molecular abnormalities/ NGS at the time of diagnosis and if available prior to transplant.
- Cytogenetics reported- conventional vs. FISH

Treatment prior to transplant:

- Induction chemotherapy (conventional- “7+3”) or others- including HMA etc
- Number of induction chemotherapies (>1) to achieve CR1/ Cri
- Disease status at the time of Allo-HCT (CR1 vs. CR2 vs. induction failure/active relapse)
- WBC at diagnosis (≤10 vs. 10-100 vs. ≥100 x109/L)
- Cytogenetic abnormalities at diagnosis: poor vs. intermediate vs. favourable
- Presence of extramedullary disease
- Cytogenetic remission at the time of transplant: yes/ no
- FISH/ NGS (if available) at the time of transplant
- Time of diagnosis to complete remission to allo-HCT
- Consolidation treatment: received / not received; type of chemotherapy and number of treatments
- MRD status prior to transplant: Positive vs. Negative

Transplant related:

- Transplant type: related, unrelated, haploidentical or cord blood.
- Donor (HLA-identical vs. other related vs. well matched unrelated [URD] (8/8) vs. partially matched URD vs. haploidentical vs. umbilical cord blood (UCB) .
- Graft type: bone marrow vs. peripheral blood
- Conditioning intensity: Myeloablative (MA) vs. Reduced intensity (RIC) vs. non myeloablative (NMA). MA conditioning will be defined as: any regimen including Total Body Irradiation (TBI) of more than 8 Gy or a busulfan dose of more than 10 mg/kg. RIC includes intermediate doses of alkylating agents such as 8-10 mg/kg busulfan, 80-140 mg/m2melphalan, 600-1200 mg/m2 cyclophosphamide or 5-10 mg/kg thiotepa, and/or low dose TBI (<3Gy).

- TBI based conditioning: Yes/ No and the dose
- T cell depletion: Yes (in vivo/ex vivo) vs. no T cell depletion
- CMV status of donor and recipient
- GvHD prophylaxis: CNI- tacrolimus/ cyclosporine, methotrexate, cyclophosphamide, MMF, ATG and others
- Engraftment information
- Cause of death

Post-transplant variables + outcomes:

- Acute GvHD: Grade 0-1 vs. 2-4 (as time dependent variable)
- Chronic graft versus host disease
- Post-transplant preemptive/maintenance therapy (azacitidine, decitabine, sorafenib or other): yes vs. no
- Relapse incidence / Relapse mortality
- Non-relapse mortality (NRM)
- Overall survival (OS)
- Event-Free Survival (EFS)
- Death and cause of death where applicable

Outcomes:

The following end points would be determined:

- Primary end point: Overall survival: based on death from any cause. Surviving patients will be censored at the time of last follow up. OS will be at 1-year post allo-HCT
- Secondary endpoints: Leukemia Free survival (LFS): defined as survival without relapse; patients alive without relapse, for 1 year
- Cumulative incidence of relapse (CIR) - Relapse free survival and time of relapse
- Non relapse mortality (NRM) defined as death without evidence of disease relapse. Relapse is a competing risk.
- Subgroup analysis based:
    - Effect of donor source: UCB vs haplo vs MRD/MUD
    - Pre-transplant disease status (CR vs not) (MRD vs not)
    - Type of AML (De Novo, MDS/AML, tAML)
    - Type of 17 abnormality
    - Any post-transplant therapy – azacytidine, decitabine, other chemotherapy, cellular therapy
- Acute and chronic GvHD free/ relapse free survival (GRFS)- defined as survival without grade 3-4 acute GvHD, extensive chronic GVHD, relapse or death. Death is a competing risk

Sample requirements:

No biologic samples are requested for this study.

Study design:

This is an observational retrospective registry data analysis of CIBMTR data between 2007 and 2018. All patients who have undergone an allo-HCT between 2007-2018 will be screened to determine whether they meet inclusion criteria for the study. All patients with chromosome 17 abnormalities and those with or without TP53 mutations will be included for analysis.

Variables found to be significantly associated with survival will be assigned a score depending on hazard ratio (HR). Ultimately, a risk score will be built which can predict outcomes.

The probabilities for OS and LFS will be calculated by the Kaplan- Meier test and relapse by the cumulative incidence estimator to accommodate competing risks. Results will be expressed with a 95% confidence interval (CI).
For all prognostic analyses continuous variables will be categorized and median will be used as a cut-off point. A Cox proportional hazards model will be used for multivariate regression. Factors associated with a p value less than 0.05 by univariate analyses will be included in the model. Results will be expressed as a HR with 95% confidence interval.
Type 1 error will be fixed at 0.05 for determination of factors associated with time to event outcomes.

We intend to work with a statistician for all analyses.

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Characteristics of adult patients receiving first allo-HCT for AML with chromosome 17 abnormality between 2007-2018, as reported to the CIBMTR

Characteristic	N (%)
No. of patients	632
No. of centers	131
Age at HCT	
Median (min-max)	55.6 (18.27-87.77)
18-29	71 (11.2)
30-39	56 (8.9)
40-49	107 (16.9)
50-59	186 (29.4)
60-69	176 (27.8)
≥70	36 (5.7)
Gender	
Male	374 (59.2)
Female	258 (40.8)
Clinical onset of AML	
De-novo	425 (67.2)
Transformed from MDS/MPS	151 (23.9)
Therapy linked	56 (8.9)
Disease status prior to HCT	
Primary induction failure	124 (19.6)
CR1	330 (52.2)
CR2	87 (13.8)
≥CR3	7 (1.1)
Relapse	64 (10.1)
Missing	20 (3.2)
TP53 mutation	
Yes	55 (8.7)
Not tested	235 (37.2)
Unknown	342 (54.1)
Karnofsky score	
<90	271 (42.9)
≥90	346 (54.7)
Missing	15 (2.4)
HCT-CI	
0	92 (14.6)
1	69 (10.9)
2	77 (12.2)
3+	309 (48.9)
TBD, inconsistencies between parent and sub-questions	21 (3.3)

Characteristic	N (%)
NA, f2400 (pre-TED) not completed	51 (8.1)
Missing	13 (2.1)
Donor type	
HLA-identical sibling	155 (24.5)
Other related	87 (13.8)
Well-matched unrelated (8/8)	219 (34.7)
Partially-matched unrelated (7/8)	64 (10.1)
Mis-matched unrelated (≤ 6/8)	6 (0.9)
Multi-donor	1 (0.2)
Unrelated (matching TBD)	7 (1.1)
Cord blood	92 (14.6)
Missing	1 (0.2)
Graft type	
Bone marrow	91 (14.4)
Peripheral blood	448 (70.9)
Cord blood	92 (14.6)
PB + other	1 (0.2)
GVHD prophylaxis	
No GVHD prophylaxis	3 (0.5)
Ex-vivo T-cell depletion	4 (0.6)
CD34 selection	17 (2.7)
Post-CY + other(s)	85 (13.4)
TAC + MMF ± other(s) (except post-CY)	114 (18)
TAC + MTX ± other(s) (except MMF, post-CY)	246 (38.9)
TAC + other(s) (except MMF, MTX, post-CY)	25 (4)
TAC alone	10 (1.6)
CSA + MMF ± other(s) (except post-CY)	66 (10.4)
CSA + MTX ± other(s) (except MMF, post-CY)	35 (5.5)
CSA + other(s) (except MMF, MTX, post-CY)	6 (0.9)
CSA alone	4 (0.6)
Other(s)	5 (0.8)
Missing	12 (1.9)
Conditioning regimen intensity	
MAC	350 (55.4)
RIC	172 (27.2)
NMA	84 (13.3)
TBD	15 (2.4)
Missing	11 (1.7)
Year of HCT	
2007	56 (8.9)
2008	81 (12.8)

Characteristic	N (%)
2009	73 (11.6)
2010	49 (7.8)
2011	18 (2.8)
2012	20 (3.2)
2013	63 (10)
2014	91 (14.4)
2015	74 (11.7)
2016	47 (7.4)
2017	35 (5.5)
2018	25 (4)
Median follow-up of survivors (range), months	72.04 (2.99-144.67)

Combined Proposal: 1911-73/1911-205

Title:
Comparison of outcomes of myeloablative versus reduced-intensity conditioning for allogeneic hematopoietic cell transplant in adults with B-cell acute lymphoblastic leukemia.

