Not for publication or presentation

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

A G E N D A
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**
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Statistician:	**Jonathan Sanchez-Garcia, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-4681; E-mail: jsanchez@mcw.edu**

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1. Introduction

a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
b. Introduction of incoming co-chair: **Partow Kebriaei, MD;** MD Anderson; E-mail: pkebriae@mdanderson.org

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

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 (Attachment 3)

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

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) (Attachment 4)
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) (Attachment 5)
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) (Attachment 6)
d. **PROP 1811-41** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era (Maxwell Krem, Richard Maziarz) (Attachment 7)
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) (Attachment 8)
f. **PROP 1811-113** Outcomes of alloHCT for adult acute lymphoblastic leukemia in a second or subsequent complete remission (Lyndsey Runaas, Guru Murthy) (Attachment 9)
g. **PROP 1811-137** Outcomes of acute lymphoblastic leukemia arising from a prior hematologic malignancy (Trent Wang, Antonio Jimenez) (Attachment 10)
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) in first complete remission (Marc Schwartz, Matthew Wieduwilt) (Attachment 11)
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) (Attachment 12)
j. **PROP 1809-02** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm (Hemant Murthy) (Attachment 13)
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) (Attachment 14)

Proposed studies; not accepted for consideration at this time

a. **PROP 1807-01** Age and allogeneic stem cell transplantation using TBI-based conditioning regimens
b. **PROP 1810-03** Allogeneic hematopoietic cell transplant in adult patients with normal karyotype IDH mutated AML
c. **PROP 1811-07** Outcomes After Cranial or Craniospinal Irradiation Plus Total-Body Irradiation Before Stem Cell Transplantation in Adult Lymphoblastic Leukemia Patients with CNS involvement
d. **PROP 1811-09** Acute myeloid leukemia with chromosome 17 abnormalities and outcomes after hematopoietic stem cell transplantation
e. **PROP 1811-17** The effect of TKI maintenance on the incidence and severity of acute and chronic GVHD and non-relapse mortality following HCT in ALL patients
f. **PROP 1811-22** Molecular disease status pre and post allogeneic stem cell transplantation in myeloid malignancies
g. **PROP 1811-74** A comparison of the use of purine-analogue vs anthracycline based induction in acute myeloid leukemia pre-transplant
h. **PROP 1811-90** The role of donor mismatch for the second allogeneic transplant in patients with AML relapsed after first matched related donor allogeneic transplant.

i. **PROP 1811-136** Induction chemotherapy vs. hypomethylating agent therapy for frail or older AML patients undergoing allogeneic hematopoietic stem cell transplantation
j. **PROP 1811-148** Survival outcomes after relapse post-allogeneic hematopoietic cell transplantation in patients with or without immunosuppression
k. **PROP 1811-92** Comparison of outcomes in patients with acute lymphoblastic leukemia (ALL) following haploidentical versus matched unrelated and matched related donor transplantation
l. **PROP 1811-63** A personalized prediction model for outcomes after AlloHCT in pts with AML
m. **PROP 1811-16** The early post-transplant morbidity and mortality in relapsed/refractory ALL patients treated with blinatumomab compared to chemotherapy

6. Other business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Salt Lake City, UT
Thursday, February 22nd, 2018, 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**
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**
Statistician:	**Hai-Lin Wang, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0647; E-mail: hwang@mcw.edu**

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1. Introduction

The CIBMTR Acute Leukemia Working Committee was called to order at 12:15 pm on Thursday, February 22rd, 2018, by Dr. Wael Saber. The chairs, scientific director and statisticians were presented. Attendees were asked to have their name badges scanned for attendance purposes and to maintain committee membership, and to fill out the Working Committee evaluations and voting sheets for proposals. Dr. Saber also introduced and welcomed Dr. Mark Litzow as new chair for LKWC. Dr. Brenda Sandmaier introduced the committee's accomplishments for the past year and progress of ongoing studies. Each proposal presentation was limited to 5 minutes to allow for adequate time for discussion (5 minutes). The minutes of the February 2017 meeting were approved without modifications.

2. Accrual summary

Dr. Brenda Sandmaier briefly mentioned the number of allo-HCT and auto-HCT accrued between 1995 and 2017 without further details.

3. Presentations, published or submitted papers

The working committee leadership invited Dr. Yeshurun to present the final results of analysis for study LK15-02. Other publication and presentations were mentioned but not presented.

a. **LK13-02** Lazaryan A, Dolan M, Zhang MJ, Wang HL, Bachanova V, de Lima M, Sandmaier BM, Saber W, Weisdorf D. Prognostic significance of cytogenetic abnormalities in patients with Philadelphia-negative ALL undergoing allogeneic hematopoietic stem cel transplantation in complete remission. ***Presentation at ASH meeting in Atlanta, GA, December 2017.***

b. **LK13-04** Segal E, Martens M, Wang HL, Brazauskas R, Weisdorf DJ, Sandmaier BM, Khoury HJ, de Lima M and Saber W (2017), Comparing outcomes of matched related donor and matched unrelated donor hematopoietic cell transplants in adults with B-Cell acute lymphoblastic leukemia. ***Cancer.*** **doi:10.1002/cncr.30737**

c. **LK14-01** Bejanyan N, Zhang MJ, Wang HL, Lazaryan A, de Lima M, Marks DI, Sandmaier BM, Bachanova V, Rowe JM, Tallman MS, Kebriaei P, Kharfan-Dabaja M, Gale RP, Lazarus HM, Ustun C, Copelan E, Hamilton BK, Schiller G, Hogan W, Hashmi S, Seftel M, Kanakry CG, Olsson RF, Martino R, Saber W, Khoury J, Weisdorf DJ. Pretransplant consolidation is not beneficial for adults with ALL undergoing myeloablative allogeneic transplantation. ***Accepted by Biol Blood and Marrow Transplant.***

d. **LK15-02** Yeshurun M, Weisdorf DJ, Zhang MJ, Wang HL, Flowers ME, de Lima M, Rowe JM, Sandmaier BM, Tallman MS, Verneris MR, Bachanova V. Graft-vs-leukemia effect in acute lymphoblastic leukemia: mild acute graft-vs-host disease protects against relapse and improves survival after allogeneic transplantation. ***Presentation at ASH meeting in Atlanta, GA, December 2017.***

e. **LK15-04** Kebriaei P, Anasetti C, Zhang MJ, Wang HL, Aldoss I, de lima M, Khoury HJ, Sandmaier BM, Horowitz MM, Artz A, Bejanyan N, Ciurea S, Lazarus HM, Gale RP, Litzow M, Bredeson C, Seftel MD, Pulsipher MA, Boelens JJ, Alvarnas J, Champlin R, Forman S, Pullarkat V, Weisdorf DJ, Marks DI. Intravenous Busulfan compared to total body irradiation pre-transplant conditioning for adults with acute lymphoblastic leukemia. ***Biol Blood Marrow Transplant.*** **2017 [Epub ahead of print]**

4. Studies in progress

The working committee leadership invited Dr. Artz to present the study progress of LK15-01. 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. **LK15-01** AlloHCT vs. other consolidation therapies per Alliance and SWOG/ECOG protocols in older AML in CR1 (A Artz / C Ustun) **Analysis**

c. **LK15-02** Impact of GVHD on outcome after allogeneic hematopoietic cell transplantation for acute lymphocytic leukemia (M Yeshurun/J Rowe/ M Tallman/ V Bachanova) **Manuscript preparation**

d. **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) **Protocol development**

e. **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) **Protocol development**

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

g. **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) **Protocol development**

h. **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) **Protocol development**

i. **LK17-02** Outcomes for AlloHCT in adult MLL-rearranged AML (K Menghrajani/ M Tallman) **Protocol development**

j. **LK17-03** Impact of post-HCT TKI on Ph+ ALL (Z DeFilipp/ YB Chen) **Protocol development**

5. Future/proposed studies

Drs. Sandmaier and de Lima led this session.

a. **PROP 1710-11** Outcomes of alloHCT of AML patients who achieved complete remission after one or more cycles of induction chemotherapy vs. patients with primary refractory AML (Michael Boyiadzis / Marcos de Lima)
Dr. Boyiadzis presented this proposal. There are 567, 795 and 313 cases in PIF, CR1 w/ 2 cycles and CR1 w/ >=2 cycles of induction group separately. Comments were received about the MRD details of the patients which won't be available for cases prior to 2013, and potential selection bias of patients who received multiple lines of induction but didn't make to HCT.

b. **PROP 1711-28** Impact of Maintenance Therapy after Allogeneic Hematopoietic Cell Transplant (HCT) on Outcomes in Acute Myeloid Leukemia (Masumi Ueda/ Marcos de Lima)
Dr. Ueda presented this proposal. There are 508 cases receiving any type of maintenance after HCT, among which 40% are hypomethylating agents. Comments were received about the unavailable dosing/cycle and duration of maintenance, and the distribution of disease status vs. conditioning intensity of HCT among HMA type of maintenance.

c. **PROP 1711-114** Identifying an ideal conditioning regimen for the elderly with AML (Saurabh Chhabra/ Gemlyn George)
Dr. George presented this proposal. There are 347, 175 and 69 cases in Flu/Bu, Flu/Mel and Flu/TBI 2Gy conditioning regimen arm. Comments were received about the detailed Melphalan dosing and excluding 7/8 matched URD donor. Also there were concerns about the potential overlap with ongoing study LK16-01, which compares Flu/Bu with Flu/Mel for AML HCT in all ages and disease status.

d. **PROP 1711-133** 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 (Antonio Martin Jimenez/ Trent Peng Wang/ Marcos De Lima/ Krishna Komanduri)
Dr. Jimenez presented this proposal. There are 1470 and 421 cases in CR1 and CR2 disease status group. Comments were received about the difference of ELN risk group vs. CIBMTR available data, and suggestion to compare ELN vs. CIBMTR vs. DFCI cytogenetic risk group.

e. **PROP 1711-134** Syngeneic stem cell transplant for hematologic malignancies (Usama Gergis)
Dr. Gergis presented this proposal. There are 672 cases receiving identical twin HCT for any malignant disease since 1990. Comments were received about the decreasing number of twin HCT by year which can be explained by the CRF selection algorithm, and different disease biology which will require separate comparison group for twin HCT across malignant diseases.

f. **PROP 1711-143 / 1510-13** 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 (Matthew Wieduwilt/ Leland Metheny/ Marcos de Lima)
Dr. Wieduwilt presented this proposal. There are 483, 700 and 1138 cases with haplo (CRF+TED), MRD and MUD donor HCT group separately. Comments were received about the MRD details of cases, which is only available after 2013, and suggestion to restrict the population to more homogeneous subgroup of Ph-, T-replete graft and post-Cy. Also there were concerns about the potential correlation between donor type, graft type and conditioning intensity.

Proposed studies; not accepted for consideration at this time

These proposals were not discussed during the meeting. Dr. Sandmaier 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 1709-01** 100-day survival and risk of developing acute graft versus host disease (aGvHD) in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) after allogeneic stem cell transplant: blinatumomab vs chemotherapy remission induction
b. **PROP 1709-06** The influence of donor source, cytogenetics and molecular markers on outcomes after a second hematopoietic cell transplant for patients with relapsed leukemia and MDS
c. **PROP 1710-02** Outcomes of older adults with acute myeloid leukemia who received hypomethylating agents followed by hematopoietic stem cell transplantation
d. **PROP 1710-07** Impact of conditioning regimen FLuMel vs CyTbi on outcomes of ALL patients 40-60 years old
e. **PROP 1711-01** Second Unrelated Allograft for Relapsed/Refractory Acute Leukemia after First Unrelated Allogeneic Stem Cell Transplantation: The Role of using the Original vs an Alternate Unrelated Donor
f. **PROP 1711-09** Transplant Outcomes in Patients with MLL (KMT2A) rearranged B-cell acute lymphoblastic leukemia (ALL), stratified by type of MLL (KMT2A) rearrangement: Analysis of the Center for International Bone and Marrow Transplant Research (CIBMTR)
g. **PROP 1711-10** Reduced Intensity versus Nonmyeloablative Conditioning for Patients Aged 65 and Older
h. **PROP 1711-16** Transplant outcomes for patients with T- and Natural Killer (NK)-cell large granular lymphocyte (LGL) leukemia
i. **PROP 1711-44** The impact of minimal residual disease by flow cytometry at the time transplantation on post-transplant outcomes in acute myeloid leukemia patients with complete remission
j. **PROP 1711-64** Development of a pre-transplant risk score for patients undergoing allogeneic HCT for acute myeloid leukemia
k. **PROP 1711-92** Autologous versus Allogeneic Hematopoietic Stem Cell Transplantation in Acute Leukemia Patients 60 Years and Older
l. **PROP 1711-104** Induction chemotherapy vs. hypomethylating agent therapy for older AML patients undergoing allogeneic hematopoietic stem cell transplantation

6. Other business

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 1711-133 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 (Antonio Martin Jimenez/ Trent Peng Wang/ Marcos De Lima/ Krishna Komanduri)

PROP 1711-143 / 1510-13 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 (Matthew Wieduwilt/ Leland Metheny/ Marcos de Lima)

Working Committee Overview Plan for 2018 - 2019

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. Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by June 2018. (Total hour:70; Allocated for the fiscal year:10)

b. **LK15-01** AlloHCT vs. other consolidation therapies per Alliance and SWOG/ECOG protocols in older AML in CR1. Analysis is underway. The goal of the study is to have the manuscript submitted by June 2018. (Total hour: 30; Allocated for the fiscal year: 10)

c. **LK15-02** Impact of GVHD on outcome after allogeneic hematopoietic cell transplantation for acute lymphocytic leukemia. Analysis is underway. Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by June 2018. (Total hour: 10; Allocated for the fiscal year: 10)

d. **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. The goal of the study is to finalize data analysis by June 2018 and have the manuscript submitted by June 2019. (Total hour: 200; Allocated for the fiscal year: 70)

e. **LK16-02** DRI-guided Choice of Conditioning Intensity for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Myeloid Leukemia and Myelodysplastic Syndromes. Protocol development is underway. The goal is to finalize the protocol and start data file preparation by June 2018 and finish analysis by June 2019. (Total hour: 270; Allocated for the fiscal year: 200)

F **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes. Protocol development is underway. The goal of the study is to finish data file preparation and start analysis by June 2018 and have the manuscript submitted by June 2019. (Total hour: 200; Allocated for the fiscal year: 150)

g. **LK16-04** Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia. Data file preparation is underway. The goal of the study is to finalize data analysis by June 2018 and have the manuscript submitted by June 2019. (Total hour: 180; Allocated for the fiscal year: 70)

h. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response. Protocol development is underway. The goal is to finish data file preparation by June 2018 and have the manuscript submitted by June 2019. (Total hour: 200; Allocated for the fiscal year: 150)

i. **LK17-02** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia. Protocol development is underway. The goal is to finalize the protocol by June 2018 and start analysis by June 2019. (Total hour: 260; Allocated for the fiscal year: 100)

j. **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 by June 2018 and start analysis by June 2019. (Total hour: 310; Allocated for the fiscal year: 100)

Oversight Assignments for Working Committee Leadership (March 2018)

Daniel Weisdorf	**LK13-02**: Prognostic significance of cytogenetic abnormalities in patients with Philadelphia-negative acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation in complete remission **LK15-01:** Comparison of Allogeneic Hematopoietic Cell Transplantation with Other Consolidation Therapies Per Alliance/SWOG/ECOG Protocols in Older (≥60 years) AML Patients in First Complete Remission.
Wael Saber	**LK17-02:** Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia
Marcos de Lima	**LK16-03:** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes. **LK16-04:** Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia. **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
Brenda Sandmaier	**LK15-02:** Impact of GVHD on outcome after allogeneic hematopoietic cell transplantation for acute lymphocytic leukemia. **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
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

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 2018

	AML	ALL
Number of patients	21962	11146
Number of centers	414	389
Age in decades		
Median (range)	44 (<1-72)	21 (<1-66)
<10	1893 (9)	2644 (24)
10-17	2108 (10)	2606 (23)
18-29	2520 (11)	1973 (18)
30-39	2957 (13)	1465 (13)
40-49	4042 (18)	1269 (11)
50-59	4697 (21)	847 (8)
60-69	3249 (15)	330 (3)
≥70	496 (2)	12 (<1)
Gender		
Male	11639 (53)	6798 (61)
Female	10322 (47)	4347 (39)
Missing	1 (<1)	1 (<1)
HCT-CI		
0	2651 (12)	1427 (13)
1	1377 (6)	544 (5)
2	1241 (6)	423 (4)
3+	3746 (17)	1020 (9)
N/A, earlier than 2007	12304 (56)	7454 (67)
Missing	643 (3)	278 (2)
Disease status prior to HCT		
PIF	2890 (13)	376 (3)
CR1	10720 (49)	4722 (42)
CR2	4591 (21)	3783 (34)
≥CR3	415 (2)	946 (8)
Relapse	3280 (15)	1309 (12)
Missing	66 (<1)	10 (<1)

	AML	ALL
Time from diagnosis to HCT		
Median (range)	6 (<1-71)	11 (<1-136)
<6 months	10541 (48)	3155 (28)
6 - 12 months	5338 (24)	2634 (24)
>12 months	6064 (28)	5345 (48)
Missing	19 (<1)	12 (<1)
Conditioning regimen intensity		
MAC	15798 (72)	10014 (90)
RIC	3793 (17)	558 (5)
NMA	1686 (8)	338 (3)
TBD	471 (2)	143 (1)
Missing	214 (<1)	93 (<1)
Graft type		
Bone marrow	7171 (33)	5072 (46)
Peripheral blood	12076 (55)	4078 (37)
Umbilical cord blood	2699 (12)	1983 (18)
Missing	16 (<1)	13 (<1)
Type of donor		
HLA-identical sibling	6876 (31)	3132 (28)
Identical twin	88 (<1)	64 (<1)
Other relative	1330 (6)	672 (6)
Unrelated	10433 (48)	5066 (45)
Cord blood	2699 (12)	1983 (18)
Missing	536 (2)	229 (2)

	AML	ALL
Year of HCT		
1995-1996	1710 (8)	1306 (12)
1997-1998	1516 (7)	1135 (10)
1999-2000	1466 (7)	1068 (10)
2001-2002	1826 (8)	1101 (10)
2003-2004	2171 (10)	1121 (10)
2005-2006	2609 (12)	1250 (11)
2007-2008	2469 (11)	1075 (10)
2009-2010	2147 (10)	638 (6)
2011-2012	904 (4)	430 (4)
2013-2014	2154 (10)	814 (7)
2015-2016	2122 (10)	851 (8)
2017-current	868 (4)	357 (3)
Median follow-up of survivors (range), months	75 (1-271)	80 (1-271)

[a] Patients have available comprehensive research form (CRF) and consented for research
[b] Cases continue to be reported in this interval

Accrual Summary for Acute Leukemia Working Committee

Characteristics of recipients of first autologous transplants for AML and ALL reported[a] to the CIBMTR between 1995 and 2018

	AML	ALL
Number of patients	994	157
Number of centers	182	60
Age in decades		
Median (range)	44 (<1-70)	30 (1-66)
<10	61 (6)	16 (10)
10-17	68 (7)	25 (16)
18-29	125 (13)	38 (24)
30-39	165 (17)	19 (12)
40-49	188 (19)	28 (18)
50-59	219 (22)	23 (15)
60-69	159 (16)	8 (5)
≥70	9 (<1)	0
Gender		
Male	505 (51)	99 (63)
Female	489 (49)	58 (37)
HCT-CI		
0	54 (5)	3 (2)
1	20 (2)	2 (1)
2	13 (1)	4 (3)
3+	43 (4)	2 (1)
N/A, earlier than 2007	862 (87)	146 (93)
Missing	2 (<1)	0
Disease status prior to HCT		
PIF	10 (1)	2 (1)
CR1	641 (64)	100 (64)
CR2	260 (26)	44 (28)
≥CR3	14 (1)	6 (4)
Relapse	66 (7)	5 (3)
Missing	3 (<1)	0
Median (range)	7 (<1-86)	9 (2-133)
Time from diagnosis to HCT		
<6 months	410 (41)	23 (15)
6 - 12 months	269 (27)	74 (47)
>12 months	314 (32)	60 (38)
Missing	1 (<1)	0

	AML	ALL
Conditioning regimen intensity		
MAC	798 (80)	148 (94)
RIC	14 (1)	3 (2)
NMA	2 (<1)	0
TBD	172 (17)	2 (1)
Missing	8 (<1)	4 (3)
Graft type		
Bone marrow	171 (17)	25 (16)
Peripheral blood	823 (83)	132 (84)
Year of HCT		
1995-1996	266 (27)	55 (35)
1997-1998	221 (22)	45 (29)
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-current	6 (<1)	0
Median follow-up of survivors (range), months	110 (1-265)	145 (2-266)

[a] Patients have available comprehensive research form and consented for research
[b] Cases continue to be reported in this interval

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	18751	5365	3448
Source of data			
CRF	9904 (53)	2470 (46)	2008 (58)
TED	8847 (47)	2895 (54)	1440 (42)
Number of centers	231	199	295
Disease at transplant			
AML	12782 (68)	3782 (70)	2223 (64)
ALL	5581 (30)	1464 (27)	1153 (33)
Other acute leukemia	388 (2)	119 (2)	72 (2)
AML Disease status at transplant			
CR1	6446 (50)	1924 (51)	970 (44)
CR2	2591 (20)	762 (20)	469 (21)
CR3+	257 (2)	70 (2)	50 (2)
Advanced or active disease	3341 (26)	989 (26)	687 (31)
Missing	143 (1)	37 (1)	43 (2)
ALL Disease status at transplant			
CR1	2643 (47)	730 (50)	464 (40)
CR2	1641 (29)	402 (27)	344 (30)
CR3+	466 (8)	120 (8)	111 (10)
Advanced or active disease	787 (14)	198 (14)	202 (18)
Missing	44 (1)	14 (1)	31 (3)
Recipient age at transplant			
0-9 years	1438 (8)	374 (7)	368 (11)
10-19 years	1942 (10)	493 (9)	476 (14)
20-29 years	2348 (13)	646 (12)	496 (14)
30-39 years	2259 (12)	605 (11)	468 (14)
40-49 years	2888 (15)	817 (15)	520 (15)
50-59 years	3605 (19)	1000 (19)	553 (16)
60-69 years	3569 (19)	1178 (22)	486 (14)
70+ years	702 (4)	252 (5)	81 (2)
Median (Range)	45 (0-84)	47 (0-79)	38 (0-76)
Recipient race/ethnicity			
Caucasian, non-Hispanic	15606 (85)	4459 (85)	2554 (82)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
African-American, non-Hispanic	696 (4)	194 (4)	141 (5)
Asian, non-Hispanic	435 (2)	175 (3)	122 (4)
Pacific islander, non-Hispanic	23 (<1)	8 (<1)	9 (<1)
Native American, non-Hispanic	75 (<1)	21 (<1)	15 (<1)
Hispanic	1411 (8)	372 (7)	259 (8)
Other	18 (<1)	11 (<1)	10 (<1)
Unknown	487 (N/A)	125 (N/A)	338 (N/A)
Recipient sex			
Male	10386 (55)	2978 (56)	1960 (57)
Female	8365 (45)	2387 (44)	1488 (43)
Karnofsky score			
10-80	6508 (35)	1962 (37)	1048 (30)
90-100	11534 (62)	3120 (58)	2125 (62)
Missing	709 (4)	283 (5)	275 (8)
HLA-A B DRB1 groups - low resolution			
≤3/6	13 (<1)	16 (<1)	0
4/6	86 (<1)	42 (1)	14 (<1)
5/6	2655 (14)	674 (14)	531 (16)
6/6	15809 (85)	3927 (84)	2693 (83)
Unknown	188 (N/A)	706 (N/A)	210 (N/A)
High-resolution HLA matches available out of 8			
≤5/8	370 (2)	43 (1)	18 (1)
6/8	813 (4)	58 (2)	60 (3)
7/8	3761 (21)	687 (19)	502 (24)
8/8	13280 (73)	2800 (78)	1513 (72)
Unknown	527 (N/A)	1777 (N/A)	1355 (N/A)
HLA-DPB1 Match			
Double allele mismatch	4696 (30)	320 (28)	158 (30)
Single allele mismatch	8405 (54)	569 (49)	284 (53)
Full allele matched	2548 (16)	269 (23)	93 (17)
Unknown	3102 (N/A)	4207 (N/A)	2913 (N/A)
High resolution release score			
No	229 (2)	71 (44)	194 (70)
Yes	14457 (98)	92 (56)	83 (30)
Unknown	4065 (N/A)	5202 (N/A)	3171 (N/A)
KIR typing available			
No	10254 (55)	5300 (99)	3426 (99)
Yes	8497 (45)	65 (1)	22 (1)
Graft type			
Marrow	6595 (35)	1776 (33)	1489 (43)
PBSC	12145 (65)	3525 (66)	1957 (57)
BM+PBSC	4 (<1)	5 (<1)	1 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
BM+UCB	0	1 (<1)	0
PBSC+UCB	7 (<1)	58 (1)	1 (<1)
Number of cord units			
1	3 (100)	0	1 (100)
Conditioning regimen			
Myeloablative	13747 (73)	3778 (70)	2623 (76)
RIC/Nonmyeloablative	4928 (26)	1574 (29)	781 (23)
TBD	76 (<1)	13 (<1)	44 (1)
Donor age at donation			
To Be Determined/NA	95 (1)	666 (12)	29 (1)
0-9 years	8 (<1)	10 (<1)	0
10-19 years	548 (3)	155 (3)	81 (2)
20-29 years	8357 (45)	2110 (39)	1292 (37)
30-39 years	5304 (28)	1375 (26)	1076 (31)
40-49 years	3379 (18)	802 (15)	747 (22)
50+ years	1060 (6)	247 (5)	223 (6)
Median (Range)	31 (0-61)	30 (0-73)	33 (18-67)
Donor/Recipient CMV serostatus			
+/+	4848 (26)	1537 (30)	872 (27)
+/-	2104 (11)	636 (12)	420 (13)
-/+	6571 (36)	1707 (33)	1126 (34)
-/-	4946 (27)	1265 (25)	860 (26)
CB - recipient +	0	3 (<1)	0
CB - recipient -	0	1 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Unknown	282 (N/A)	215 (N/A)	170 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	539 (3)	133 (2)	160 (5)
CD34 selection	290 (2)	122 (2)	53 (2)
Tacrolimus + MMF ± others	2056 (11)	575 (11)	237 (7)
Tacrolimus + MTX ± others (except MMF)	8887 (47)	2528 (47)	1062 (31)
Tacrolimus + others (except MTX, MMF)	1003 (5)	345 (6)	136 (4)
Tacrolimus alone	470 (3)	150 (3)	64 (2)
CSA + MMF ± others (except Tacrolimus)	1002 (5)	242 (5)	226 (7)
CSA + MTX ± others (except Tacrolimus, MMF)	3015 (16)	763 (14)	1082 (31)
CSA + others (except Tacrolimus, MTX, MMF)	318 (2)	107 (2)	125 (4)
CSA alone	220 (1)	69 (1)	132 (4)
Other GVHD prophylaxis	302 (2)	87 (2)	57 (2)
Missing	649 (3)	244 (5)	114 (3)
Donor/Recipient sex match			
Male-Male	7375 (40)	2003 (38)	1301 (38)
Male-Female	5093 (27)	1391 (26)	871 (25)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Female-Male	2962 (16)	919 (17)	648 (19)
Female-Female	3231 (17)	932 (18)	604 (18)
CB - recipient M	2 (<1)	31 (1)	0
CB - recipient F	5 (<1)	28 (1)	1 (<1)
Unknown	83 (N/A)	61 (N/A)	23 (N/A)
Year of transplant			
1986-1990	119 (1)	17 (<1)	32 (1)
1991-1995	708 (4)	189 (4)	252 (7)
1996-2000	1320 (7)	475 (9)	430 (12)
2001-2005	2477 (13)	516 (10)	736 (21)
2006-2010	4581 (24)	957 (18)	740 (21)
2011-2015	6598 (35)	1865 (35)	877 (25)
2016-2019	2948 (16)	1346 (25)	381 (11)
Follow-up among survivors, Months			
N Eval	7780	2392	1242
Median (Range)	48 (1-337)	36 (1-325)	47 (1-337)