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Objectives:
In adults aged >18 years with acute lymphoblastic leukemia (ALL) in CR1 or CR2 undergoing first allogeneic hematopoietic cell transplantation (HCT):

- To compare overall survival (OS) after allogeneic HCT between the following groups: (1) myeloablative conditioning (MAC), (2) reduced intensity conditioning (RIC)
- To compare relapse-free survival (RFS), relapse, non-relapse mortality (NRM), grade 2-4 and Grade 3-4 acute graft-versus-host disease (GVHD), chronic GVHD, GVHD-free/relapse-free survival (GRFS) and causes of death rates between the groups.
- To compare primary and secondary outcomes above between RIC preparative regimens: Flu/Mel vs. FluBu2.

Scientific justification:
For adults with B-cell ALL, allogeneic HCT reduces relapse and provides a survival advantage for adults in complete remission.[1, 2] Total body irradiation (TBI)- or high-dose chemotherapy-based myeloablative conditioning (MAC) is the standard of care for younger adults with ALL undergoing HCT. In an individual patient data meta-analysis of trials that randomized adults with ALL in CR1 to MAC allogeneic HCT versus autologous HCT or chemotherapy based on availability of a matched sibling donor, a survival benefit for having a donor was seen for younger (<35 years old) patients (OR=0.79, p=0.0003) but not for older (>35 years old) patients (OR=1.01, p=0.9).[3] The difference in survival benefit according to age was driven by higher NRM among older patients receiving MAC HCT.
Reduced intensity conditioning (RIC) regimens provide an immune-mediated graft-versus-leukemia effect with less toxicity in older adults, permitting the use of allogeneic HCT in this population. A major concern with this approach however is that reducing intensity of the preparative regimen will negatively impact long-term disease control. Several analyses of RIC allogeneic HCT in ALL have attempted to address this question.[4-7] An EBMT analysis of 576 patients aged ≥45 years with ALL in complete remission who received an allogeneic HCT between 1997-2007 found increased relapse rate but lower NRM in patients who received RIC (n=127) versus MAC (n=449) regimens.[4] In multivariate analysis, conditioning intensity did not have a significant impact on OS or LFS. The CIMBTR analyzed patients aged >16 years with Ph-negative ALL in complete remission who received allo-HCT between 1995-2006 (RIC n=93; MAC n=1438) and found no effect of conditioning intensity on NRM, relapse risk, or overall survival in multivariate analysis.[5] A CIBMTR analysis of 273 adults aged 55 years or older who underwent RIC HCT for ALL between 2001-2012 reported a 3-year overall survival (OS) of 38%, with more favorable outcomes for patients transplanted in CR1 versus those in CR2 or with relapsed/refractory disease.[6] A CIBMTR analysis of adults aged 18 or older with Ph-positive ALL who received allo-HCT in CR1 between 2000-2009 compared RIC vs. MAC using matched pair analysis (RIC n=67; MAC n=130) and found no

difference in 3-year DFS and OS between groups. In multivariate analysis, factors that significantly increased relapse risk were MRD-positivity prior to HCT and failure to receive a TKI prior to HCT.[7]
Two of the most commonly used RIC regimens are Flu/Bu2, defined as a busulfan at the dose of ≤8 mg/kg p.o. or 6.4 mg/kg IV, and Flu/Mel, defined as melphalan dose <150 mg/m^2. Results of prior retrospective studies suggest that Flu/Mel may be associated with lower relapse, while Flu/Bu2 shows lower NRM, resulting in similar OS for both regimens.[8-10] However, these regimens have never been formally and directly compared, specifically in a registry study restricted to ALL patients.

Scientific impact:
The published retrospective comparative data on RIC vs. MAC HCT in ALL suggests no differences in long-term survival according to conditioning intensity. However, limitations of these studies include small numbers of patients receiving RIC compared to MAC, different age cutoffs for inclusion, and lack of information about pre-transplant MRD status in some studies. The data generated from a larger retrospective analysis would inform clinicians regarding the differential outcomes of MAC vs. RIC HCT in ALL and to determine if factors such as age, Ph status, and pre-HCT MRD status have a differential impact on HCT outcomes according to conditioning intensity. Additionally, for adults who undergo RIC HCT, data generated from this analysis would inform clinicians regarding the differential outcomes of the commonly used alkylator-based, Flu/Mel and Flu/Bu2 regimens.

Study populations:
- Adult patients ≥18 years old with ALL in first complete remission (CR1) or in second complete remission (CR2) undergoing MAC or RIC allogeneic HCT between 2000-2017 using a matched-related donor, 8/8 HLA-matched-unrelated donor, or 7/8 HLA-matched unrelated donor (haploidentical donor and cord blood transplant will be excluded).
- Adult patients ≥18 years old with ALL in first complete remission (CR1) or in second complete remission (CR2) undergoing RIC allogeneic HCT between 2000-2017 with Flu/Mel or FluBu2 conditioning using a matched-related donor, 8/8 HLA-matched-unrelated donor, or 7/8 HLA-matched unrelated donor (haploidentical donor and cord blood transplant will be excluded).

Outcomes:
Primary:
- Overall survival (OS): Time to death from any cause. Surviving patients censored at last time reported alive.

Secondary:
- Relapse-free survival (RFS): Time to leukemia relapse or death from any cause. Surviving patients censored at last time reported alive and relapse-free.
- Non-relapse mortality (NRM): Time to death without evidence of leukemia recurrence.
- Relapse: Relapse is the event. Event will be summarized by the cumulative incidence estimate with treatment related mortality as a competing risk.
- Acute GVHD: Occurrence of grade II, III and/or IV skin, gastrointestinal or liver abnormalities fulfilling the Consensus criteria of acute GVHD.
- Chronic GVHD: Occurrence of symptoms in any organ system fulfilling the diagnostic criteria of chronic GVHD.
- GVHD-free/relapse-free survival (GRFS): occurrence of grade 3-4 acute GVHD, chronic GVHD requiring systemic therapy, relapse, or death occurring in the first year post-HCT.
- Causes of death: Descriptive analysis of causes of death in each transplant/donor group.

- Minimal residual disease (MRD): To describe the impact of MRD at allogeneic HCT on outcomes (OS, RFS, relapse, NRM) in the MAC and RIC cohorts.

Data requirements:
We may request supplemental data for pre-transplant MRD status evaluation and for receipt of post-transplant TKI maintenance for Ph+ patients. Otherwise, the data required for this study is expected to be readily available from the CIBMTR.