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	3077	689	670
Source of data			
CRF	2324 (76)	533 (77)	454 (68)
TED	753 (24)	156 (23)	216 (32)
Number of centers	135	111	154
Disease at transplant			
AML	1937 (63)	411 (60)	381 (57)
ALL	1060 (34)	259 (38)	268 (40)
Other acute leukemia	80 (3)	19 (3)	21 (3)
AML Disease status at transplant			
CR1	966 (50)	219 (53)	192 (50)
CR2	548 (28)	104 (25)	104 (27)
CR3+	51 (3)	6 (1)	11 (3)
Advanced or active disease	364 (19)	80 (20)	72 (19)
Missing	8 (<1)	1 (<1)	2 (1)
ALL Disease status at transplant			
CR1	477 (45)	108 (42)	122 (46)
CR2	397 (37)	100 (39)	95 (35)
CR3+	118 (11)	35 (14)	28 (10)
Advanced or active disease	68 (6)	16 (6)	23 (9)
Recipient age at transplant			
0-9 years	689 (22)	211 (31)	181 (27)
10-19 years	460 (15)	110 (16)	121 (18)
20-29 years	351 (11)	51 (7)	61 (9)
30-39 years	346 (11)	70 (10)	75 (11)
40-49 years	348 (11)	70 (10)	68 (10)
50-59 years	445 (14)	84 (12)	84 (13)
60-69 years	387 (13)	81 (12)	74 (11)
70+ years	51 (2)	12 (2)	6 (1)
Median (Range)	31 (0-81)	26 (0-75)	25 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1733 (59)	409 (63)	371 (62)
African-American, non-Hispanic	388 (13)	77 (12)	66 (11)
Asian, non-Hispanic	191 (7)	35 (5)	48 (8)
Pacific islander, non-Hispanic	16 (1)	2 (<1)	7 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Native American, non-Hispanic	16 (1)	3 (<1)	6 (1)
Hispanic	572 (20)	126 (19)	101 (17)
Unknown	161 (N/A)	37 (N/A)	71 (N/A)
Recipient sex			
Male	1610 (52)	373 (54)	373 (56)
Female	1467 (48)	316 (46)	297 (44)
Karnofsky score			
10-80	813 (26)	173 (25)	159 (24)
90-100	2197 (71)	484 (70)	483 (72)
Missing	67 (2)	32 (5)	28 (4)
HLA-A B DRB1 groups - low resolution			
≤3/6	43 (1)	18 (3)	3 (<1)
4/6	1317 (45)	236 (44)	246 (39)
5/6	1287 (44)	211 (40)	301 (48)
6/6	311 (11)	67 (13)	74 (12)
Unknown	119 (N/A)	157 (N/A)	46 (N/A)
High-resolution HLA matches available out of 8			
≤5/8	1543 (59)	236 (60)	277 (55)
6/8	623 (24)	90 (23)	127 (25)
7/8	313 (12)	37 (9)	76 (15)
8/8	142 (5)	28 (7)	28 (6)
Unknown	456 (N/A)	298 (N/A)	162 (N/A)
HLA-DPB1 Match			
Double allele mismatch	391 (39)	30 (53)	28 (41)
Single allele mismatch	510 (51)	21 (37)	32 (47)
Full allele matched	92 (9)	6 (11)	8 (12)
Unknown	2084 (N/A)	632 (N/A)	602 (N/A)
High resolution release score			
No	105 (11)	21 (40)	22 (85)
Yes	818 (89)	32 (60)	4 (15)
Unknown	2154 (N/A)	636 (N/A)	644 (N/A)
KIR typing available			
No	2385 (78)	684 (99)	666 (99)
Yes	692 (22)	5 (1)	4 (1)
Cord blood number of units			
1	2021 (66)	0	494 (74)
2	1055 (34)	0	176 (26)
3	1 (<1)	0	0
Unknown	0 (N/A)	689 (N/A)	0 (N/A)
Graft type			
UCB	2938 (95)	630 (91)	633 (94)
BM+UCB	0	1 (<1)	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
PBSC+UCB	139 (5)	58 (8)	37 (6)
Conditioning regimen			
Myeloablative	2202 (72)	506 (73)	464 (69)
RIC/Nonmyeloablative	869 (28)	183 (27)	205 (31)
TBD	6 (<1)	0	1 (<1)
Donor age at donation			
To Be Determined/NA	80 (3)	35 (5)	35 (5)
0-9 years	2752 (89)	544 (79)	578 (86)
10-19 years	158 (5)	62 (9)	30 (4)
20-29 years	28 (1)	13 (2)	7 (1)
30-39 years	27 (1)	22 (3)	11 (2)
40-49 years	11 (<1)	6 (1)	3 (<1)
50+ years	21 (1)	7 (1)	6 (1)
Median (Range)	3 (0-72)	4 (0-73)	4 (0-67)
Donor/Recipient CMV serostatus			
+/+	803 (26)	154 (22)	146 (22)
+/-	283 (9)	70 (10)	54 (8)
-/+	603 (20)	124 (18)	135 (20)
-/-	363 (12)	73 (11)	92 (14)
CB - recipient +	653 (21)	162 (24)	135 (20)
CB - recipient -	331 (11)	84 (12)	93 (14)
CB - recipient CMV unknown	41 (1)	22 (3)	15 (2)
GvHD Prophylaxis			
Ex vivo T-cell depletion	16 (1)	6 (1)	2 (<1)
CD34 selection	108 (4)	42 (6)	30 (4)
Tacrolimus + MMF ± others	836 (27)	167 (24)	100 (15)
Tacrolimus + MTX ± others (except MMF)	125 (4)	38 (6)	35 (5)
Tacrolimus + others (except MTX, MMF)	108 (4)	29 (4)	18 (3)
Tacrolimus alone	69 (2)	20 (3)	10 (1)
CSA + MMF ± others (except Tacrolimus)	1530 (50)	306 (44)	358 (53)
CSA + MTX ± others (except Tacrolimus, MMF)	52 (2)	13 (2)	19 (3)
CSA + others (except Tacrolimus, MTX, MMF)	123 (4)	47 (7)	59 (9)
CSA alone	30 (1)	9 (1)	27 (4)
Other GVHD prophylaxis	62 (2)	5 (1)	10 (1)
Missing	18 (1)	7 (1)	2 (<1)
Donor/Recipient sex match			
CB - recipient M	1610 (52)	373 (54)	372 (56)
CB - recipient F	1467 (48)	316 (46)	297 (44)
CB - recipient sex unknown	0	0	1 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	55 (2)	53 (8)	11 (2)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2006-2010	1031 (34)	226 (33)	215 (32)
2011-2015	1520 (49)	268 (39)	342 (51)
2016-2019	471 (15)	141 (20)	99 (15)
Follow-up among survivors, Months			
N Eval	1409	350	315
Median (Range)	48 (1-176)	37 (2-187)	48 (1-145)

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

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	3007	481	181
Source of data			
CRF	987 (33)	126 (26)	55 (30)
TED	2020 (67)	355 (74)	126 (70)
Number of centers	78	56	39
Disease at transplant			
AML	1980 (66)	297 (62)	118 (65)
ALL	946 (31)	170 (35)	60 (33)
Other acute leukemia	81 (3)	14 (3)	3 (2)
AML Disease status at transplant			
CR1	1215 (61)	189 (64)	72 (61)
CR2	312 (16)	33 (11)	12 (10)
CR3+	23 (1)	4 (1)	0
Advanced or active disease	423 (21)	69 (23)	32 (27)
Missing	7 (<1)	2 (1)	2 (2)
ALL Disease status at transplant			
CR1	597 (63)	112 (66)	43 (72)
CR2	257 (27)	35 (21)	10 (17)
CR3+	39 (4)	5 (3)	2 (3)
Advanced or active disease	53 (6)	18 (11)	5 (8)
Recipient age at transplant			
0-9 years	193 (6)	21 (4)	10 (6)
10-19 years	298 (10)	32 (7)	14 (8)
20-29 years	292 (10)	61 (13)	21 (12)
30-39 years	307 (10)	51 (11)	15 (8)
40-49 years	465 (15)	81 (17)	27 (15)
50-59 years	717 (24)	114 (24)	43 (24)
60-69 years	642 (21)	103 (21)	44 (24)
70+ years	93 (3)	18 (4)	7 (4)
Median (Range)	49 (1-76)	49 (1-76)	51 (1-74)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1944 (68)	248 (55)	117 (67)
African-American, non-Hispanic	269 (9)	34 (8)	9 (5)
Asian, non-Hispanic	132 (5)	47 (10)	13 (7)
Pacific islander, non-Hispanic	9 (<1)	1 (<1)	0
Native American, non-Hispanic	13 (<1)	1 (<1)	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Hispanic	507 (18)	118 (26)	36 (21)
Unknown	133 (N/A)	32 (N/A)	6 (N/A)
Recipient sex			
Male	1710 (57)	274 (57)	101 (56)
Female	1297 (43)	207 (43)	80 (44)
Karnofsky score			
10-80	1132 (38)	215 (45)	81 (45)
90-100	1812 (60)	259 (54)	93 (51)
Missing	63 (2)	7 (1)	7 (4)
Graft type			
Marrow	737 (25)	91 (19)	50 (28)
PBSC	2265 (75)	387 (80)	130 (72)
BM+PBSC	2 (<1)	2 (<1)	0
BM+UCB	3 (<1)	1 (<1)	0
PBSC+UCB	0	0	1 (1)
Conditioning regimen			
Myeloablative	2162 (72)	335 (70)	129 (71)
RIC/Nonmyeloablative	840 (28)	145 (30)	50 (28)
TBD	5 (<1)	1 (<1)	2 (1)
Donor age at donation			
To Be Determined/NA	22 (1)	1 (<1)	0
0-9 years	141 (5)	11 (2)	9 (5)
10-19 years	263 (9)	41 (9)	12 (7)
20-29 years	422 (14)	78 (16)	21 (12)
30-39 years	418 (14)	81 (17)	31 (17)
40-49 years	502 (17)	87 (18)	21 (12)
50+ years	1239 (41)	182 (38)	87 (48)
Median (Range)	45 (0-80)	43 (0-79)	48 (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	38 (1)	10 (2)	1 (1)
CD34 selection	39 (1)	11 (2)	6 (3)
Post-CY + other(s)	570 (19)	83 (17)	29 (16)
Post-CY alone	23 (1)	6 (1)	3 (2)
TAC + MMF ± other(s) (except post-CY)	312 (10)	27 (6)	16 (9)
TAC + MTX ± other(s) (except MMF, post-CY)	1326 (44)	173 (36)	88 (49)
TAC + other(s) (except MMF, MTX, post-CY)	307 (10)	133 (28)	18 (10)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
TAC alone	21 (1)	2 (<1)	0
CSA + MMF ± other(s) (except post-CY)	42 (1)	4 (1)	2 (1)
CSA + MTX ± other(s) (except MMF, post-CY)	239 (8)	18 (4)	13 (7)
CSA alone	24 (1)	6 (1)	0
Other(s)	30 (1)	3 (1)	2 (1)
Missing	36 (1)	5 (1)	3 (2)
Donor/Recipient sex match			
Male-Male	955 (32)	176 (37)	58 (32)
Male-Female	677 (23)	101 (21)	41 (23)
Female-Male	753 (25)	97 (20)	43 (24)
Female-Female	619 (21)	106 (22)	38 (21)
CB - recipient M	2 (<1)	1 (<1)	0
CB - recipient F	1 (<1)	0	1 (1)
Year of transplant			
2006-2010	224 (7)	20 (4)	14 (8)
2011-2015	1589 (53)	250 (52)	91 (50)
2016-2019	1194 (40)	211 (44)	76 (42)
Follow-up among survivors, Months			
N Eval	1817	305	106
Median (Range)	24 (1-124)	23 (3-100)	24 (2-96)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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

LK13-02: Prognostic significance of cytogenetic abnormalities in patients with Philadelphia-negative ALL undergoing allogeneic Hematopoietic Stem Cell Transplantation in complete remission (A Lazaryan/ V Bachanova) The purpose of this study is:
(1) To develop allo-HCT specific cytogenetic classification of Ph-negative ALL for prognostication of relapse and survival outcomes following allo-HCT.
(2) To validate within the CIBMTR database the prognostic significance of existing cytogenetic classifications of Ph-negative ALL in the context of the allo-HCT.
(3) To compare the performance of both CIBMTR-based and existing classifications of Ph-negative ALL treated with allo-HCT.
Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by July 2019.

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) 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.
Data file preparation underway. The goal of the study is to have the data finalized and start analysis by July 2019.

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 (Z Gul/ G Ahmed/ M Khan/ G Hilderbrandt/ H Alkhateeb/ M Damlaj/ M Patnaik/ R Nath/ Z Zhou/ J Cerny).
The purpose of this study is:
(1) To compare the treatment related toxicity of M based and B based RIC regimens in terms of non-relapse mortality and incidence and severity of acute and chronic GVHD.

(2) To compare hematologic recovery, engraftment kinetics, incidence of relapse, progression free survival and overall survival between the two regimens.
Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by July 2019.

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). 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).
Data file preparation underway. The goal of the study is to have the manuscript finalized by July 2019.

LK16-03: Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes (N Callander/ L Metheny/ M De Lima / A Hall). 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.
Data file preparation underway. The goal of the study is to finalize data analysis and manuscript preparation by July 2019.

LK16-04: Comparing outcomes between HLA-haploidentical and matched sibling allogeneic transplants in patients with acute myeloid leukemia (R Romee/ A Rashidi/ M Hamadani/ W Saber).
The purpose of this study is:
(1) To compare post-transplantation outcomes in patients with AML undergoing T-replete matched sibling allo-HCT versus T-replete haploidentical related donor allo-HCT (with PT-CY) including: neutrophil and platelet recovery, acute and chronic GVHD, non-relapse mortality, relapse, Leukemia-free survival and overall survival.
Manuscript preparation is underway. The goal of the study is to have the manuscript submitted by July 2019.

LK17-01: Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response (M Percival / B Sandmaier / E Estey). 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.
Data file preparation underway. The goal of the study is to finalize data analysis and submit manuscript by July 2019.

LK17-02: Allogeneic Hematopoietic Transplant Outcomes in Adult Patients with MLL-rearranged Acute Myeloid Leukemia (K Menghrajani/ M Tallman). The purpose of this study is:
(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.
Protocol development is underway. The goal of the study is to finalize data analysis and manuscript preparation by July 2019.

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).
The purpose of this study is:
(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).
Protocol development is underway. The goal is to finalize the protocol, start data file preparation and analysis by July 2019.

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).
The purpose of the 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 each ELN group.
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2019.

LK18-02 Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia (Matthew Wieduwilt)
The Purpose of the 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.
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2019.

Proposal 1808-01

Title:
Myeloablative or reduced intensity conditioning allogeneic hematopoietic transplantation in acute leukemia: CIBMTR analysis of long term outcomes

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Hypothesis:
Long-term outcomes of myeloablative (MA) or reduced intensity conditioning (RIC) allogeneic hematopoietic transplantation in acute leukemia are similar, a result of major tradeoffs

Specific aims:

- Compare treatment related mortality (TRM) at 100 days, 1 year and 3 years between MA and RIC allogeneic hematopoietic transplantation in acute leukemia.
- Compare disease free survival (DFS) at 100 days, 1 year and 3 years between MA and RIC allogeneic hematopoietic transplantation in acute leukemia.
- Compare overall survival (OS) at 100 days, 1 year and 3 years between MA and RIC allogeneic hematopoietic transplantation in acute leukemia.

Scientific justification:
Allogeneic hematopoietic transplantation (allo-HCT) cures patients by cytoreduction of their residual tumor and by graft-versus-leukemia (GVL). This clinical dilemma balancing tolerable toxicities (influenced by patients' performance status and associated comorbidities) and influenced by the graft source may require lesser intensity regimens to ensure safety. While RIC allo-HCT offers lesser TRM, not every patient is a candidate for RIC. Patient with young age, no comorbidity and those receiving T cell depletion benefit with MA allo-HCT.[1]
Consensus discussions reported from the Center for International Blood and Marrow Transplant Research (CIBMTR) have defined myeloablative or high-dose regimens, most often including single or multiple alkylators and sometimes including total body irradiation (TBI).[2] These high-dose regimens are called myeloablative because they preclude hematologic recovery in the setting of graft rejection. Additionally, they are profoundly myelosuppressive and thus, induce pancytopenia promptly after transplantation. RIC regimens are less myelosuppressive, although potently immunosuppressive, to facilitate engraftment of matched donor cell infusions, but offer little in antineoplastic potency.[3]
Majority of transplants, particularly in older people, are now performed using intermediate intensity or RIC, which generally use lower dose alkylator or even intermediate to low dose TBI. Cyclophosphamide and TBI or busulfan plus cyclophosphamide have been the long standing and most commonly used myeloablative conditioning regimens. Both combine the immunosuppressive, marrow ablative, and hopefully tumor ablative capabilities of each regimen component to yield effective engraftment with tolerable toxicity and disease control. In the last decade, fludarabine plus high-dose alkylators (melphalan or busulfan) have been widely applied as reduced-toxicity myeloablative regimens. [4]
Fludarabine, coupled with low-dose (200 cGy) TBI was the original, widely used non-myeloablative regimen. [4] While extensively tested, it has been recognized that in more resistant disease, relapse rates are excessive. Intermediate-dose alkylators (often busulfan or melphalan) are added to supplement the anti-tumor potency of these RIC regimens. While initial engraftment is also often incomplete and mixed donor chimerism evolves over time to full donor chimerism, these regimens have not substantially truncated the risks of GVHD and the accompanying immunologically-based anti-tumor effects. However,

RIC regimens have been used more often for older patients and those with comorbidities, thereby making formal comparisons of NRM and relapse confounded by the populations chosen for each treatment. These regimens might be more suited for the highly GVL-sensitive tumors mentioned earlier or the lower risk phenotypes of acute leukemia.
No prospective randomized data has been reported directly comparing ablative and reduced-intensity regimens.[5] Retrospective analysis from the CIBMTR and the European Group for Blood and Marrow Transplantation (EBMT) as well as individual or multicenter analyses have described modestly lower NRM for the reduced-intensity regimens, but countered with generally higher relapse rates (table-1). [5-18] These comparisons are, of course, confounded by the selection habits of applying reduced-intensity regimens to older patients, those with comorbidities or those who are frailer, leaving them more vulnerable to transplant toxicity and mortality. Conversely, good clinical judgment may have selected more patients for reduced-intensity regimens who had more GVL-sensitive phenotypes, less heavily-treated patients, and those with diseases more likely to be controlled by the GVL effect of the allograft. As shown in the table, it is difficult to generalize about the comparative benefit of MA versus RIC transplants for the major diseases where it has been explored, namely AML or ALL.
We propose to compare outcomes of MA and RIST allo-HCT in a large cohort of adult patients reported to CIBMTR

Eligible patient population:

- Age > 18 or older
- Diagnosis of AML or ALL

Data collection:
Data will be collected using existing CIBMTR forms for acute leukemia for patients receiving allo-HCT between January 2005 and December 2016

Study design (scientific plan):
The conditioning regimen will be distributed in total of 2 categories (MA or RIST). Conditioning regimen that is not MA will define RIST. All non myeloablative conditioning regimens will be included as RIST. Examples of MA regimens include: CY/TBI, BU/CY, and similar while Flu-Mel, Flu-bu, Flu-cy with or without TBI comprises most RIST regimens. Only patients with AML and ALL will be included. Patients with chronic leukemia, lymphoma or any other allo-HCT indications will be excluded. Standard definitions will be used for TRM, DFS and OS. Survival curves were calculated according to the Kaplan–Meier method and compared by the two-sided log-rank test, with the use of the Lifetest procedure in the SAS statistical package. Differences were considered significant if the P value was less than 0.05. Other comparisons were performed with the chi-square and Fisher's exact tests.
An event was defined as a relapse, evidence of disease progression, or death, whatever the cause. The date of the first event was used in calculating event-free survival.

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Table-1: Reported outcomes in MA or RIC conditioning allo-HCT in acute leukemia

Author	N	Relapse MA vs RIC	NRM MA vs RIC	OS MA vs RIC	FU
Scott 2015	272	14% vs 48%	15.8% vs 4.4%	77% vs 68%	18 M
Bornhauser 2009	197	RIC superior overall			24 M
Luger 2004	4772	MA superior overall			NA
Abdul 2014	15258	MA better	RIC better	MA better	NA
Mohty 2010	576	MA better	RIC better	NA	NA
Ringden 2019	1555	MA superior overall			NA
Shimoni 2016	1423	MA superior overall			10 Y
Flynn 2007	219	MA superior overall			NA
Lim 2010	1333	MA better	RIC better	NA	NA
Bachanova 2013	197	MA better	RIC better	NA	NA
Sibai 2016	248	14% vs 26%	NA	NA	NA
Baron 2016	894	MA better	RIC better	NA	NA
Savani 2016	1924	RIC superior overall			NA
Warlick 2015	414	MA better overall			NA

N= number, M= months, Y= years, NA= not applicable, FU= follow-up

Table 2. Characteristics of adult patients receiving first allo-HCT for AML and ALL between 2005 -2016 reported to CIBMTR

	AML	ALL
Number of patients	35767	12542
Number of centers	386	361
Age at HCT		
Median (range)	52 (18-84)	38 (18-77)
18-29	4251 (12)	4271 (34)
30-39	4611 (13)	2513 (20)
40-49	6867 (19)	2546 (20)
50-59	9916 (28)	2168 (17)
60-69	8787 (25)	988 (8)
≥70	1335 (4)	56 (<1)
Track		
TED	24611 (69)	9109 (73)
CRF	11156 (31)	3433 (27)
Gender		
Male	18895 (53)	7362 (59)
Female	16872 (47)	5180 (41)
Race		
Caucasian	26557 (74)	8466 (68)
African-American	1398 (4)	482 (4)
Asian	2608 (7)	1105 (9)
Pacific islander	96 (<1)	46 (<1)
Native American	95 (<1)	68 (<1)
Other	285 (<1)	144 (1)
More than one race	83 (<1)	46 (<1)
Missing	4645 (13)	2185 (17)
Karnofsky score		
<90	11223 (31)	3597 (29)
≥90	20086 (56)	7390 (59)
Missing	4458 (12)	1555 (12)

	AML	ALL
HCT-CI		
0	8992 (25)	3850 (31)
1	3880 (11)	1296 (10)
2	3446 (10)	1193 (10)
3+	10105 (28)	2846 (23)
TBD, review needed for history of malignancies	12 (<1)	3 (<1)
NA, f2400 (pre-TED) not completed	7007 (20)	2423 (19)
Missing	2325 (7)	931 (7)
Disease status prior to HCT		
CR1	4609 (13)	443 (4)
CR2	20661 (58)	8143 (65)
≥CR3	6135 (17)	2565 (20)
Relapse	141 (<1)	98 (<1)
No treatment	3333 (9)	872 (7)
Missing	888 (2)	421 (3)
Conditioning as reported by center		
MAC	21501 (60)	9894 (79)
RIC/NMA	13364 (37)	2331 (19)
Missing	902 (3)	317 (3)
Donor type		
HLA-identical sibling	12923 (36)	4934 (39)
Other related	2705 (8)	871 (7)
Well-matched unrelated	9599 (27)	2793 (22)
Partially-matched unrelated	2369 (7)	805 (6)
Mis-matched unrelated	192 (<1)	66 (<1)
Multi-donor	166 (<1)	62 (<1)
Unrelated (matching TBD)	5106 (14)	1830 (15)
Cord blood	2297 (6)	941 (8)
Missing	410 (1)	240 (2)

	AML	ALL
Graft type		
Bone marrow	4909 (14)	2268 (18)
Peripheral blood	28521 (80)	9313 (74)
Umbilical cord blood	2294 (6)	937 (7)
Donor Leukocyte Infusion (buffy coat)	2 (<1)	1 (<1)
Other, specify	4 (<1)	2 (<1)
BM + Other	1 (<1)	0
PB + Other	32 (<1)	17 (<1)
UCB + Other	3 (<1)	4 (<1)
BM + PB + Other	1 (<1)	0
Year of HCT		
2005	2419 (7)	856 (7)
2006	2422 (7)	844 (7)
2007	2352 (7)	809 (6)
2008	2694 (8)	950 (8)
2009	2834 (8)	1013 (8)
2010	3138 (9)	1097 (9)
2011	3249 (9)	1106 (9)
2012	3309 (9)	1212 (10)
2013	3468 (10)	1154 (9)
2014	3306 (9)	1132 (9)
2015	3234 (9)	1164 (9)
2016	3342 (9)	1205 (10)
Median follow-up of survivors (range), months	49 (<1-160)	48 (1-151)

Proposal: 1810-01

Title:
Does the Novel Scoring System (I-CBFit) Predict Outcomes After Allogeneic Hematopoietic Cell Transplantation in Core Binding Factor (CBF) AML with t(8;21)?

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Hypothesis:
I-CBFit can predict outcomes [relapse, disease-free survival (DFS), overall survival (OS)] after allogeneic hematopoietic cell transplantation (HCT) in patients with t(8;21).

Specific aims:
- To evaluate if I-CBFit predicts relapse rate after allogeneic HCT in patients with t(8;21).
- To evaluate if I-CBFit predicts DFS after allogeneic HCT in patients with t(8;21).
- To evaluate if I-CBFit predicts OS after allogeneic HCT in patients with t(8;21).
- To evaluate if I-CBF predicts these outcomes after allogeneic HCT in CR1 and CR2.
- To evaluate if I-CBF predicts these outcomes after RIC and MAC allogeneic HCT.

Scientific justification:
Acute myeloid leukemia (AML) with rearrangements involving genes encoding subunits of core-binding factor (CBF), a group of DNA-binding transcription factor complexes composed of α and β subunits, share similar pathogenesis and clinical features and are considered as a distinct subset in AML.[1-4] Translocation(8;21)(q22;q22) and inv(16)(p13q22), leading to the creation of the fusion genes *RUNX1/RUNXT1* and *CBFB/MYH11* that disrupt, respectively, the α and β subunits of CBF, dysregulate hematopoiesis, and thus contribute to leukemogenesis.[5]
Although the prognosis of CBF-AML is better than other subtypes of AML, approximately 30-40% of the patients still relapse and may require allogeneic hematopoietic cell transplantation (HCT).[6-8] A scoring system to predict who has a higher risk of relapse at the time of diagnosis may be clinically valuable to guide decision-making about whether for any subsets, HCT might be beneficial in first complete remission (CR1). There have been only a few studies attempting to develop a scoring system for poor outcomes of CBF-AML [e.g., relapse, disease-free survival (DFS)].[6,8] Moreover, recent studies clearly indicate that AMLs with t(8;21) (q22;q22) and AMLs with inv(16) (p13q22) are two different diseases with somewhat different patient and disease characteristics.[2,6,8-13] Each cytogenetic subgroup, therefore, should be evaluated separately to develop a specific prognostic scoring system.
In a multicenter study, we created an extensive database including US and European centers for CBF-AML patients with t(8;21) (q22;q22), and developed a significant risk scoring system (I-CBFit) with high predictive probabilities. DFS rate at 2 years was 76% for patients with a low-risk I-CBFit score compared with 36% for those with a high-risk I-CBFit score (P<0.0001). Low versus high risk OS at 2 years was 89% versus 51% (P<0.0001) (Figure 1 and 2). [14]
I-CBFit Score = [0.03 x Age (years) + 0.02 x WBC (at diagnosis) + 1.47 (*KIT* D816V Mutation Positive) + 0.94 (*KIT* D816V Mutation Non-Tested/Missing) + 0.94 (pseudodiploidy)] - 3.05
When I-CBFit > 0, a patient is classed as being at high risk of death or relapse within two years.

Patient eligibility population:
Any patient with t(8;21) receiving an HCT between January 2000 and June 2017.

Variables to be analyzed:
Patient related variables:

- Age at transplantation (continuous)
- Gender: Female vs. male
- Karnofsky performance score: < 80% vs. ≥ 80%
- Previous history of transplant
- Hematopoietic stem cell transplantation-specific comorbidity index (HCT-CI)

Disease related variables at diagnosis and treatment prior to allo-HSCT

- At Diagnosis
    - Cytogenetics (full karyotype) and
    - Cytogenetic risk group by ELN
    - WBC
    - KIT mutation, tested, positive or negative
    - Other molecular markers: FLT3, NPM1
- Disease status at HCT
    - CR1 or CR2
    - MRD status documented by flow cytometry, FISH or molecular techniques.

Transplant related variables:

- Donor type: HLA matched sibling vs. HLA matched unrelated donor (matched for HLA –A, B, C, DRB1) vs. partially matched unrelated donor (single locus mismatches at HLA –A, B, C, DRB1) vs. mismatched unrelated donor (2 or more mismatches at HLA –A, B, C, DRB1) vs. UCB vs. haploidentical donor.
- Donor-Recipient Sex M-M vs. M-F vs. F-M vs. F-F
- Donor Age
- Donor-recipient CMV serostatus: -/- vs. -/+ vs. +/- vs. +/+
- GVHD prophylaxis: CSA or Tac plus MTX vs. MMF+others vs. ex vivo T cell depletion vs. post-HCT Cy
- Alemtuzumab (yes/no) or ATG (yes/no)
- Transplant period: 2000-2008 vs. 2009-2017
- Conditioning regimen: TBI vs. non-TBI; myeloablative vs. non-myeloablative/reduced intensity and combined MAC-TBI^{+} vs. MAC-TBI^{-} vs. RIC
- Source of stem cells: Bone marrow (BM) vs. peripheral blood stem cell (PBSC) vs. UCB
- CD34+ cell dose (for PBSC and UCB)
- Nucleated cell dose (for BM)
- DCTR (time from Diagnosis to CR1 divided by CR1 to HCT) for CR1 patients
- CR1 duration for CR2 patients
- Consolidation: number of cycles

Post-transplant related variables:

- Acute GVHD: as a time-to-event variable in allogeneic recipients.

Study end points and outcomes:

- Relapse at 2-year. This event will be summarized by cumulative incidence estimate with TRM as the competing risk.
- DFS at 2 years: Time to death or relapse, patients censored at last follow-up.
- OS at 2-years: Time to death, patients censored at last follow-up.

Sample requirements:

All requested data is available from existing data collection forms since 2000.

Study design (scientific plan):

This is a retrospective cohort analysis to evaluate if I-CBFit predicts relapse, DFS or OS after HCT. The Kaplan-Meier estimates will be used to analyze the median and range of follow-up time. Probabilities of relapse will be calculated using cumulative incidence curves to accommodate competing risks. Potential risk factors for outcomes of interest will be evaluated in multivariate analyses using Cox proportional hazards regression. Patient characteristics that are significant in the univariate models at the 0.10 level, and those that are clinically relevant will be included in the multivariate model. Backward elimination will be implemented until all remaining predictors reached a significance level of 5% or less ($p \leq 0.05$). Further adjustments will be applied when test indicates that interactions are significant.

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Figure 1. Disease-Free Survival by I-CBFit (a high risk shown in green curve corresponds to a risk score of 0 or greater).

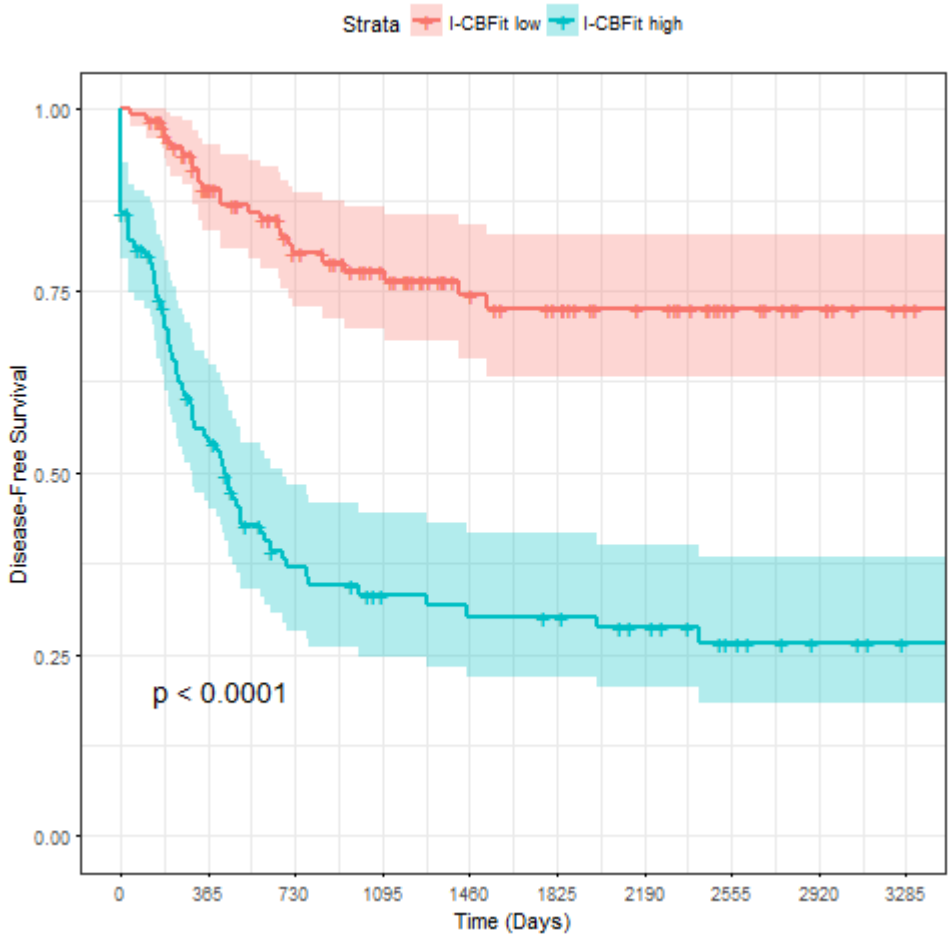

Figure 2. Overall survival by I-CBFit (a high risk shown in green curve corresponds to a risk score of 0 or greater).