Variables to be described:
Patient-related:
- Number of patients
- Number of centers
- Age, years: continuous/range
- Age, years: 18-29, 30-39, 40-49, 50-59, 60-69, 70+
- Gender: male, female
- Race: non-Hispanic white vs. Hispanic white vs. Black vs. Asian vs. not specified/other
- Body mass: Obese (BMI ≥30) vs. non-obese
- Karnofsky performance score: <90, ≥90
- HCT-CI: 0,1,2,3+

Disease-related:
- WBC at diagnosis, (x109/L): continuous and <30, ≥30
- Ph status: positive, negative
- Pre-transplant TKI: yes, no
- Cytogenetics risk group at diagnosis: Ph-negative/Poor [(hypodiploid (<44 chromosomes), MLL rearranged, complex (>4 abnormalities)], Ph-negative/other, Ph-positive
- Minimal residual disease (MRD) pre-transplant: positive, negative
- Extramedullary disease at diagnosis: yes, no
- CNS disease at diagnosis: yes, no
- Remission status: CR1, CR2
- Time to documentation of CR1: ≤4 weeks, >4-8 weeks, >8 weeks
- Cycles of chemotherapy prior to transplantation (for CR1): 1,2,3, >3
- Time from documentation of CR1 to transplantation, months: <3, 3-6, >6
- Duration of CR1 (for CR2): <6 months, 6-12 months, >12 months, not available
- Relapse on chemotherapy: yes, no
- Time from documentation of CR2 to transplantation, months: <3, 3-6, >6

Transplant-related:
- Graft source: peripheral blood, bone marrow
- Conditioning regimen intensity: myeloablative TBI-based, myeloablative without TBI, RIC-Flu/Mel, RIC-FluBu2, RIC-other
- In vivo T-cell depletion with ATG, campath: yes, no
- GVHD prophylaxis: Tacrolimus/CSA + MTX ± other(s) except MMF, Tacrolimus/CSA + MMF ± others except MTX; Tacrolimus/CSA ± other(s) except MTX, MMF; Tacrolimus/CSA alone; others; none
- Post-transplant TKI maintenance: yes, no

- Type of donor: matched related donor, 8/8 HLA-matched unrelated donor, 7/8 HLA-matched unrelated donor
- Donor age: continuous
- Sex match: M-M, M-F, F-M, F-F
- D/R CMV status: +/+, +/-, -/+, -/-
- Years of transplant: 2000-2008, 2009-2017
- Median follow up: months

Variables to be analyzed:

Main effect:

- Conditioning intensity: Myeloablative vs. Reduced Intensity Conditioning

Patient-related:

- Age, years: 18-29 vs. 30-39 vs. 40-49 vs. 50-59 vs. 60-69 vs. 70+
- Gender: male vs. female
- Race: non-Hispanic white vs. Hispanic white vs. Black vs. Asian vs. not specified/other
- Body mass: Obese (BMI ≥30) vs. non-obese
- Karnofsky performance score: <90 vs. ≥90
- HCT-CI: 0 vs. 1 vs. 2 vs. 3+

Disease-related:

- WBC at diagnosis, (x109/L): continuous and <30 vs. ≥30
- Ph status: positive vs. negative
- Pre-transplant TKI (for Ph-positive): yes vs. no
- Cytogenetics risk group at diagnosis: Ph-negative/Poor [(hypodiploid (<44 chromosomes), MLL rearranged, complex (>4 abnormalities)] vs. Ph-negative/other vs. Ph-positive
- Minimal residual disease (MRD) pre-transplant: positive vs. negative
- Extramedullary disease at diagnosis: yes vs. no
- CNS disease at diagnosis: yes vs no
- Remission status: CR1 vs. CR2
- Time to documentation of CR1: ≤4 weeks vs. >4-8 weeks vs. >8 weeks
- Time from documentation of CR1 to transplantation, months: <3 vs. 3-6 vs. >6
- Duration of CR1 (for CR2): <6 months vs. 6-12 months vs. >12 months
- Time from documentation of CR2 to transplantation, months: <3 vs. 3-6 vs. >6

Transplant-related:

- Graft source: peripheral blood vs. bone marrow
- Reduced-intensity conditioning regimen: Flu/Mel vs. Flu/Bu2
- Myeloablative Conditioning regimen: TBI-based vs. No TBI
- In vivo T-cell depletion with ATG, campath: yes vs. no
- GVHD prophylaxis: Tacrolimus/CSA + MTX ± other(s) except MMF, Tacrolimus/CSA + MMF ± others except MTX; Tacrolimus/CSA ± other(s) except MTX, MMF; Tacrolimus/CSA alone; others; none
- Post-transplant TKI maintenance (for Ph-positive): yes vs. no
- Type of donor: matched related donor vs. 8/8 HLA-matched unrelated donor vs. 7/8 HLA-matched unrelated donor
- Sex match: F-M vs. other

- D/R CMV status: -/- vs. other
- Years of transplant: 2000-2008 vs. 2009-2017

Study design:
This is a retrospective cohort analysis of patients who underwent their first HCT for treatment of ALL with either MAC or RIC preparative regimens. Classification of MAC vs. RIC regimens will be according to previously published consensus definitions.[11] There will also be preplanned analysis of FluBu2 vs. FluMel RIC regimens. Depending on power, a subanalysis of the superior RIC regimen (FluBu2 or FluMel) vs. MAC will also be requested.
Patient, disease and transplant-related factors will be compared between transplant groups using Chi-square test for categorical and Mann-Whitney test for continuous variables. Probabilities of overall survival and relapse-free survival will be calculated using the Kaplan-Meier estimator. Log-rank testing will be used to compare survival curves. Cumulative incidence curves will be made to present relapse and non-relapse mortality with time to relapse and time to NRM as competing risks. Differences between curves in setting of competing risks will be tested using the Gray method[12-13].

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Table 1. Characteristics of adult patients receiving first allo-HCT for ALL with MAC/RIC between 2000-2017, as reported to the CIBMTR

Characteristic	MAC	RIC
No. of patients	2276	250
No. of centers	233	102
Age at HCT		
Median (min-max)	35.22 (18-72.15)	56.26 (18.69-70.59)
18-29	850 (37.3)	24 (9.6)
30-39	541 (23.8)	21 (8.4)
40-49	494 (21.7)	38 (15.2)
50-59	343 (15.1)	76 (30.4)
60-69	46 (2)	89 (35.6)
≥70	2 (0.1)	2 (0.8)
Gender		
Male	1361 (59.8)	139 (55.6)
Female	914 (40.2)	111 (44.4)
Missing	1 (0)	0
Immunophenotype		
T-cell	351 (15.4)	30 (12)
B-cell	1815 (79.7)	204 (81.6)
Unspecified	110 (4.8)	16 (6.4)
Disease status prior to HCT		
CR1	1591 (69.9)	178 (71.2)
CR2	685 (30.1)	72 (28.8)
Karnofsky score		
<90	619 (27.2)	114 (45.6)
≥90	1568 (68.9)	132 (52.8)
Missing	89 (3.9)	4 (1.6)
HCT-CI		
0	308 (13.5)	30 (12)
1	124 (5.4)	23 (9.2)
2	138 (6.1)	15 (6)
3+	271 (11.9)	80 (32)
TBD, inconsistencies between parent and sub-questions	44 (1.9)	7 (2.8)
NA, f2400 (pre-TED) not completed	1370 (60.2)	92 (36.8)
Missing	21 (0.9)	3 (1.2)
Donor type		
HLA-identical sibling	1008 (44.3)	100 (40)
Well-matched unrelated (8/8)	901 (39.6)	123 (49.2)
Partially-matched unrelated (7/8)	367 (16.1)	27 (10.8)