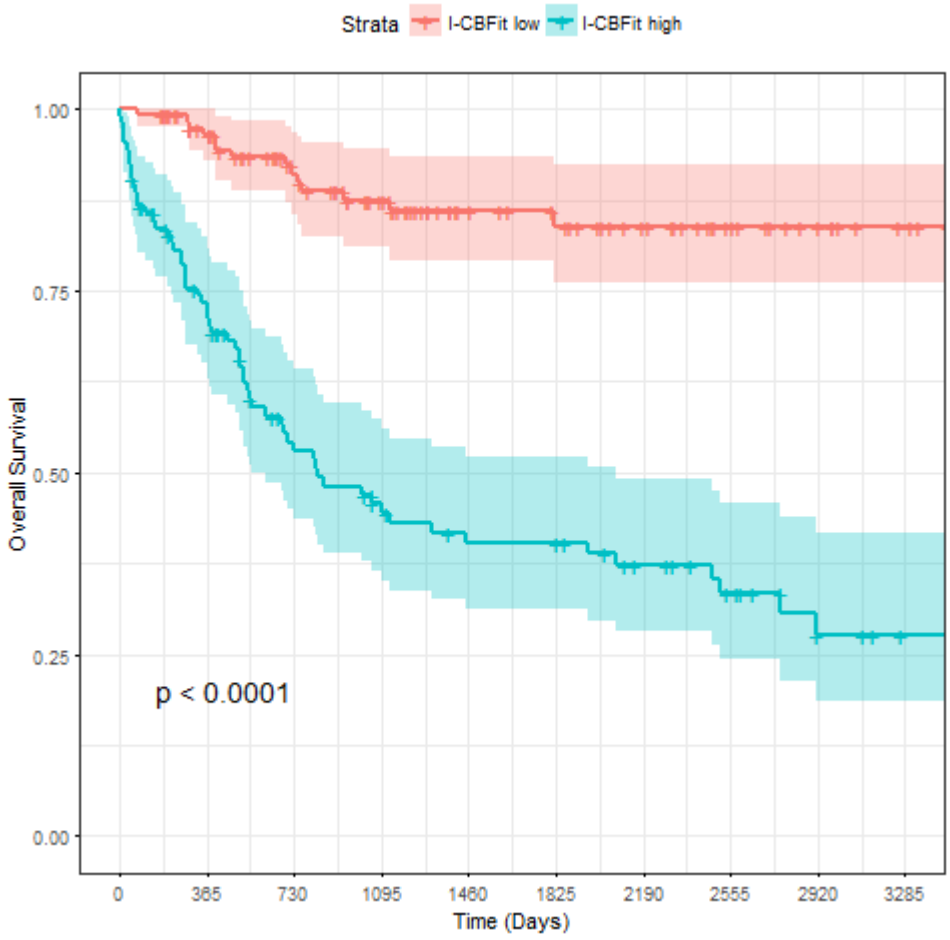

Table 1. Characteristics of adult patients receiving first allo-HCT for AML in CR1\CR2 with t(8;21) between 2013-2017 reported to CIBMTR

	TED	CRF
Number of patients	222	402
Number of centers	107	129
Age at HCT		
Median (range)	43 (18-75)	42 (18-76)
18-29	59 (27)	118 (29)
30-39	44 (20)	73 (18)
40-49	33 (15)	93 (23)
50-59	54 (24)	72 (18)
60-69	28 (13)	33 (8)
≥70	4 (2)	13 (3)
Gender		
Male	122 (55)	234 (58)
Female	100 (45)	168 (42)
Race		
Caucasian	148 (67)	270 (67)
African-American	11 (5)	26 (6)
Asian	20 (9)	84 (21)
Pacific islander	0	3 (<1)
Native American	1 (<1)	1 (<1)
More than one race	1 (<1)	3 (<1)
Missing	41 (18)	15 (4)
Karnofsky score		
< 90	79 (36)	85 (21)
≥ 90	137 (62)	208 (52)
Missing	6 (3)	109 (27)
HCT-CI		
0	55 (25)	63 (16)
1	32 (14)	27 (7)
2	29 (13)	32 (8)
3+	98 (44)	91 (23)
TBD	3 (1)	5 (1)
NA, f2400 (pre-TED) not completed	5 (2)	178 (44)
Missing	0	6 (1)

	TED	CRF
KIT		
Negative	72 (32)	35 (9)
Positive	104 (47)	61 (15)
Missing	46 (21)	306 (76)
Disease status prior to HCT		
CR1	137 (62)	209 (52)
CR2	85 (38)	193 (48)
Conditioning as reported by center		
MAC	143 (64)	271 (67)
RIC/NMA	75 (34)	102 (25)
Missing	4 (2)	29 (7)
Donor type		
HLA-identical sibling	81 (36)	122 (30)
Other related	18 (8)	34 (8)
Well-matched unrelated	73 (33)	138 (34)
Partially-matched unrelated	11 (5)	38 (9)
Mis-matched unrelated	1 (<1)	11 (3)
Multi-donor	0	3 (<1)
Unrelated (matching TBD)	37 (17)	10 (2)
Cord blood	1 (<1)	46 (11)
GVHD prophylaxis		
Ex-vivo T-cell depletion	0	8 (2)
CD34 selection	6 (3)	13 (3)
Post-CY + other(s)	21 (9)	20 (5)
Post-CY alone	2 (<1)	2 (<1)
TAC + MMF ± other(s) (except post-CY)	21 (9)	33 (8)
TAC + MTX ± other(s) (except MMF, post-CY)	81 (36)	127 (32)
TAC + other(s) (except MMF, MTX, post-CY)	11 (5)	11 (3)
TAC alone	4 (2)	5 (1)
CSA + MMF ± other(s) (except post-CY)	15 (7)	48 (12)
CSA + MTX ± other(s) (except MMF, post-CY)	56 (25)	114 (28)
CSA + other(s) (except MMF, MTX, post-CY)	1 (<1)	3 (<1)
CSA alone	4 (2)	7 (2)
Other(s)	0	4 (<1)
Missing	0	7 (2)

	TED	CRF
Graft type		
Bone marrow	37 (17)	114 (28)
Peripheral blood	184 (83)	242 (60)
Umbilical cord blood	1 (<1)	46 (11)
Year of HCT		
2000	0	22 (5)
2001	0	24 (6)
2002	1 (<1)	14 (3)
2003	1 (<1)	11 (3)
2004	0	38 (9)
2005	1 (<1)	25 (6)
2006	1 (<1)	26 (6)
2007	1 (<1)	19 (5)
2008	0	34 (8)
2009	0	25 (6)
2010	0	18 (4)
2011	0	10 (2)
2012	0	11 (3)
2013	19 (9)	27 (7)
2014	41 (18)	31 (8)
2015	52 (23)	31 (8)
2016	60 (27)	26 (6)
2017	45 (20)	10 (2)
Median follow-up of survivors (range), months	24 (1-166)	69 (3-218)

Proposal: 1811-23

Title:
The influence of FLT3 internal tandem duplication (ITD) Vs FLT3 tyrosine kinase domain (TKD) with or without NPM1 or IDH1/2 on transplant outcome

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Hypothesis:
FLT3/IDH dual mutants may have inferior outcomes related to a more proliferative
FLT3 TKD with NPM1 dual mutants may have better outcomes despite high WBC at diagnosis.

Specific aims:
- Primary end points of the study is OS.
- Other end points of interest are PFS, TRM, and GRFS.
- Stratify results by patient age, (FLT3 TKD , FLT3 ITD, IDH, and NPM1 status), Cytogenetics, DRI, regimens and by stem cell source PB vs BM

Scientific impact:
Results from this study will have important clinical relevance, providing a historical expectation for patients within this AML subsets.

Scientific justification:
Little is known regarding the outcome of double mutant AML with IDH1/2 or NPM1 mutations with FLT3-TKD mutations. Both presents with high WBC at diagnosis. NPM1 and IDH1/2 noted to co-occur with FLT3 abnormalities in AML, respectively. The prognostic influence of FLT3-ITD+ IDH+ mutation status or FLT3 TKD+ NPM1+ on outcomes in AML patients who received allo SCT is not known. Few small studies [1-3]looked at that but no multicenter large group of patients published.

Patient eligibility population:
- Patients with AML
- Year of HSCT ≥2005

Data requirements:
This study will use the following forms:
- Pre-Transplant Essential Data
- Post-transplant Essential data
- AML Pre-HSCT Data
- AML Post-HSCT Data
- Chimerism studies

Variables needed:
Age of patient at diagnosis, gender of patient, date of diagnosis, Cytogenetic abnormality at diagnosis, Molecular abnormalities at Dx and preSCT and post SCT, FLT3 TKD , FLT3 ITD, IDH, and NPM1 status, DRI,

Pre-HSCT blasts in Bone marrow and peripheral blood, conditioning regimen, GVHD prophylaxis, date of relapse or progression, date of death, presence of GVHD, date of last follow up, percentage of host cells between day 30-60 and at day 100.

Study design:
Overall survival and progression free survival will be estimated using the Kaplan-Meier method. Relapse and NRM will be summarized using cumulative incidence estimated with NRM a competing risk for relapse and relapse a competing risk for NRM

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Table 1. Characteristics of adult patients receiving first allo-HCT for AML in CR1/CR2/CR3/Relapse between 2009-2017, reported to CIBMTR

	CR1	CR2	≥CR3	Relapse	No treatment
Number of patients	128	873	243	15	80
Number of centers	46	128	91	12	41
Age at HCT					
Median (range)	56 (21-76)	56 (18-76)	54 (20-76)	54 (25-76)	55 (21-82)
18-29	16 (13)	73 (8)	12 (5)	1 (7)	9 (11)
30-39	14 (11)	86 (10)	30 (12)	0	6 (8)
40-49	19 (15)	147 (17)	47 (19)	3 (20)	15 (19)
50-59	24 (19)	240 (27)	79 (33)	6 (40)	26 (33)
60-69	43 (34)	273 (31)	65 (27)	4 (27)	19 (24)
≥70	12 (9)	54 (6)	10 (4)	1 (7)	5 (6)
Gender					
Male	79 (62)	415 (48)	113 (47)	8 (53)	45 (56)
Female	49 (38)	458 (52)	130 (53)	7 (47)	35 (44)
Karnofsky score					
<90	64 (50)	335 (38)	93 (38)	8 (53)	48 (60)
≥90	61 (48)	529 (61)	146 (60)	7 (47)	31 (39)
Missing	3 (2)	9 (1)	4 (2)	0	1 (1)
FLT3I-TD					
No	42 (33)	285 (33)	149 (61)	10 (67)	26 (33)
Yes	80 (63)	561 (64)	84 (35)	5 (33)	53 (66)
Missing	6 (5)	27 (3)	10 (4)	0	1 (1)
FLT3-point mutation					
No	83 (65)	541 (62)	149 (61)	6 (40)	51 (64)
Yes	11 (9)	135 (15)	48 (20)	4 (27)	14 (18)
Missing	34 (27)	197 (23)	46 (19)	5 (33)	15 (19)
NPM1					
No	69 (54)	300 (34)	37 (15)	2 (13)	21 (26)
Yes	37 (29)	479 (55)	191 (79)	11 (73)	52 (65)
Missing	22 (17)	94 (11)	15 (6)	2 (13)	7 (9)
IDH					
No	23 (18)	207 (24)	43 (18)	1 (7)	23 (29)
Yes	36 (28)	160 (18)	25 (10)	0	9 (11)
Missing	69 (54)	506 (58)	175 (72)	14 (93)	48 (60)

	CR1	CR2	≥CR3	Relapse	No treatment
FLT3-point mutation/NPM1 or IDH double mutant vs other					
No	127 (99)	810 (93)	210 (86)	13 (87)	72 (90)
Yes	1 (<1)	63 (7)	33 (14)	2 (13)	8 (10)
FLT3-point mutation/NPM1 double mutant vs other					
No	127 (99)	813 (93)	211 (87)	13 (87)	72 (90)
Yes	1 (<1)	60 (7)	32 (13)	2 (13)	8 (10)
FLT3-ITD/IDH vs FLT3-point mutation/NPM1 vs other					
FLT3-ITD/IDH	4 (3)	51 (6)	6 (2)	0	4 (5)
FLT3-point mutation/NPM1	1 (<1)	55 (6)	32 (13)	2 (13)	8 (10)
Other	123 (96)	767 (88)	205 (84)	13 (87)	68 (85)
Donor type					
HLA-identical sibling	27 (21)	202 (23)	45 (19)	5 (33)	11 (14)
Other related	28 (22)	169 (19)	53 (22)	5 (33)	18 (23)
Well-matched unrelated	47 (37)	290 (33)	70 (29)	3 (20)	39 (49)
Partially-matched unrelated	8 (6)	47 (5)	17 (7)	0	7 (9)
Mis-matched unrelated	0	5 (<1)	1 (<1)	0	0
Multi-donor	0	1 (<1)	1 (<1)	0	0
Unrelated (matching TBD)	4 (3)	28 (3)	8 (3)	0	0
Cord blood	14 (11)	131 (15)	48 (20)	2 (13)	5 (6)
Graft type					
Bone marrow	26 (20)	148 (17)	29 (12)	1 (7)	7 (9)
Peripheral blood	88 (69)	593 (68)	166 (68)	12 (80)	68 (85)
Umbilical cord blood	14 (11)	127 (15)	48 (20)	2 (13)	5 (6)
PB + Other	0	1 (<1)	0	0	0
UCB + Other	0	4 (<1)	0	0	0
Year of HCT					
2009	0	0	1 (<1)	0	0
2011	0	2 (<1)	0	0	1 (1)
2012	0	2 (<1)	1 (<1)	0	0
2013	12 (9)	74 (8)	17 (7)	1 (7)	4 (5)
2014	32 (25)	203 (23)	64 (26)	2 (13)	26 (33)
2015	27 (21)	196 (22)	67 (28)	6 (40)	18 (23)
2016	44 (34)	220 (25)	49 (20)	3 (20)	22 (28)
2017	13 (10)	176 (20)	44 (18)	3 (20)	9 (11)
Median follow-up of survivors (range), months	24 (3-52)	24 (2-61)	24 (3-97)	24 (6-50)	25 (4-51)

Proposal: 1811-41

Title:
Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era

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Hypothesis:
We hypothesize that the negative prognosis of Ph-positive chromosome status in ALL has been reduced or eliminated by the introduction of TKIs that target BCR-ABL. Long-term post-transplant outcomes in the TKI era should be equivalent to those of transplanted patients with Ph-negative status.

Specific aims:
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.

Primary objective:

- Overall survival

Secondary objectives:

- Cumulative incidence of disease relapse
- Cumulative incidence of acute and chronic GVHD
- Cumulative incidence of NRM
- Progression-free survival
- Association of conditioning regimen type with outcome
- Cause of death
- Impact of MRD on post-transplant outcomes
- Impact of TKI presence or absence on post-transplant outcomes
- Impact of additional cytogenetic abnormalities on outcomes

Scientific impact:
More sophisticated prognostic understanding of Ph+ ALL in the TKI era will better guide therapy.

Scientific justification:
Philadelphia chromosome-positive ALL (Ph+ ALL), characterized by the BCR-ABL fusion protein, is considered as a distinct entity within ALL with its own treatment algorithms. Treatment is similar to that of Ph- ALL in terms of combination chemotherapy. Due to the poor prognosis historically associated with Ph+ ALL, post-remission consolidation with allogeneic hematopoietic stem cell transplant (allo-HCT) is recommended for appropriate candidates with donors (NCCN 2018).

The BCR-ABL tyrosine kinase inhibitor (TKI) imatinib gained initial FDA approval for treatment of CML in 2001. Imatinib demonstrated efficacy for Ph+ ALL; phase 2 data supporting use of imatinib in conjunction with combination chemotherapy was published in 2004 (Thomas et al. 2004). The second-generation, high-affinity BCR-ABL TKI dasatinib similarly demonstrated efficacy in Ph+ ALL and garnered FDA approval for that disease state in 2009.

TKI therapy in Ph+ ALL, in addition to allo-HCT, has become standard of care. TKI therapy pre-transplant appears to improve post-allo-HCT survival, with 5-year survival favoring TKI patients, 47 vs 38% in an EBMT retrospective study. In that study, MRD status did not impact post-transplant outcomes (Brissot et al. 2015). A single-arm study of reduced intensity conditioning (RIC) in Ph+ ALL and Ph- ALL showed promising long-term survival outcomes (50% at 3 years), leading to a CIBMTR study examining RIC versus ablative conditioning in Ph+ ALL. OS was similar for the two groups, but RIC lowered TRM. Absence of TKI pre-transplant increased relapse risk. Patients receiving pre-transplant TKI with MRD negativity had the best post-transplant outcomes (Bachanova et al. 2009; Bachanova et al. 2014). The benefits of post-transplant TKI maintenance were validated in an EBMT consensus statement that recommended TKI use post-transplant and suggested imatinib as the first-line choice based upon the number of studies with that agent (Giebel et al. 2016).