Characteristic	MAC	RIC
Graft type		
Bone marrow	670 (29.4)	33 (13.2)
Peripheral blood	1606 (70.6)	217 (86.8)
GVHD prophylaxis		
No GVHD prophylaxis	24 (1.1)	5 (2)
Ex-vivo T-cell depletion	65 (2.9)	1 (0.4)
CD34 selection	53 (2.3)	3 (1.2)
Post-CY + other(s)	13 (0.6)	8 (3.2)
Post-CY alone	4 (0.2)	0
TAC + MMF ± other(s) (except post-CY)	178 (7.8)	37 (14.8)
TAC + MTX ± other(s) (except MMF, post-CY)	912 (40.1)	80 (32)
TAC + other(s) (except MMF, MTX, post-CY)	107 (4.7)	17 (6.8)
TAC alone	27 (1.2)	9 (3.6)
CSA + MMF ± other(s) (except post-CY)	53 (2.3)	27 (10.8)
CSA + MTX ± other(s) (except MMF, post-CY)	764 (33.6)	42 (16.8)
CSA + other(s) (except MMF, MTX, post-CY)	18 (0.8)	3 (1.2)
CSA alone	36 (1.6)	14 (5.6)
Other(s)	16 (0.7)	3 (1.2)
Missing	6 (0.3)	1 (0.4)
Year of HCT		
2000	104 (4.6)	7 (2.8)
2001	132 (5.8)	3 (1.2)
2002	158 (6.9)	11 (4.4)
2003	150 (6.6)	9 (3.6)
2004	195 (8.6)	17 (6.8)
2005	244 (10.7)	10 (4)
2006	233 (10.2)	17 (6.8)
2007	179 (7.9)	18 (7.2)
2008	180 (7.9)	17 (6.8)
2009	108 (4.7)	18 (7.2)
2010	68 (3)	1 (0.4)
2011	85 (3.7)	3 (1.2)
2012	55 (2.4)	4 (1.6)
2013	91 (4)	15 (6)
2014	117 (5.1)	35 (14)
2015	70 (3.1)	34 (13.6)
2016	69 (3)	23 (9.2)
2017	38 (1.7)	8 (3.2)
Median follow-up of survivors (range), months	96.15 (1.45-217.37)	67.2 (3.19-215.46)

Table 2. Characteristics of adult patients receiving first allo-HCT for ALL with Flu/Bu2 or Flu/Mel based RIC between 2000-2017

Characteristic	Flu/Bu2 based	Flu/Mel based
No. of patients	68	117
No. of centers	38	52
Age at HCT		
Median (min-max)	58.97 (19.42-68.73)	55.55 (22.31-70.59)
18-29	6 (8.8)	5 (4.3)
30-39	4 (5.9)	12 (10.3)
40-49	7 (10.3)	24 (20.5)
50-59	22 (32.4)	35 (29.9)
60-69	29 (42.6)	39 (33.3)
≥70	0	2 (1.7)
Gender		
Male	37 (54.4)	68 (58.1)
Female	31 (45.6)	49 (41.9)
Immunophenotype		
T-cell	6 (8.8)	16 (13.7)
B-cell	59 (86.8)	93 (79.5)
Unspecified	3 (4.4)	8 (6.8)
Disease status prior to HCT		
CR1	57 (83.8)	80 (68.4)
CR2	11 (16.2)	37 (31.6)
Karnofsky score		
<90	32 (47.1)	52 (44.4)
≥90	36 (52.9)	61 (52.1)
Missing	0	4 (3.4)
HCT-CI		
0	1 (1.5)	15 (12.8)
1	5 (7.4)	14 (12)
2	1 (1.5)	9 (7.7)
3+	29 (42.6)	35 (29.9)
TBD, inconsistencies between parent and sub-questions	1 (1.5)	2 (1.7)
NA, f2400 (pre-TED) not completed	31 (45.6)	41 (35)
Missing	0	1 (0.9)
Donor type		
HLA-identical sibling	20 (29.4)	49 (41.9)
Well-matched unrelated (8/8)	38 (55.9)	58 (49.6)
Partially-matched unrelated (7/8)	10 (14.7)	10 (8.5)
Graft type		

Characteristic	Flu/Bu2 based	Flu/Mel based
Bone marrow	10 (14.7)	15 (12.8)
Peripheral blood	58 (85.3)	102 (87.2)
GVHD prophylaxis		
No GVHD prophylaxis	3 (4.4)	1 (0.9)
Ex-vivo T-cell depletion	0	1 (0.9)
CD34 selection	0	2 (1.7)
Post-CY + other(s)	1 (1.5)	4 (3.4)
TAC + MMF ± other(s) (except post-CY)	9 (13.2)	15 (12.8)
TAC + MTX ± other(s) (except MMF, post-CY)	30 (44.1)	39 (33.3)
TAC + other(s) (except MMF, MTX, post-CY)	2 (2.9)	12 (10.3)
TAC alone	2 (2.9)	5 (4.3)
CSA + MMF ± other(s) (except post-CY)	5 (7.4)	7 (6)
CSA + MTX ± other(s) (except MMF, post-CY)	9 (13.2)	20 (17.1)
CSA + other(s) (except MMF, MTX, post-CY)	1 (1.5)	2 (1.7)
CSA alone	5 (7.4)	6 (5.1)
Other(s)	1 (1.5)	2 (1.7)
Missing	0	1 (0.9)
Year of HCT		
2000	2 (2.9)	1 (0.9)
2001	1 (1.5)	1 (0.9)
2002	3 (4.4)	3 (2.6)
2003	3 (4.4)	4 (3.4)
2004	7 (10.3)	7 (6)
2005	5 (7.4)	4 (3.4)
2006	4 (5.9)	11 (9.4)
2007	5 (7.4)	10 (8.5)
2008	4 (5.9)	9 (7.7)
2009	5 (7.4)	6 (5.1)
2010	0	1 (0.9)
2011	0	1 (0.9)
2012	0	2 (1.7)
2013	6 (8.8)	6 (5.1)
2014	9 (13.2)	17 (14.5)
2015	11 (16.2)	16 (13.7)
2016	2 (2.9)	13 (11.1)
2017	1 (1.5)	5 (4.3)
Median follow-up of survivors (range), months	72.83 (3.22-215.46)	60.36 (3.19-195.53)

Proposal: 1911-78

Title:
Busulfan based conditioning in ALLO-HCT for acute myeloid leukemia or myelodysplastic syndromes from HLA matched related and unrelated donors

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Research hypothesis:
With the improvement in transplant practices during recent years, non-relapse mortality (NRM) following allogeneic hematopoietic cell transplantation (allo-HCT) has significantly improved. Regimen-related toxicity and transplant-related mortality preclude the use of conventional myeloablative conditioning (MAC) regimens in older patients or in those who have a poor functional status. Reduced-intensity conditioning (RIC) regimens have extended the use of allo-HCT to older and less fit patients who are not able to tolerate MAC regimens albeit at the cost of higher rates of relapse. These RIC regimens rely on the graft-versus tumor effect mediated by immune cells transferred in the graft (1). To date, most of the published results comparing RIC and MAC come in majority from retrospective registry studies showing increased relapse rates and decreased NRM with RIC but comparable overall results between RIC and MAC, thus, there is controversy about the role and contribution of the conditioning regimen for long-term progression-free and overall survival (2).
Busulfan (Bu) has been used since approximatively four decades as a major component of chemotherapy- based conditioning before allo-HSCT (3). A recent survey carried out by the EBMT about centers practice in the use of busulfan for conditioning in allogeneic transplantation showed marked variation between centers in the details of busulfan administration, the most used I.V. dose of Bu in conventional or myeloablative settings was 12.8 mg/kg while in the reduced intensity settings the dose is down to 6.4 mg/kg (4). Most of the centers reported the use of reduced BU doses either to as per protocol (51%), patient age (25%), presence of comorbidities (13%) or other reasons unspecified (11%).
At the Ottawa Hospital, IV-BU dose in MAC is 12.8 mg/kg (BU12.8) and in those not eligible for MAC, it is 9.6 mg/kg (BU9.6). The goal of BU9.6 is to improve tolerability without increasing disease recurrence. The choice of BU12.8 or 9.6 is determined by consensus based on patient age, Karnofsky score, comorbidities and disease risk. In this context, we performed recently a retrospective study at our center with the aim to compare the impact of BU9.6 to BU12.8 on outcomes in patients with acute leukemia (AL) or myelodysplastic syndromes (MDS) who received allo-HCT after BU-based conditioning from matched related or unrelated donors *(Sobh M. et al. ASH 2019, poster 3263)*. This study included 181 patients, 134 AL and 47 MDS patients who received allo-HCT between Jan 2012 and Dec 2018. At time of conditioning, among AL patients, 99 (74%) were in CR1, 19 (14%) in CR2 and 16 (12%) not in CR, and among MDS patients, 22 (47%) were not treated. All patients received PBSC from HLA matched related [N=68 (38%)] or unrelated [N=113 (62%)] donors. Patients were classified according to the refined Disease Risk Index
(DRI): 94 (52%) intermediate, 81 (45%) high and 6 (3%) very high. GVHD prophylaxis consisted of tacrolimus and short course methotrexate for all patients. Rabbit antithymocyte globulin (rATG, Thymoglobulin) was used in all transplants from unrelated donors (n=113) and in BU12.8 transplants from related donors (n=28). Bu dose was 9.6 mg/kg for 74 (41%) patients and 12.8 mg/kg for 107 (59%).
With a median follow-up of 22 months (range: 5-74) for survivors, no significant difference in survival, relapse (REL) or NRM was observed between BU9.6 and BU12.8. Two-year OS, REL and NRM for the

whole population were 65% (95%CI: 57-73), 29% (95%CI: 22-37) and 10.8% (95%CI: 6-16) respectively. When stratified according to DRI: intermediate, high and very high scores had 2-year OS of 76% (95%CI: 65-84), 53% (95%CI: 38-66) and 0% respectively, p=0.001; and 1-year REL rates of 12% (95%CI: 6-20), 31% (95%CI: 21-42) and 67% (95%CI: 12-92) respectively, p<0.001. In multivariable analysis adjusted for conditioning, DRI, the use of rATG and rATG dose, the only factors that significantly impacted OS were DRI [high-very high vs intermediate: HR=1.98 (95%CI: 1.15-3.4), p=0.013] and the use of ATG [No ATG vs ATG 4.5mg/kg: HR=2.2 (95% CI: 1.06-4.6), p=0.033], while only DRI [high-very high vs intermediate: HR=3.56 (95%CI: 1.86- 6.8), p=0.0001] impacted on REL.
Our results validate the efficacy of a reduced 9.6 mg/kg BU-based conditioning regimen for patients not suitable for traditional 12.8mg/kg dose. Relapse was not increased, unlike what has been reported with BU6.4mg/kg. We confirmed the value of DRI in prognosticating both relapse and survival.
Further studies are needed to determine whether the BU9.6 can replace BU12.8 but also to determine if we can increase the dose for those receiving BU6.4 mg/kg.

Specific aims:

- To describe the use of IV. Busulfan in allo-HCT conditioning among CIBMTR centers
- To compare the impact of different BU-based conditioning regimens according to three doses categories: 6.4mg/kg, 9.6 mg/kg and 12.8 mg/kg, on allo-HCT outcomes (OS, PFS, Relapse, NRM and GVHD).

Scientific impact:

Our hypothesis is based on the results we obtained from our study showing similar outcomes between the standard high Busulfan dose 12.8 mg/kg and the intermediate 9.6 mg/kg. We suggest that the intermediate dose can be used as a standard dose for all patient regardless of their age or fitness.

Scientific justification:

In addition to the proposition above for using a standardized 9.6 mg/kg Busulfan dose in conditioning, the results from our proposed CIBMTR study will allow us to validate our hypothesis but also to compare with patients receiving 6.4 mg/kg Bu-based conditioning. If validated, our study should recommend the use of 9.6 mg/kg Bu instead of 6.4 mg/kg which could lead to a significant decrease in relapse rates.

Patient eligibility population:

- Adult patients with AML or MDS
- Allo-HCT from 10/10 HLA matched related or unrelated donors
- Cells source: PBSCs
- Minimum follow-up after allo-HCT of 2 years
- IV. Busulfan-based conditioning

Data requirements:

<u>Data from CIBMTR TED forms:</u>

- Disease characteristics: type of disease, prognosis, cytogenetics, molecular markers, disease status at transplant
- Patient characteristics: age, comorbidities, Karnofsky, HCT-CI
- Type of donor
- CMV status: patient/donor
- Conditioning details
- GVHD prophylaxis

- Engraftment
- GVHD
- Relapse
- Disease status at last follow-up
- Deaths and causes of death

Sample requirements:
Not applicable

Non-CIBMTR data source:
Not applicable

Conflicts of interest:
No

References:
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Characteristics of adult patients receiving first allo-HCT for AML or MDS with IV busulfan based conditioning and peripheral blood graft between 2008-2017, as reported to the CIBMTR

Characteristic	6.4 mg/kg*	9.6 mg/kg*	12.8 mg/kg*
No. of patients	458	49	366
No. of centers	61	22	67
Age at HCT			
Median (min-max)	65.4 (23.12-79.36)	59.59 (22.4-72.78)	52.9 (19.04-73.53)
18-29	9 (2)	1 (2)	31 (8.5)
30-39	10 (2.2)	3 (6.1)	40 (10.9)
40-49	22 (4.8)	4 (8.2)	77 (21)
50-59	69 (15.1)	18 (36.7)	134 (36.6)
60-69	268 (58.5)	18 (36.7)	80 (21.9)
≥70	80 (17.5)	5 (10.2)	4 (1.1)
Gender			
Male	286 (62.4)	29 (59.2)	203 (55.5)
Female	172 (37.6)	20 (40.8)	163 (44.5)
Disease			
AML	201 (43.9)	18 (36.7)	244 (66.7)
MDS	257 (56.1)	31 (63.3)	122 (33.3)
Karnofsky score			
<90	225 (49.1)	26 (53.1)	144 (39.3)
≥90	233 (50.9)	22 (44.9)	214 (58.5)
Missing	0	1 (2)	8 (2.2)
HCT-CI			
0	61 (13.3)	9 (18.4)	78 (21.3)
1	58 (12.7)	3 (6.1)	63 (17.2)
2	53 (11.6)	9 (18.4)	48 (13.1)
3+	261 (57)	28 (57.1)	155 (42.3)
TBD, inconsistencies between parent and sub-questions	18 (3.9)	0	18 (4.9)
NA, f2400 (pre-TED) not completed	5 (1.1)	0	2 (0.5)
Missing	2 (0.4)	0	2 (0.5)
Donor type			
HLA-identical sibling (10/10)	65 (14.2)	13 (26.5)	67 (18.3)
Matched unrelated (10/10)	393 (85.8)	36 (73.5)	299 (81.7)
GVHD prophylaxis			
No GVHD prophylaxis	2 (0.4)	1 (2)	0
Ex-vivo T-cell depletion	0	1 (2)	0
CD34 selection	0	9 (18.4)	1 (0.3)
Post-CY + other(s)	6 (1.3)	1 (2)	3 (0.8)