One of the key challenges in TKI therapy is the emergence of TKI-resistant BCR-ABL fusions, especially T315I mutation. The immune mechanism of allo-HCT is a potential means for overcoming TKI resistance, though relapse may still occur post-allo-HCT (Leoni and Biondi 2015).

Second-generation TKIs, especially dasatinib, are being used with increasing frequency in Ph+ ALL. A retrospective comparison of upfront use of imatinib (n=45) vs dasatinib (n=30) or nilotinib (n=2) yielded similar post-allo-HCT survival outcomes, but there was a trend towards better post-allo-HCT disease-free survival with 2nd-generation drugs. On the other hand, more T315I resistance mutations developed in the dasatinib group (Yu et al. 2017).

A single-institution retrospective study presented at ASBMT in 2015 showed better-than-expected outcomes for Ph+ ALL patients, with 60% survival at 5 years, but the study was limited by the extensive time frame of the study covering different eras of supportive care and disease treatment (Olsen et al. 2015). Nevertheless, emerging data supports a change in prognostic paradigms in the TKI era.

TKI therapy has also revolutionized Ph+ ALL in the pediatric setting. A single-institution pediatric retrospective study analyzed patients from 2001 to 2015 who were treated with chemotherapy and imatinib, 44% of whom were transplanted. Initial CR rates were 90%. Overall survival did not differ for transplanted and non-transplanted patients, though disease-free survival favored the transplant group. MRD monitoring identified those at lower risk of relapse, though the impact of MRD on post-transplant outcomes was inconclusive (Kanfar et al. 2016). A long-term Children's Oncology Group follow-up study analyzed imatinib and intensive chemotherapy with and without allo-HCT. Five-year disease-free survival was similar in the related and unrelated donor transplant groups (Schultz et al. 2014).

Overall, the above data suggest that treatment outcomes have improved in the TKI era for Ph+ ALL. Patients likely receive TKI therapy pre-allo-HCT in the current era. However, detailed outcomes information from a comprehensive multicenter study is still lacking. The prognostic impact and treatment implications of Ph+ status in ALL have changed and therefore necessitate a detailed reassessment. Refining the prognosis of Ph+ ALL may prompt further study of ideal first CR consolidation for MRD-negative Ph+ ALL patients.

The advantages of this study are:

- Larger sample size than prior single-institution studies to better evaluate prognostic impact of Ph+ status.

- Review contemporary post-transplant outcomes for Ph+ ALL in the TKI era.
- Assess how additional cytogenetic changes impact risk stratification.
- Larger sample size to assess significance of MRD and the utility of MRD testing in the TKI era.

Patient eligibility population:

Inclusion criteria:

- Adults ≥ 16 years at time of first allo-HCT between 2001 and 2015
- Diagnosis of acute lymphoblastic leukemia (ALL)
- Recipients of matched related, matched unrelated, mismatched unrelated, cord blood, and haploidentical donor transplants
- Patients transplanted in first CR (CR1)
- Recipients of first allo-HCT
- Cytogenetic information (karyotype, FISH, or BCR-ABL molecular test) available to assess Ph chromosome status

Exclusion criteria:

- Ex-vivo T-cell depletion or CD34+ selection in GVHD prophylaxis
- Recipients of second or later allo-HCT
- Patients not transplanted in CR1
- Patients who did not consent to research
- No information (karyotype, FISH, or BCR-ABL molecular test) available to assess Ph chromosome status
- Patients with Ph+ CML lymphoblastic crisis

Study design:

A retrospective multicenter study will be conducted using the CIBMTR database. Patients will be eligible if they meet Inclusion criteria and have no Exclusion criteria according to Patient Eligibility. Patients will be stratified according to the era in which they underwent allo-HCT (2001-2005, 2006-2010, and 2011-2015). Patients will be grouped according to Ph+ ALL or Ph- ALL status based on database records of Ph chromosome testing results at diagnosis. Ph+ ALL patients will be grouped according to TKI treatment status pre- and post-allo-HCT.

Descriptive tables of patient-, disease-, and transplant-related factors will be created for each group. The tables will list median and range for continuous variables and percent of the total for categorical variables. Cumulative incidence of chronic GVHD, disease relapse, and non-relapse mortality will be calculated while accounting for competing events. Acute GVHD rate at day 100 will be calculated. Probabilities of OS and PFS will be calculated using the Kaplan-Meier survival function method. Multivariable regression analyses will be performed using Cox proportional hazards models for chronic GVHD, relapse, NRM, PFS, and OS and logistic regression for acute GVHD. A stepwise model building approach will then be used to identify 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. Center effect will be tested. If there is a significant center effect, marginal models will be used to adjust for the center effect.

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Conflicts of interest:

None

Table 1. Characteristics of patients receiving first allo-HCT for ALL in CR1 and Ph diagnosis between 2001-2015, reported to CIBMTR

	Ph-	Ph+
Number of patients	959	1392
Number of centers	195	203
Age at HCT		
Median (range)	33 (16-75)	41 (16-73)
16-29	397 (41)	358 (26)
30-39	201 (21)	285 (20)
40-49	175 (18)	348 (25)
50-59	127 (13)	290 (21)
60-69	58 (6)	107 (8)
≥70	1 (<1)	4 (<1)
Gender		
Male	578 (60)	794 (57)
Female	381 (40)	598 (43)
Race		
Caucasian	746 (78)	1040 (75)
African-American	48 (5)	70 (5)
Asian	92 (10)	198 (14)
Pacific islander	5 (<1)	5 (<1)
Native American	9 (<1)	4 (<1)
Other	1 (<1)	5 (<1)
More than one race	3 (<1)	9 (<1)
Missing	55 (6)	61 (4)
Karnofsky score		
<90	260 (27)	415 (30)
≥90	648 (68)	940 (68)
Missing	51 (5)	37 (3)
HCT-CI		
0	187 (19)	290 (21)
1	67 (7)	123 (9)
2	60 (6)	122 (9)
3+	160 (17)	242 (17)
NA, f2400 (pre-TED) not completed	475 (50)	597 (43)
Missing	10 (1)	18 (1)

	Ph-	Ph+
TKI Status		
TKI pre and post	8 (<1)	293 (21)
pre-TKI	14 (1)	347 (25)
post-TKI	25 (3)	100 (7)
No TKI	912 (95)	652 (47)
GVHD prophylaxis		
No GVHD prophylaxis	12 (1)	14 (1)
Post-CY + other(s)	30 (3)	35 (3)
TAC + MMF ± other(s) (except post-CY)	104 (11)	176 (13)
TAC + MTX ± other(s) (except MMF, post-CY)	295 (31)	489 (35)
TAC + other(s) (except MMF, MTX, post-CY)	41 (4)	82 (6)
TAC alone	12 (1)	25 (2)
CSA + MMF ± other(s) (except post-CY)	85 (9)	141 (10)
CSA + MTX ± other(s) (except MMF, post-CY)	285 (30)	357 (26)
CSA + other(s) (except MMF, MTX, post-CY)	14 (1)	24 (2)
CSA alone	23 (2)	19 (1)
Other(s)	13 (1)	11 (<1)
Missing	45 (5)	19 (1)
Donor type		
HLA-identical sibling	313 (33)	486 (35)
Other related	79 (8)	69 (5)
Well-matched unrelated	294 (31)	449 (32)
Partially-matched unrelated	110 (11)	140 (10)
Mis-matched unrelated	21 (2)	27 (2)
Multi-donor	0	3 (<1)
Unrelated (matching TBD)	25 (3)	22 (2)
Cord blood	117 (12)	195 (14)
Missing	0	1 (<1)
Graft type		
Bone marrow	253 (26)	313 (22)
Peripheral blood	589 (61)	884 (64)
Umbilical cord blood	117 (12)	195 (14)

	Ph-	Ph+
Year of HCT		
2001	58 (6)	44 (3)
2002	54 (6)	74 (5)
2003	62 (6)	75 (5)
2004	53 (6)	98 (7)
2005	91 (9)	110 (8)
2006	80 (8)	122 (9)
2007	85 (9)	93 (7)
2008	63 (7)	160 (11)
2009	37 (4)	107 (8)
2010	30 (3)	71 (5)
2011	32 (3)	76 (5)
2012	24 (3)	55 (4)
2013	65 (7)	95 (7)
2014	128 (13)	107 (8)
2015	97 (10)	105 (8)
Median follow-up of survivors (range), months	64 (1-192)	71 (1-195)

Proposal: 1811-106

Title:
Outcomes of allo-HCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy

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Hypothesis:
We hypothesized that the use of multiple cycles of induction chemotherapy causes undue toxicity, which negatively impacts treatment-related mortality and survival following allo-HCT.

Specific aims:
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.

Scientific impact:
The number of cycles of induction chemotherapy in AML is associated with significant mortality. In addition, medical complications associated with multiple cycles of induction chemotherapy may make patients ineligible for allo-HCT despite having achieved CR. **The outcome of patients who required 2 or more cycles of induction chemotherapy to achieve CR followed by allo-HCT has not been extensively investigated.** If the proposed study demonstrates worse outcomes for AML patients who received multiple cycles of induction chemotherapy to achieve CR and proceeded to allo-HCT, then novel strategies will need to be developed to reduce treatment-related mortality post-allo-HCT.

Scientific justification:
The goal of induction chemotherapy in AML is to achieve complete remission with restoration of normal bone marrow.[1,2] Attainment of CR is an important first goal in the treatment of AML, as this is associated with improved survival. The first cycle of chemotherapy for newly diagnosed patients with AML who are not enrolled in a clinical trial consists of an anthracycline combined with cytarabine.[3,4] If residual leukemia is present after the first cycle of therapy, patients receive a second cycle identical to the first, or receive non-cross-resistant antileukemic regimens.[5] However, AML patients may require a third or fourth cycle of induction chemotherapy for achieving CR and then proceed to allo-HCT.[6] **Additional cycles of induction chemotherapy are associated with significantly high treatment-related mortality and morbidity and may result in complications that cause patients to be at high risk for post-transplant complications.[7-12]**
The objective of the proposed study is to compare TRM and survival of patients that achieved CR after 1 or 2 induction cycles and underwent allo-HCT with patients who received multiple cycles of induction chemotherapy in order to achieve CR and then proceeded to allo-HCT.

Patient eligibility population:
- Age: > 18 years
- Year of transplant: 2008-2015 (the number of induction cycles of therapy for AML have been reported to CIBMTR since 2008)

- Disease status: Newly diagnosed AML patients who received 2 or more cycles of induction chemotherapy and achieved CR
- Graft and donor type: First myeloablative/non-myeloablative allogeneic bone marrow or peripheral blood transplantation performed; HLA identical sibling, well matched/partially matched unrelated/mismatched unrelated
- Transplant regimen: Use of total body irradiation or busulfan- based myeloablative conditioning regimen, non-myeloablative regimens

Data requirements:

- Variables proposed in the study are included in the data collection forms, including the AML form. In the AML form, items 93 and 122 collect the first and second line of induction therapy and items 97 and 126 collect the number of cycles and the specifics for each chemotherapy course (98-111, 127-140). Information on more than 2 lines of therapy are also captured.
- In a 2017 preliminary CIBMTR data analysis performed by Hai-Lin Wang that was included in a past proposal (1710-11) by Drs. Boyiadzis and deLima **during the period of 2008-2015, 2540 AML patients were identified who received 1-2 cycles to achieve CR and 313 AML patients who received ≥3 cycles to achieve CR.**
- No supplementary data are required.
- The following variables will be required from the CIBMTR Research Database: age at transplantation, donor and recipient gender, Karnofsky or Lansky performance score at allo-HCT, MRD status at allo-HCT (if available), number of induction cycles prior to HCT, number of consolidation cycles, pre-HCT extramedullary leukemia, prior MDS, cytogenetics for AML, prior fungal infection, conditioning regimen, donor-recipient gender and gender match, donor-recipient HLA match, donor-recipient cytomegalovirus (CMV) status, graft type, GVHD prophylaxis, and year of transplantation.

Study design:

Retrospective study with TRM and overall survival as the end points. Overall survival is defined as the time from the date of allo-HCT to the date of death or last contact. Overall survival will be calculated using the Kaplan-Meir estimator. The effect of pre-transplantation variables on overall survival will be compared using a regression model. Factors influencing outcomes at the time of allo HCT and prior cycles of induction chemotherapy will be identified with multivariate analysis.

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Conflicts of interest:
No conflicts of interest

Table 1. Characteristics of adult patients receiving first allo-HCT for AML in CR1 who received 2 or more cycles of induction chemotherapy between 2008-2015

	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
Number of patients	526	1760	797	322
Number of centers	103	142	134	108
Age at HCT				
Median (range)	56 (18-82)	54 (18-81)	54 (18-76)	58 (18-77)
18-29	49 (9)	170 (10)	103 (13)	42 (13)
30-39	59 (11)	201 (11)	83 (10)	26 (8)
40-49	74 (14)	309 (18)	130 (16)	49 (15)
50-59	152 (29)	512 (29)	237 (30)	72 (22)
60-69	154 (29)	485 (28)	215 (27)	100 (31)
≥70	38 (7)	83 (5)	29 (4)	33 (10)
Gender				
Male	308 (59)	901 (51)	436 (55)	183 (57)
Female	218 (41)	859 (49)	361 (45)	139 (43)
Race				
Caucasian	431 (82)	1472 (84)	702 (88)	267 (83)
African-American	31 (6)	91 (5)	44 (6)	19 (6)
Asian	41 (8)	138 (8)	32 (4)	19 (6)
Pacific islander	1 (<1)	5 (<1)	4 (<1)	0
Native American	2 (<1)	6 (<1)	1 (<1)	3 (<1)
More than one race	3 (<1)	11 (<1)	1 (<1)	0
Missing	17 (3)	37 (2)	13 (2)	14 (4)
Karnofsky score				
<90	269 (51)	601 (34)	294 (37)	106 (33)
≥90	249 (47)	1135 (64)	496 (62)	213 (66)
Missing	8 (2)	24 (1)	7 (<1)	3 (<1)
HCT-CI				
0	89 (17)	419 (24)	184 (23)	68 (21)
1	67 (13)	271 (15)	114 (14)	50 (16)
2	70 (13)	249 (14)	115 (14)	66 (20)
3+	263 (50)	711 (40)	339 (43)	118 (37)
TBD	23 (4)	83 (5)	35 (4)	13 (4)
NA, f2400 (pre-TED) not completed	0	1 (<1)	1 (<1)	1 (<1)
Missing	14 (3)	26 (1)	9 (1)	6 (2)