Characteristic	6.4 mg/kg*	9.6 mg/kg*	12.8 mg/kg*
TAC + MMF ± other(s) (except post-CY)	121 (26.4)	9 (18.4)	51 (13.9)
TAC + MTX ± other(s) (except MMF, post-CY)	258 (56.3)	21 (42.9)	277 (75.7)
TAC + other(s) (except MMF, MTX, post-CY)	26 (5.7)	3 (6.1)	11 (3)
TAC alone	21 (4.6)	1 (2)	3 (0.8)
CSA + MMF ± other(s) (except post-CY)	9 (2)	0	5 (1.4)
CSA + MTX ± other(s) (except MMF, post-CY)	7 (1.5)	2 (4.1)	10 (2.7)
CSA alone	1 (0.2)	0	2 (0.5)
Other(s)	5 (1.1)	1 (2)	1 (0.3)
Missing	2 (0.4)	0	2 (0.5)
Conditioning regimen			
MAC			
TBI/Cy	1 (0.2)	0	0
TBI/Flu	0	0	24 (6.6)
Bu/Cy	4 (0.9)	4 (8.2)	184 (50.3)
Bu/Mel	0	10 (20.4)	2 (0.5)
Flu/Bu	2 (0.4)	31 (63.3)	145 (39.6)
Treosulfan	0	0	1 (0.3)
Other(s)	0	0	1 (0.3)
RIC			
TBI/Flu	14 (3.1)	0	0
TBI/other(s)	0	0	1 (0.3)
Flu/Bu	430 (93.9)	4 (8.2)	0
TBD			
Other(s)	7 (1.5)	0	8 (2.2)
Busulfan dose determined by pharmacokinetics			
Yes	15 (3.3)	19 (38.8)	96 (26.2)
No	442 (96.5)	30 (61.2)	270 (73.8)
Missing	1 (0.2)	0	0
Year of HCT			
2008	49 (10.7)	0	69 (18.9)
2009	43 (9.4)	1 (2)	53 (14.5)
2010	26 (5.7)	2 (4.1)	55 (15)
2011	25 (5.5)	3 (6.1)	20 (5.5)
2012	40 (8.7)	6 (12.2)	20 (5.5)
2013	94 (20.5)	10 (20.4)	59 (16.1)
2014	59 (12.9)	11 (22.4)	39 (10.7)
2015	53 (11.6)	4 (8.2)	26 (7.1)

Characteristic	6.4 mg/kg*	9.6 mg/kg*	12.8 mg/kg*
2016	33 (7.2)	7 (14.3)	14 (3.8)
2017	36 (7.9)	5 (10.2)	11 (3)
Median follow-up of survivors (range), months	72.07 (24.05-122.73)	65.49 (36.38-97.37)	79.28 (24.64-121.78)

* Groups include individuals receiving doses +/- 2% of the stated value

Combined Proposal: 1911-162/1911-194/1911-242

Title:
Outcomes of Second Allogeneic Hematopoietic Cell Transplant Vs Donor Lymphocyte Infusion in Patients with Relapsed Acute Lymphoblastic Leukemia Relapse After the First Allogeneic Hematopoietic Cell Transplant

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Research hypothesis:
We hypothesize that survival is significantly different between the patients who received second allogeneichematopoietic cell transplantation (HCT2) versus donor lymphocyte infusion (DLI) for relapsed acutelymphoblastic leukemia (ALL) after the first allogeneic hematopoietic cell transplantation (HCT1).

Specific aims:
Primary endpoint:

- Compare progression-free and overall survival (PFS and OS, respectively) of patients who received DLI vs HCT2 for relapsed ALL.

Secondary endpoints:

- Compare the cumulative incidence of relapse incidence, non-relapse mortality (NRM); and acute and chronic graft-versus-host disease (aGvHD, cGvHD, respectively) between DLI vs HCT2.
- Evaluate the effect of donor choice (same as HCT1 vs. different) on clinical outcomes following HCT2
- Assess the impact of specific disease and treatment variables (i.e. baseline cytogenetic abnormalities, relapse interval from HCT1, disease status at HCT2/DLI, conditioning regimen of HCT2) on post-HCT2 outcomes

Scientific impact:
Disease is a relatively common problem after allo-HCT in patients with ALL. DLI and HCT2, both are valid therapeutic options in patients with relapsed ALL.
This study aims to compare the outcomes of patients with relapsed ALL who underwent DLI vs HCT2. Given
the complexity of conducting a prospective study to answer this question, we believe that CIBMTR-based
observational study will provide important results to guide clinical management of these high-risk patients.

Scientific justification:

Disease relapse remains a major cause of post-all-HCT mortality in ALL patients, with cumulative incidence of relapse (CIR) approximately 30-50% (1, 2). Survival of ALL patients who relapsed after an allo-HCT remain poor with long-term leukemia-free survival (LFS) <10%(3, 4). Optimal management strategy of these high-risk patients is yet to be determined. A HCT2 can achieve durable remissions in a subset of patients with relapsed acute leukemia after allo-HCT (allo-HCT1)(5-9). Our group has previously showed that outcomes of HCT2 for relapse ALL remain poor with 5-year OS of 14% with high non-relapse mortality(10). Similarly, poor outcomes have been reported after DLI for relapsed ALL. The retrospective studies have reported complete remission rates of 18 to >50 percent (although most patients also received chemotherapy) and two-year OS 5 to 20 percent(11). The optimal treatment approach to patients with ALL who relapse after an allo-HCT (HCT1) remains elusive. No randomized clinical trial comparing survival outcomes of a HCT2 vs DLI has been conducted to date. Recently, Kharfan-Dabaja et al. analyzed the outcomes of acute myelogenous leukemia patients from the European Society for Blood and Marrow Transplantation and showed comparable survival after DLI vs. HCT2(12).
We propose a study to describe outcomes of patients with relapsed ALL who received DLI vs HCT2 in CIBMTR database.

Patient eligibility population:
Adult patients ≥18 years of age who received DLI or HCT2 as the first intervention for relapsed ALL after HCT1 and reported to CIBMTR

Data requirements:
Patient and disease specific (forms 2400, 2011,2111 and 2402):

- Age at transplant: continuous and by decade
- Sex: male vs. female
- Ethnicity: Hispanic or Latino vs. not Hispanic or Latino vs. not applicable vs. unknown
- Race: Caucasian vs. African-American vs. others
- Karnofsky performance status prior to transplant: < 90% vs. 90-100%
- HCT-CI: 0 vs. 1 vs. 2 vs. ≥3
- Disease: Ph+ vs. Ph- B-ALL vs T-ALL
- DRI at transplant: low vs. intermittent vs. high
- Disease status at transplant: CR1 vs CR2 vs ≥CR3 vs non-CR

Transplant specific for both HCT1 and HCT2 (forms 2400):

- Conditioning regimen intensity: myeloablative vs. reduced intensity and non-myeloablative
- Type of conditioning regimen: MAC vs. RIC/NMA
- Donor-recipient HLA match: HLA-identical sibling and well-matched URD vs. haplo-identical vs. mis-matched unrelated donor vs cord blood unit
- Donor-recipient relationship
- GVHD prophylaxis: CNI + MMF ± others vs. CNI + MTX ± others vs. CNI ± others vs. pt-Cy ± others vs. others
- Graft source: BM vs. PBSC vs cord blood unit
- Previous acute GVHD: none vs. Grade 1 vs Grade 2 vs Grade 3-4 (for HCT2 only)
- Donor for HCT2: same as HCT1 vs. different from HCT1

Relapse specific (forms 2111, 2450, 4000, 4006):

- Disease status at relapse: molecular vs flow cytometry vs cytogenetic vs radiological vs clinical/hematologic
- H/O CNS relapse post-HCT1: yes vs no
- H/O extra-medullary relapse post-HCT1: yes vs no
- Time from HCT1 to ALL relapse: continuous / 0-12 months vs. 12-36 months vs. ≥ 36 months
- Time from relapse to DLI or HCT2: continuous
- Post-HCT1 salvage therapy other than DLI/HCT2: yes vs no
- Type of post-HCT1 salvage therapy other than DLI/HCT2: chemotherapy vs. TKI based vs. immunotherapy/monoclonal antibodies/chimeric antigen receptor T-cell therapy
- Disease status prior to DLI or HCT2: CR vs non-CR
- Karnofsky performance status prior to DLI or HCT2: < 90% vs. 90-100%
- HCT-CI prior to DLI or HCT2: 0 vs. 1 vs. 2 vs. ≥3
- Year of DLI or HCT2: continuous
- Number of DLI infusions: 1 vs. 2 vs. ≥3
- CD3 cell dose of DLI: continuous

<u>Outcome specific (form 2450):</u>

- Best response after DLI vs HCT2
- Response duration after DLI vs HCT2: will be assessed as time from DLI until subsequent relapse/progression (patients who received DLI→ HCT2 will be censored at the time of HCT2; patients who received HCT2→ DLI will be censored at the time of first DLI)
- Graft-versus-host disease: will be assessed as cases of GVHD after DLI/HCT2
- Duration of response: will be define as time from DLI/HCT2 to subsequent relapse/progression
- Overall survival: will be defined as time from DLI/HCT2 to death from any cause. OS will also be assessed as time from relapse to death from any cause, given the variable timing of DLI as part of salvage therapy. Patients are censored at last follow-up.
- Cause of death: descriptive

Sample requirements:
None

Study design:
This retrospective study will investigate the who received DLI or HCT2 for relapsed ALL and were reported to CIBMTR. We will use the methodology and outcomes based on a recently published study by Kharfan-Dabaja et al.(12)
Descriptive statistics of patients, disease and transplant-related factors will be reported as median (range) for continuous variables and percent of total for categorical variables. Overall survival and progression free survival probabilities will be estimated by Kaplan-Meier method. Survival probabilities will be calculated from date of first intervention (DLI or HCT2) to date of death or last follow up. In patients who received just DLI or HCT2, a pre-planned subgroup analysis will be conducted for survival outcomes. If adequate number of patients are found in the registry, we will consider analyzing outcomes of DLI recipients who subsequently did and did not undergo HCT2. Cumulative incidence of relapse/progression and NRM will be calculated using the Fine and Gray competing risk regression model(13).
If sample size and number of events allow, a multivariate analysis will be performed using Cox proportional hazards models for various outcomes. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. Factors, which are significant

at a 5% level, will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested.

Non-CIBMTR data source:
None

Conflicts of interest:
No

References:

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Characteristics of adult patients receiving first allo-HCT for ALL between 2000-2018 and received second allo-HCT or DLI to treat relapse, at time of first allo-HCT

Characteristic	2nd allo-HCT	DLI
No. of patients	155	120
No. of centers	79	68
Age at HCT		
Median (min-max)	31.15 (18.03-68.08)	37.58 (18.5-73.15)
18-29	72 (46.5)	43 (35.8)
30-39	35 (22.6)	24 (20)
40-49	19 (12.3)	20 (16.7)
50-59	23 (14.8)	20 (16.7)
60-69	6 (3.9)	12 (10)
≥70	0	1 (0.8)
Gender		
Male	92 (59.4)	77 (64.2)
Female	63 (40.6)	43 (35.8)
Immunophenotype		
T-cell	22 (14.2)	20 (16.7)
B-cell	122 (78.7)	96 (80)
Unspecified	11 (7.1)	4 (3.3)
Disease status prior to HCT		
Primary induction failure	10 (6.5)	3 (2.5)
CR1	71 (45.8)	62 (51.7)
CR2	48 (31)	31 (25.8)
≥CR3	3 (1.9)	1 (0.8)
Relapse	18 (11.6)	19 (15.8)
Missing	5 (3.2)	4 (3.3)
Karnofsky score		
<90	49 (31.6)	42 (35)
≥90	102 (65.8)	69 (57.5)
Missing	4 (2.6)	9 (7.5)
HCT-CI		
0	22 (14.2)	24 (20)
1	15 (9.7)	9 (7.5)
2	12 (7.7)	6 (5)
3+	22 (14.2)	28 (23.3)
TBD, inconsistencies between parent and sub-questions	1 (0.6)	6 (5)
NA, f2400 (pre-TED) not completed	80 (51.6)	44 (36.7)
Missing	3 (1.9)	3 (2.5)
Donor type		

Characteristic	2nd allo-HCT	DLI
HLA-identical sibling	48 (31)	56 (46.7)
Other related	15 (9.7)	11 (9.2)
Well-matched unrelated (8/8)	54 (34.8)	43 (35.8)
Partially-matched unrelated (7/8)	17 (11)	8 (6.7)
Mis-matched unrelated (≤6/8)	5 (3.2)	1 (0.8)
Multi-donor	0	1 (0.8)
Cord blood	16 (10.3)	0
Graft type		
Bone marrow	37 (23.9)	31 (25.8)
Peripheral blood	102 (65.8)	89 (74.2)
Cord blood	16 (10.3)	0
GVHD prophylaxis		
No GVHD prophylaxis	1 (0.6)	4 (3.3)
Ex-vivo T-cell depletion	4 (2.6)	1 (0.8)
CD34 selection	2 (1.3)	1 (0.8)
Post-CY + other(s)	12 (7.7)	12 (10)
TAC + MMF ± other(s) (except post-CY)	20 (12.9)	7 (5.8)
TAC + MTX ± other(s) (except MMF, post-CY)	62 (40)	54 (45)
TAC + other(s) (except MMF, MTX, post-CY)	7 (4.5)	3 (2.5)
TAC alone	4 (2.6)	2 (1.7)
CSA + MMF ± other(s) (except post-CY)	7 (4.5)	4 (3.3)
CSA + MTX ± other(s) (except MMF, post-CY)	27 (17.4)	24 (20)
CSA + other(s) (except MMF, MTX, post-CY)	2 (1.3)	2 (1.7)
CSA alone	1 (0.6)	4 (3.3)
Other(s)	1 (0.6)	1 (0.8)
Missing	5 (3.2)	1 (0.8)
Conditioning regimen intensity		
MAC	115 (74.2)	92 (76.7)
RIC	16 (10.3)	17 (14.2)
NMA	13 (8.4)	9 (7.5)
TBD	5 (3.2)	2 (1.7)
Missing	6 (3.9)	0
Year of HCT		
2000	9 (5.8)	1 (0.8)
2001	3 (1.9)	4 (3.3)
2002	16 (10.3)	6 (5)
2003	10 (6.5)	7 (5.8)
2004	7 (4.5)	8 (6.7)
2005	12 (7.7)	3 (2.5)
2006	12 (7.7)	6 (5)
2007	13 (8.4)	15 (12.5)

Characteristic	2nd allo-HCT	DLI
2008	14 (9)	15 (12.5)
2009	9 (5.8)	7 (5.8)
2010	5 (3.2)	5 (4.2)
2011	4 (2.6)	4 (3.3)
2012	4 (2.6)	2 (1.7)
2013	12 (7.7)	8 (6.7)
2014	4 (2.6)	14 (11.7)
2015	8 (5.2)	8 (6.7)
2016	8 (5.2)	3 (2.5)
2017	3 (1.9)	3 (2.5)
2018	2 (1.3)	1 (0.8)
Median follow-up of survivors (range), months	117.04 (7.7-210.99)	72.14 (3.29-165.16)

Proposal: 1911-190

Title:
Outcomes of Allogeneic Hematopoietic Cell Transplantation (HCT) Among Germline *RUNX1* Mutation Carriers with Acute Myeloid Leukemia (AML).

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Research hypothesis:
This is largely a descriptive study.
If sample size allows, then we propose the following two hypotheses: There are patient-, disease-, and HCT-related factors among AML patients with pathogenic germline *RUNX1* mutations undergoing allogeneic HCT that are associated with post-HCT out- comes.
AML patients undergoing allogeneic HCT with pathogenic germline *RUNX1* mutations experi- ence distinct clinical outcomes from patients without such mutations.

Specific aims:
The purpose of this retrospective study is to:

- Determine the prevalence of germline *RUNX1* mutations in a cohort of patients positive for *RUNX1* mutations undergoing allogeneic HCT for AML.
- Describe pre-HCT clinical characteristics and chemotherapy regimens for patients with germline *RUNX1* mutations.
- Describe post-HCT overall survival, leukemia-free survival, transplant-related toxicity, and mortality, and disease relapse for patients with germline RUNX1 mutations.

If sample size permits:

- 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.