	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
White blood count at diagnosis				
Median (range)	6 (<1-1900)	7 (<1-1230)	5 (<1-451)	5 (<1-363)
≤ 30	360 (68)	1190 (68)	579 (73)	218 (68)
30 - 100	79 (15)	315 (18)	109 (14)	52 (16)
> 100	40 (8)	146 (8)	50 (6)	25 (8)
Missing	47 (9)	109 (6)	59 (7)	27 (8)
Total cycles of induction				
1	63 (12)	1760	0	0
2	231 (44)	0	797	0
3	106 (20)	0	0	162 (50)
4	59 (11)	0	0	66 (20)
5+	67 (13)	0	0	94 (29)
Cytogenetic score				
Favorable	12 (2)	62 (4)	14 (2)	6 (2)
Intermediate	282 (54)	1134 (64)	439 (55)	180 (56)
Poor	204 (39)	465 (26)	308 (39)	107 (33)
TBD (needs rev.)	21 (4)	59 (3)	24 (3)	15 (5)
Not tested	4 (<1)	21 (1)	5 (<1)	6 (2)
Missing	3 (<1)	19 (1)	7 (<1)	8 (2)
Conditioning regimen intensity				
MAC	323 (61)	968 (55)	475 (60)	164 (51)
RIC	152 (29)	529 (30)	205 (26)	110 (34)
NMA	29 (6)	227 (13)	100 (13)	42 (13)
TBD	21 (4)	32 (2)	16 (2)	6 (2)
Missing	1 (<1)	4 (<1)	1 (<1)	0
Blast in marrow prior to HCT				
0	58 (11)	488 (28)	246 (31)	99 (31)
1-4%	199 (38)	1143 (65)	502 (63)	198 (61)
≥5%	227 (43)	44 (3)	15 (2)	4 (1)
Missing	42 (8)	85 (5)	34 (4)	21 (7)
Blast in blood prior to HCT				
No	208 (40)	1606 (91)	716 (90)	283 (88)
Yes	249 (47)	0	0	0
Missing	69 (13)	154 (9)	81 (10)	39 (12)
Donor type				
HLA-identical sibling	136 (26)	520 (30)	233 (29)	77 (24)
Other related	54 (10)	163 (9)	54 (7)	22 (7)

	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
Well-matched unrelated	231 (44)	669 (38)	295 (37)	135 (42)
Partially-matched unrelated	40 (8)	125 (7)	84 (11)	29 (9)
Mis-matched unrelated	1 (<1)	7 (<1)	1 (<1)	3 (<1)
Multi-donor	0	2 (<1)	1 (<1)	1 (<1)
Unrelated (matching TBD)	1 (<1)	11 (<1)	8 (1)	2 (<1)
Cord blood	63 (12)	263 (15)	120 (15)	53 (16)
Missing	0	0	1 (<1)	0
Graft type				
Bone marrow	71 (13)	205 (12)	103 (13)	36 (11)
Peripheral blood	392 (75)	1292 (73)	574 (72)	233 (72)
Umbilical cord blood	63 (12)	263 (15)	120 (15)	53 (16)
GVHD prophylaxis				
No GVHD prophylaxis	6 (1)	4 (<1)	1 (<1)	0
Ex-vivo T-cell depletion	6 (1)	15 (<1)	6 (<1)	1 (<1)
CD34 selection	11 (2)	35 (2)	20 (3)	6 (2)
Post-CY + other(s)	25 (5)	110 (6)	35 (4)	22 (7)
TAC + MMF ± other(s) (except post-CY)	105 (20)	305 (17)	143 (18)	62 (19)
TAC + MTX ± other(s) (except MMF, post-CY)	244 (46)	798 (45)	366 (46)	123 (38)
TAC + other(s) (except MMF, MTX, post-CY)	18 (3)	94 (5)	31 (4)	20 (6)
TAC alone	21 (4)	37 (2)	10 (1)	8 (2)
CSA + MMF ± other(s) (except post-CY)	47 (9)	213 (12)	104 (13)	40 (12)
CSA + MTX ± other(s) (except MMF, post-CY)	29 (6)	111 (6)	53 (7)	32 (10)
CSA + other(s) (except MMF, MTX, post-CY)	2 (<1)	8 (<1)	11 (1)	1 (<1)
CSA alone	6 (1)	14 (<1)	13 (2)	4 (1)
Other(s)	6 (1)	15 (<1)	4 (<1)	3 (<1)
Missing	0	1 (<1)	0	0
ATG/Campath				
ATG alone	141 (27)	465 (26)	212 (27)	97 (30)
CAMPATH alone	12 (2)	29 (2)	15 (2)	6 (2)
No ATG or CAMPATH	373 (71)	1266 (72)	570 (72)	219 (68)

	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
Year of HCT				
2008	79 (15)	228 (13)	143 (18)	44 (14)
2009	76 (14)	211 (12)	116 (15)	31 (10)
2010	54 (10)	201 (11)	93 (12)	32 (10)
2011	29 (6)	97 (6)	34 (4)	29 (9)
2012	19 (4)	88 (5)	43 (5)	25 (8)
2013	75 (14)	259 (15)	96 (12)	57 (18)
2014	110 (21)	333 (19)	139 (17)	50 (16)
2015	84 (16)	343 (19)	133 (17)	54 (17)
Median follow-up of survivors (range), months	49 (3-122)	49 (3-126)	59 (3-122)	49 (3-122)

Proposal: 1811-113

Title:
Outcomes of allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia in second or subsequent complete remission

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Hypothesis:
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.

Specific aims:
Primary aim:

- To assess the temporal trends in overall survival (OS) of ALL patients undergoing allo-HCT in CR2 or beyond

Secondary aims:
To assess the temporal trends in the following outcomes for ALL patients undergoing allo-HCT in CR2 or beyond

- Disease-free survival (DFS)
- Relapse rate (RR)
- Non-relapse mortality (NRM)
- Acute and chronic GVHD

Scientific impact:
The results of this study would provide retrospective CIBMTR data in determining the role and outcomes of allo-HCT beyond first CR in patients with ALL in the current era where newer therapies are increasing the proportion of patients who achieve CR2 or beyond.

Scientific justification:
The optimal role of allo-HCT in adult patients with ALL continues to be surrounded with some uncertainty and controversy. There are conflicting results as to whether the survival benefit of transplant in first CR exists for standard risk patients [1, 2] or high risk patients [3, 4]. Couple this with an evolving treatment landscape with use of pediatric inspired regimens in the upfront setting [5] as well as with novel therapies such as blinatumomab [6-12], inotzumab ozogamicin [13-15] and chimeric antigen receptor T cell therapy [16] to treat minimal residual disease or relapsed/refractory disease, and utilization of reduced intensity conditioning regimens and it becomes clear why there is so much confusion.
At the heart of the issue is whether adult patients with ALL can be "salvaged" by an allo-HCT in CR2 or not. Of course, this presumes that patients are able to achieve a second remission, but historically CIBMTR data reveals a long term OS of 40-50% for patients undergoing transplant in CR2 [17]. Our hypothesis is that with increasing use of novel agents that improve the depth of response for relapsed ALL patients, potentially with less pre-transplant toxicity, as well as with improvements in transplant

related mortality (TRM), that OS for a transplant in CR2 and beyond for ALL patients will have improved with time.

Study population:

Inclusion criteria:

- Adult patients with age≥18years
- Underwent allo-HCT for ALL
- In CR2 or beyond
- Period 2000 to 2016

Exclusion criteria:

- Prior allogeneic transplant

Data requirements:

This retrospective study requires analysis of CIBMTR collected data related to allogeneic HCT from 2000– 2016. This proposal does not require biologic samples

Outcomes:

Primary:

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

Secondary:

- Disease-free survival (DFS): time to treatment failure (relapse or death from any cause). Patients alive and in CR will be censored at last follow-up.
- Non-relapse mortality (NRM): Death without relapse. The outcome will be evaluated by the cumulative incidence estimate, with relapse as its competing risk.
- Relapse: Incidence of relapse. The outcome will be evaluated by the cumulative incidence estimate with non-relapse mortality as its competing risk. Patients are censored at the date of last follow up.
- Acute and chronic GVHD: Cumulative incidence of grade II-IV acute GVHD per consensus criteria and cumulative incidence of limited and extensive chronic GVHD. The outcomes will be evaluated by cumulative incidence estimates, with death without acute or chronic GVHD as competing risk. Patients will be censored at the date of last follow up.

Variables to be analyzed:

Main effect:

- Period: 2000-2005 vs 2006-2010 vs 2011-2016

Disease related:

- Disease status: CR2 vs CR3 and beyond
- Disease subtype: B-ALL vs T-ALL

Patient related:

- Age – 18-39 years vs 40-59 years vs ≥60 years
- Gender
- Race
- HCT-CI

- Performance status - < 90% vs. 90-100%

Donor related:

- Donor-recipient sex match: M/M vs. M/F vs. F/M vs. F/F
- Donor-recipient CMV status match: +/+ vs. +/- vs. -/+ vs. -/-

Transplant related:

- Graft source: Matched sibling vs. 8/8 matched unrelated donors vs. Mismatched unrelated donors vs. haploidentical donors vs. cord blood
- Conditioning type: MA vs. RIC/NMA
- Conditioning regimen: TBI based vs. non-TBI based
- Source of stem cell : PB vs BM
- GVHD prophylaxis

Study design:
This is a retrospective analysis of the CIBMTR database. The study would include patients aged ≥18 years with a diagnosis of ALL who underwent first allo-HCT after achieving CR2 or beyond and meet the above mentioned study criteria. Baseline characteristics of the study population will be summarized using descriptive statistics. The primary outcome is to determine the trend in OS over time in this cohort by dividing them in three time periods – 2000-2005, 2006-2010, 2011-2016. The secondary outcomes will include the trend in DFS, relapse rate, NRM, and incidence of acute GVHD and chronic GVHD in this cohort. A stratified analysis of primary and secondary outcomes will be performed based on the patient's age group - adolescents and young adults (18-39 years), adults (40-59 years) and older adults (≥60 years). Patient related, donor related and transplant related variables summarized above will be considered as prognostic factors which determine the outcomes. A multivariate logistic regression model will be built using these variables to identify independent prognostic factors associated with the outcomes.

Conflict of interest: None

References:

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Table 1. Characteristics of adult patients receiving first allo-HCT for ALL in CR2 or beyond between 2000-2016, reported to CIBMTR

Characteristic	2000-2005	2006-2010	2011-2016	Total
Number of patients	1233	1130	1370	3733
Number of centers	277	233	229	361
Age at HCT				
Median (range)	27 (18-83)	29 (18-72)	32 (18-77)	29 (18-83)
18-29	710 (58)	600 (53)	631 (46)	1941 (52)
30-39	247 (20)	198 (18)	265 (19)	710 (19)
40-49	154 (12)	168 (15)	210 (15)	532 (14)
50-59	96 (8)	119 (11)	169 (12)	384 (10)
60-69	25 (2)	43 (4)	87 (6)	155 (4)
≥70	1 (<1)	2 (<1)	8 (<1)	11 (<1)
Track				
TED	671 (54)	699 (62)	998 (73)	2368 (63)
CRF	562 (46)	431 (38)	372 (27)	1365 (37)
Gender				
Male	765 (62)	718 (64)	852 (62)	2335 (63)
Female	468 (38)	412 (36)	518 (38)	1398 (37)
Race				
Caucasian	836 (68)	826 (73)	882 (64)	2544 (68)
African-American	37 (3)	47 (4)	91 (7)	175 (5)
Asian	68 (6)	33 (3)	94 (7)	195 (5)
Pacific islander	3 (<1)	3 (<1)	7 (<1)	13 (<1)
Native American	5 (<1)	6 (<1)	7 (<1)	18 (<1)
Other	32 (3)	37 (3)	0	69 (2)
More than one race	1 (<1)	5 (<1)	10 (<1)	16 (<1)
Missing	251 (20)	173 (15)	279 (20)	703 (19)
Immunophenotype				
T-cell	182 (15)	208 (18)	245 (18)	635 (17)
B-cell	771 (63)	811 (72)	1034 (75)	2616 (70)
Unspecified	280 (23)	111 (10)	91 (7)	482 (13)
Karnofsky score				
<90	119 (10)	251 (22)	448 (33)	818 (22)
≥90	199 (16)	570 (50)	893 (65)	1662 (45)
Missing	915 (74)	309 (27)	29 (2)	1253 (34)

Characteristic	2000-2005	2006-2010	2011-2016	Total
HCT-CI				
0	2 (<1)	281 (25)	411 (30)	694 (19)
1	0	92 (8)	181 (13)	273 (7)
2	0	55 (5)	175 (13)	230 (6)
3+	0	131 (12)	453 (33)	584 (16)
TBD	0	39 (3)	57(4)	96 (3)
NA, f2400 (pre-TED) not completed	1231	447 (40)	0	1678 (45)
Missing	0	85 (8)	93 (7)	178 (5)
Disease status prior to HCT				
CR2	1052 (85)	1034 (92)	1306 (95)	3392 (91)
CR3	169 (14)	59 (5)	0	228 (6)
> CR3	12 (<1)	37 (3)	64 (5)	113 (3)
Conditioning as reported by center				
MAC	908 (74)	943 (83)	1123 (82)	2974 (80)
RIC/NMA	98 (8)	140 (12)	237 (17)	475 (13)
Missing	227 (18)	47 (4)	10 (<1)	284 (8)
Donor type				
HLA-identical sibling	484 (39)	416 (37)	401 (29)	1301 (35)
Other related	85 (7)	60 (5)	137 (10)	282 (8)
Well-matched unrelated	192 (16)	244 (22)	345 (25)	781 (21)
Partially-matched unrelated	121 (10)	79 (7)	115 (8)	315 (8)
Mis-matched unrelated	50 (4)	13 (1)	5 (<1)	68 (2)
Multi-donor	11 (<1)	7 (<1)	3 (<1)	21 (<1)
Unrelated (matching TBD)	216 (18)	157 (14)	171 (12)	544 (15)
Cord blood	69 (6)	127 (11)	165 (12)	361 (10)
Missing	5 (<1)	27 (2)	28 (2)	60 (2)
Donor/recipient CMV serostatus				
+/+	55 (4)	250 (22)	265 (19)	570 (15)
+/-	24 (2)	78 (7)	77 (6)	179 (5)
-/+	97 (8)	168 (15)	213 (16)	478 (13)
-/-	93 (8)	177 (16)	176 (13)	446 (12)
CB - recipient +	1 (<1)	63 (6)	115 (8)	179 (5)
CB - recipient -	6 (<1)	38 (3)	48 (4)	92 (2)
CB - recipient CMV unknown	62 (5)	26 (2)	2 (<1)	90 (2)
Missing	895 (73)	330 (29)	474 (35)	1699 (46)

Characteristic	2000-2005	2006-2010	2011-2016	Total
Donor/recipient sex match				
M-M	432 (35)	404 (36)	466 (34)	1302 (35)
M-F	233 (19)	189 (17)	233 (17)	655 (18)
F-M	256 (21)	227 (20)	269 (20)	752 (20)
F-F	200 (16)	160 (14)	203 (15)	563 (15)
CB - recipient M	45 (4)	72 (6)	102 (7)	219 (6)
CB - recipient F	24 (2)	55 (5)	63 (5)	142 (4)
Missing	43 (3)	23 (2)	34 (2)	100 (3)
GVHD prophylaxis				
Ex-vivo T-cell depletion	52 (4)	15 (1)	10 (<1)	77 (2)
CD34 selection	39 (3)	26 (2)	44 (3)	109 (3)
Post-CY + other(s)	0	0	97 (7)	97 (3)
Post-CY alone	0	0	7 (<1)	7 (<1)
TAC + MMF ± other(s) (except post-CY)	37 (3)	99 (9)	141 (10)	277 (7)
TAC + MTX ± other(s) (except MMF, post-CY)	222 (18)	365 (32)	459 (34)	1046 (28)
TAC + other(s) (except MMF, MTX, post-CY)	10 (<1)	41 (4)	50 (4)	101 (3)
TAC alone	14 (1)	33 (3)	29 (2)	76 (2)
CSA + MMF ± other(s) (except post-CY)	39 (3)	94 (8)	156 (11)	289 (8)
CSA + MTX ± other(s) (except MMF, post-CY)	459 (37)	298 (26)	265 (19)	1022 (27)
CSA + other(s) (except MMF, MTX, post-CY)	38 (3)	19 (2)	15 (1)	72 (2)
CSA alone	48 (4)	65 (6)	54 (4)	167 (4)
Other(s)	16 (1)	22 (2)	31 (2)	69 (2)
Missing	259 (21)	53 (5)	12 (<1)	324 (9)
Graft type				
Bone marrow	478 (39)	213 (19)	260 (19)	951 (25)
Peripheral blood	685 (56)	788 (70)	942 (69)	2415 (65)
Umbilical cord blood	68 (6)	127 (11)	162 (12)	357 (10)
Other, specify	1 (<1)	0	0	1 (<1)
PB + Other	0	2 (<1)	3 (<1)	5 (<1)
UCB + Other	1 (<1)	0	3 (<1)	4 (<1)

Characteristic	2000-2005	2006-2010	2011-2016	Total
Year of HCT				
2000	180 (15)	0	0	180 (5)
2001	225 (18)	0	0	225 (6)
2002	206 (17)	0	0	206 (6)
2003	206 (17)	0	0	206 (6)
2004	206 (17)	0	0	206 (6)
2005	210 (17)	0	0	210 (6)
2006	0	247 (22)	0	247 (7)
2007	0	219 (19)	0	219 (6)
2008	0	220 (19)	0	220 (6)
2009	0	228 (20)	0	228 (6)
2010	0	216 (19)	0	216 (6)
2011	0	0	220 (16)	220 (6)
2012	0	0	241 (18)	241 (6)
2013	0	0	225 (16)	225 (6)
2014	0	0	227 (17)	227 (6)
2015	0	0	230 (17)	230 (6)
2016	0	0	227 (17)	227 (6)
Median follow-up of survivors (range), months	96 (1-220)	89 (1-145)	36 (1-85)	

Proposal: 1811-137

Title:
Outcomes of acute lymphoblastic leukemia arising from a prior hematologic malignancy

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Hypothesis:
Acute lymphoblastic leukemia arising from a prior hematologic malignancy (or secondary acute lymphoblastic leukemia, "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.