Scientific impact:
This study is the first-ever to evaluate the prevalence and clinical outcomes of germline *RUNX1* AML patients receiving an allogeneic HCT within a large bone marrow transplant registry. The study results may inform prognostic stratification and the selection of conditioning regimens in patients with AML. This study is an essential step towards future innovative, prospective studies of *RUNX1* familial platelet disorder patients (*RUNX1*-FPD or FPDMM) in need of an allogeneic HCT, or an autologous gene edited stem cell therapy. It will also draw attention to the under ap- preciated frequency of germline mutations in AML patients and the need for clinicians to more regularly consider genetic testing of germline mutations in patients receiving an allogeneic HCT.

Scientific justification:
Lifetime risk of developing a hematologic malignancy in *RUNX1*-FPD patients is 44%.[1] Of those that progress, the majority develop AML, a disease with only a 28% 5-year overall survival rate. [2,3.] AML patients with *RUNX1* mutations have a poor prognosis.[4] To date, there is no known analysis of the impact of germline *RUNX1* mutations on outcomes in patients receiving allo- geneic HCT for AML.

Understanding how patients respond to different conditioning regimens including both short- and long-term outcomes, such as transplant-related mortality and overall survival, is a necessary step towards ensuring outcomes in patients with *RUNX1* mutations im- prove overall. Additionally, results from the study will form baseline knowledge from which to build future prospective studies to further advance clinical care of this rare disease.

Patient eligibility population:
The study will include US patients undergoing their first allogeneic HCT for AML with a reported *RUNX1* mutation between 2013-2019. To enrich for patients with germline *RUNX1* mutations, patients must be less than 60 years old and have a banked pre-HCT blood sample. A query of CIBMTR identified 497 AML patients with reported RUNX1 mutation that underwent HCT from 2013-2019 but not known whether the mutation is somatic or germline. Among these patients we identified 180 patients that were younger than 60 with available pre-HCT whole blood. Medi- an follow up is 24 months and all of them were on CRF track.

Data requirements:
AML CRF pre-HCT and post HCT forms. Additionally we will work closely with the NMDP Bio bank to retrieve samples for the 180 patients.

Sample requirements:
The study will use banked biologic samples, as noted above in the patient eligibility section. Whole blood samples prior to the preparative conditioning regimen for HCT will be processed for DNA extraction. Extracted DNA will then be sequenced for *RUNX1* mutations using a tar- geted next generation sequencing platform. Since most patients eligible for transplant should have low or undetected minimal residual disease at the time of transplant, a variant allele fre- quency (VAF) threshold of 0.4 or greater will be used to categorize patients with germline *RUNX1* mutations. Patients with a VAF of less than 0.4 to below the detection limit will be cate- gorized as somatic *RUNX1* mutation carriers based on the clinical report listing a RUNX1 muta- tion status. Funding for DNA extraction from whole blood samples will be provided by the *RUNX1* Research Program and the sequencing and associated analysis will be funded by the NHGRI.
Dr. Paul Liu investigates the molecular mechanisms of leukemia, with the long-term goal of translating research findings to improved clinical practices, including better diagnosis and treat- ment of leukemia and related hematological diseases. He is the Principal Investigator of an on- going RUNX1-FPD natural history study at the NHGRI, formally titled “Longitudinal Studies of Patients with FPDMM”, NCT03854318. In this study he is routinely overseeing genomic analy- ses using NGS and WES on patient bone marrow samples collected on an annual basis.

Study design:
Using the CIBMTR research database, we will obtain access to de-identified patient data from patients who received HCT for AML and were reported as *RUNX1* mutation carriers. To enrich for, and identify germline *RUNX1* mutation carriers we plan to sequence whole blood from pa- tients under 60 years of age. The average age of onset of leukemia in patients with *RUNX1*- FPD is 33 years, in contrast with sporadic AML which is 68 years.[2,5] Preliminary CIBMTR data queries reveal there is a total of 180 subjects under the age of 60 at the time of allogeneic HCT with *RUNX1* mutations and banked whole blood in the research database and repository, re- spectively.
Once all relevant samples are sequenced, only those subjects with a confirmed *RUNX1* muta- tion above a VAF of 0.4 will be included as part of the germline *RUNX1* mutation cohort. All other subjects will be categorized as somatic *RUNX1* mutation carriers. A third cohort will in- clude age-matched AML patients

without *RUNX1* mutations who underwent allogeneic HCT.
Clinical characteristics comparing germline *RUNX1* carriers (mutation VAF >0.4) to somatic *RUNX1* carriers (mutation VAF<0.4), and to the age-matched AML cohort without *RUNX1* muta- tions will be assessed. Clinical characteristics will include disease status such as complete re- mission status and depth of MRD prior to HCT. Furthermore, transplant-related factors will also be compared, such as type of conditioning therapy and graft type. Depending on the number in each cohort, univariate and/or multivariate associations with transplant outcomes will be evalu- ated.

Data source:
The data sources include: CIBMTR Research Database, CIBMTR Sample Repository.

Conflicts of interest:
No, Dr. Paul Liu has no conflicts of interest pertinent to this proposal. No, Dr. Wael Saber has no conflict of interest pertinent to this proposal.

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Characteristics of patients age 0-59 years receiving first allo-HCT for AML with RUNX1 mutation, with available blood sample, between 2013-2019, as reported to the CIBMTR

Characteristic	N (%)
No. of patients	180
No. of centers	76
Age at HCT	
Median (min-max)	39.52 (0.34-59.9)
<10	20 (11.1)
10-17	28 (15.6)
18-29	20 (11.1)
30-39	23 (12.8)
40-49	47 (26.1)
50-59	42 (23.3)
Gender	
Male	89 (49.4)
Female	91 (50.6)
Clinical onset of AML	
De-novo	161 (89.4)
Transformed from MDS/MPS	12 (6.7)
Therapy linked	7 (3.9)
Disease status prior to HCT	
Primary induction failure	21 (11.7)
CR1	91 (50.6)
CR2	55 (30.6)
Relapse	9 (5)
Missing	4 (2.2)
Karnofsky score	
<90	59 (32.8)
≥90	119 (66.1)
Missing	2 (1.1)
HCT-CI	
0	41 (22.8)
1	38 (21.1)
2	34 (18.9)
3+	67 (37.2)
Donor type	
HLA-identical sibling	20 (11.1)
Other related	27 (15)
Well-matched unrelated (8/8)	67 (37.2)
Partially-matched unrelated (7/8)	13 (7.2)
Mis-matched unrelated (≤6/8)	1 (0.6)

Characteristic	N (%)
Unrelated (matching TBD)	2 (1.1)
Cord blood	50 (27.8)
Graft type	
Bone marrow	49 (27.2)
Peripheral blood	81 (45)
Cord blood	50 (27.8)
GVHD prophylaxis	
Ex-vivo T-cell depletion	4 (2.2)
CD34 selection	9 (5)
Post-CY + other(s)	32 (17.8)
Post-CY alone	2 (1.1)
TAC + MMF ± other(s) (except post-CY)	29 (16.1)
TAC + MTX ± other(s) (except MMF, post-CY)	51 (28.3)
TAC + other(s) (except MMF, MTX, post-CY)	8 (4.4)
TAC alone	3 (1.7)
CSA + MMF ± other(s) (except post-CY)	27 (15)
CSA + MTX ± other(s) (except MMF, post-CY)	12 (6.7)
CSA + other(s) (except MMF, MTX, post-CY)	1 (0.6)
CSA alone	1 (0.6)
Other(s)	1 (0.6)
Conditioning regimen intensity	
MAC	143 (79.4)
RIC	24 (13.3)
NMA	9 (5)
TBD	3 (1.7)
Missing	1 (0.6)
Year of HCT	
2013	17 (9.4)
2014	35 (19.4)
2015	28 (15.6)
2016	44 (24.4)
2017	25 (13.9)
2018	26 (14.4)
2019	5 (2.8)
Median follow-up of survivors (range), months	33.82 (3.26-72.99)