Specific aims:
We propose to evaluate the allogeneic transplant outcomes of acute lymphoblastic leukemia arising from prior hematologic malignancies. To achieve this objective, we will:

- Aim 1: Evaluate transplant outcomes (overall survival, leukemia-free survival, cumulative incidence of transplant-related mortality, and cumulative incidence of relapse) in patients with secondary acute lymphoblastic leukemia (s-ALL)
- Aim 2: Describe clinical characteristics of patients with secondary acute lymphoblastic leukemia

Scientific impact:
There is a paucity of data regarding the clinical characteristics and treatment of s-ALL. Due to the rarity of the diagnosis and concurrent additional hematologic malignancy, eligible patients undergo allogeneic hematopoietic stem cell transplant (HSCT). We aim to evaluate and describe the outcomes of HSCT in this patient population.

Scientific justification:
Acute lymphoblastic leukemia is generally classified as Philadelphia chromosome positive or not. Rarely, it has been described as a secondary and usually late manifestation of a prior hematologic malignancy. It has been described often as clonally related or as a treatment-related malignancy. For example, it has been described to develop after chronic lymphocytic leukemia in a 77 year old (Yun 2018), myelodysplastic syndrome in a 90 year old (Nagler 1986), follicular lymphoma in 7 patients age 33-69 (Geyer 2015) or plasma cell neoplasm in a 55 year old (Kurant 2017), or even myeloproliferative neoplasms including CML. CML is well described to develop into lymphoblastic blast crisis in a minority of cases.
There is less data on the outcome of HSCT for s-ALL. The Geyer transformed follicular lymphoma series noted 3 patients underwent ASCT with two alive (1 ad 10 months post-transplant at time of data report). MDACC published their experience with treatment of lymphoid blast crisis from CML and showed that HSCT was associated with longer remission duration and PFS (Strati 2014).
We propose a retrospective cohort study to describe the clinical and pathologic characteristics of s-ALL, as well as evaluate HSCT related outcomes in this rare form of leukemia.

Patient eligibility population:

- Diagnosis of acute lymphoblastic leukemia, OR chronic myelogenous leukemia in lymphoid crisis. De novo Ph+ ALL will be excluded based on absence of prior or concurrent diagnosis of CML.
- Diagnosis of an additional hematologic malignancy, including but not limited to chronic myelogenous leukemia, follicular lymphoma, chronic lymphocytic leukemia, myelodysplastic syndrome.
- Any age at diagnosis (pediatric patients included)
- First allogeneic transplantation
- Transplantation dates: January 2008 to December 2016
- Available cytogenetic and mutational status at the time of diagnosis

Exclusion criteria:

- Patients with an additional hematologic malignancy which develops after the diagnosis of acute lymphoblastic leukemia will be excluded

Data requirements:

This study will use data collected from CIBMTR research centers.

Data forms required:

- Recipient Baseline Data 2000, ALL Pre-HCT Data 2011, CML Pre-HCT Data 2012, Post HCT Data 2100, ALL Post HCT Data 2111, CML Post HCT Data 2112, Pre-Transplant Essential TED 2400 (particular 135 – prior history of malignancy).

Patient related:

- Age
- Gender
- ECOG Performance status prior to transplant
- HCT-CI prior to transplant

Disease related:

- Diagnosis
- WBC, Blast percentage at diagnosis, extramedullary disease
- Induction chemotherapy regimen
- Presence of minimal residual disease prior to transplant (Ph+, flow, molecular)
- Cytogenetic/Molecular Risk Group (including available data of prior hematologic malignancy)

Transplant related:

- Conditioning regimen intensity
- Donor source (matched related donor, matched unrelated donor, mismatched related donor, mismatched unrelated donor)
- Graft type (peripheral blood, bone marrow, cord blood)
- Time from diagnosis to transplant
- Year of transplant
- GVHD prophylaxis regimen
- Donor/recipient CMV status

No supplemental database will be required.

Study design:
This is a retrospective cohort analysis to evaluate the outcomes of s-ALL after allogeneic transplantation. Continuous variables will be described as median and ranges and categorical variables will be reported as absolute numbers and percentage. The primary endpoint is LFS. The secondary endpoints are OS, TRM, relapse incidence through last follow-up, and incidences of acute and chronic GVHD. All outcomes will be measured from the time of stem cell infusion and will be reported separately for each type of s-ALL based on prior hematologic malignancy (such as follicular lymphoma vs CML vs MDS).
PFS is defined as the time until disease relapse or death from any cause; data for patients who were alive without relapse will be censored at the date of last contact. OS is defined as the time until death from any cause; surviving patients will be censored at the date of last contact. Relapse is defined as the recurrence of disease according to the 2008 WHO criteria. TRM is defined as death related to allogeneic HSCT during continuous CR. OS and PFS were calculated using the Kaplan-Meier method. Univariate comparisons of all endpoints were done using the log-rank test.
The cumulative incidence function with the competing risks method was used to estimate the endpoints of relapse, TRM, acute GVHD, and chronic GVHD. The competing risk included for TRM is relapse, and the competing risk included for relapse is death. For GVHD, the competing risks included are relapse and death. A Cox proportional hazards model or the Fine and Gray method for competing hazards is used for multivariate regression. Variables are included in the multivariate model if they are conceptually important [i.e. if they approached ($p<0.1$)] or attained statistical significance in the univariate regression model. A P value < 0.05 is considered statistically significant.

<u>Variables to be analyzed (MVA outcomes):</u>

- Cumulative incidence of engraftment
- Cumulative incidence of acute and chronic GVHD
- Overall survival (OS)
- Leukemia -free survival (LFS)
- Cumulative incidence of transplant-related mortality (TRM)
- Cumulative incidence of relapse (CIR)

Data source:
CIBMTR Research Database will be the only source required.

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Table 1. Characteristics of patients a history of malignancy receiving first allo-HCT for S-ALL between 2012-2016, reported to CIBMTR

	TED	CRF
Number of patients	57	25
Number of centers	40	23
Age at HCT		
Median (range)	56 (2-70)	52 (5-72)
<10	4 (7)	1 (4)
10-17	0	1 (4)
18-29	3 (5)	1 (4)
30-39	5 (9)	2 (8)
40-49	7 (12)	6 (24)
50-59	13 (23)	5 (20)
60-69	24 (42)	8 (32)
≥70	1 (2)	1 (4)
Gender		
Male	33 (58)	19 (76)
Female	24 (42)	6 (24)
Karnofsky score		
<90	30 (53)	10 (40)
≥90	26 (46)	15 (60)
Missing	1 (2)	0
Type of prior malignancy [a]		
Not specified	4 (7)	4 (16)
History AML/ANLL	3 (5)	3 (12)
History Hodgkin disease	9 (16)	1 (4)
History Hodgkin disease + History lymphoma	0	1 (4)
History lymphoma	18 (32)	6 (24)
History Other leukemia	3 (5)	2 (8)
History other prior malignancy	20 (35)	8 (32)
Cytogenetic score [b]		
Normal	0	5 (20)
Poor	15 (26)	7 (28)
Other	0	3 (12)
TBD (needs rev.)	41 (72)	6 (24)
Not tested	0	1 (4)
Missing	1 (2)	3 (12)

	TED	CRF
Disease status prior to HCT		
Primary induction failure	1 (2)	1 (4)
CR1	46 (81)	16 (64)
CR2	5 (9)	6 (24)
Relapse	3 (5)	1 (4)
Missing	2 (4)	1 (4)
Ph+		
Negative	43 (75)	20 (80)
Positive	12 (21)	5 (20)
Missing	2 (4)	0
Conditioning regimen		
MAC		
TBI/Cy	10 (18)	4 (16)
TBI/Cy/Flu	2 (4)	4 (16)
TBI/Cy/TT	1 (2)	1 (4)
TBI/Cy/VP	0	1 (4)
TBI/VP	1 (2)	0
TBI/Flu	3 (5)	1 (4)
Bu/Cy	2 (4)	2 (8)
Flu/Bu	3 (5)	0
Flu/Mel	1 (2)	0
RIC/NMA		
TBI/Cy/Flu	6 (11)	2 (8)
TBI/Mel	3 (5)	1 (4)
TBI/Flu	3 (5)	0
Flu/Bu	8 (14)	4 (16)
Flu/Mel	14 (25)	5 (20)
Donor type		
HLA-identical sibling	14 (25)	4 (16)
Other related	6 (11)	2 (8)
Well-matched unrelated	25 (44)	9 (36)
Partially-matched unrelated	3 (5)	4 (16)
Multi-donor	0	1 (4)
Unrelated (matching TBD)	5 (9)	0
Cord blood	4 (7)	5 (20)

	TED	CRF
Graft type		
Bone marrow	10 (18)	9 (36)
Peripheral blood	42 (74)	11 (44)
Umbilical cord blood	4 (7)	5 (20)
PB + OTH	1 (2)	0
GVHD prophylaxis		
CD34 selection	2 (4)	0
Post-CY + other(s)	6 (11)	2 (8)
TAC + MMF ± other(s) (except post-CY)	8 (14)	4 (16)
TAC + MTX ± other(s) (except MMF, post-CY)	23 (40)	10 (40)
TAC + other(s) (except MMF, MTX, post-CY)	4 (7)	2 (8)
TAC alone	2 (4)	0
CSA + MMF ± other(s) (except post-CY)	2 (4)	3 (12)
CSA + MTX ± other(s) (except MMF, post-CY)	8 (14)	2 (8)
CSA alone	1 (2)	1 (4)
Other(s)	1 (2)	0
Missing	0	1 (4)
Year of HCT		
2012	1 (2)	1 (4)
2013	4 (7)	1 (4)
2014	11 (19)	12 (48)
2015	16 (28)	5 (20)
2016	25 (44)	6 (24)
Median follow-up of survivors (range), months	25 (12-50)	36 (3-48)

[a] Excluded Prior ALL patients

[b] Cytogenetic information not collected on TED track prior to 2013

Propoal: 1811-169

Title:
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) in first complete remission.

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Objectives:
In adults ≥60 years old with AML (non-APL) in CR1 undergoing reduced intensity conditioning (RIC) allogeneic hematopoietic stem cell transplant (HCT):

- To compare overall survival after transplant 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.
- To compare the relapse-free survival, relapse incidence, and non-relapse mortality between the groups.
- To compare Grade 2-4 and Grade 3-4 acute GVHD rates between the groups.
- To compare chronic GVHD rates between the groups.
- To compare causes of death between the groups.

Scientific justification:
BMT-CTN 0901 established myeloablative conditioning (MAC) as a standard of care for fit adults between 18-65 years old with AML receiving allogeneic HCT from an HLA-matched related or unrelated donor, based on reduced incidence of relapse and improved relapse-free survival compared to similar patients receiving reduced intensity conditioning (RIC).[1] Greater than 50% of patients with AML are older than 65 years of age, however, and curative therapy with allogeneic HCT has become increasingly utilized for patients in this age group despite considerable associated morbidity and mortality.[2,3] For patients older than 60-65 years of age who are candidates for allogeneic HCT, RIC remains the preferred strategy due to prohibitively high treatment-related mortality with myeloablative conditioning.[4,5]
In vivo T-cell depletion (TCD) with anti-thymocyte globulin (ATG) or alemtuzumab has been demonstrated to reduce risks of severe acute and chronic graft-versus-host disease (GVHD) after allogeneic HCT. Whether *in vivo* T cell depletion diminishes allograft efficacy by abrogating the graft-vs-leukemia (GVL) effect remains an unanswered question, and one that is of particular concern for RIC transplants that necessarily rely more on GVL effects and less on cytotoxicity for efficacy, compared to MAC transplants. A previous CIBMTR analysis of 1,676 adults with myeloid and lymphoid malignancies undergoing RIC transplantation from an 8/8 HLA-matched related or unrelated donor or 7/8 HLA-matched unrelated donor showed that relapse rate was higher and disease-free survival lower at 3 years when either ATG or alemtuzumab was used compared with T cell replete allografts.[6] Subsequently, an analysis by the EBMT of 1,250 adults with AML undergoing RIC transplantation from an HLA-matched related donor showed no difference in relapse incidence or disease-free survival whether ATG or alemtuzumab was used versus T-cell replete allografts. Potential factors contributing to the discrepant results seen in these prior observational studies include dosing differences of the T-cell depleting agents, and different strategies regarding use of pre-emptive DLI in the case of alemtuzumab-conditioned patients.[7] Other factors such as recipient HLA-C KIR ligand status have been suggested to influence outcomes following TCD transplants.[8]

Optimal use of *in vivo* T-cell depletion for RIC allogeneic HCT in older patients with AML has yet to be defined. This study is designed to compare overall survival, relapse-free survival, relapse, and non-relapse mortality in AML patients aged 60 years or older undergoing RIC allogeneic HCT with or without *in vivo* T cell depletion using ATG or alemtuzumab.

Study populations:

- Adult patients ≥60 years old with AML in CR1 undergoing RIC HCT with *in vivo* T-cell depletion using a matched-related donor or 8/8 HLA-matched-unrelated donor.
- Adult patients ≥60 years old with AML in CR1 undergoing RIC HCT without *in vivo* T-cell depletion (T cell replete) using a matched-related donor or 8/8 HLA-matched-unrelated donor.

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 leukemia-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.
- Causes of death: Descriptive analysis of causes of death in each transplant/donor group.

Variables to be described:

Patient-related:

- Number of patients
- Number of centers
- Age, years: continuous/range
- Age, years: 60-64, 65-69, 70-74, ≥75
- 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, ($x10^9$/L): continuous and <50, ≥50
- Platelet count at diagnosis, ($x10^9$/L): continuous and <50, ≥50

- Prior MDS; yes, no
- Therapy-related disease: yes, no

- European LeukemiaNet prognostic classification (2017) at diagnosis: Favorable, Intermediate-I, Intermediate-II, Adverse
- FLT3 status at diagnosis: wild-type, FLT-ITD, FLT-TKD
- Persistent cytogenetic abnormality at transplant: yes , no
- Persistent molecular abnormality at transplant: yes, no
- Extramedullary disease at diagnosis: yes, no
- Time to documentation of CR1: ≤4 weeks, >4-8 weeks, >8 weeks
- Cycles of chemotherapy prior to transplantation: 1,2,3, >3
- Time from CR1 to transplantation, months: <3, 3-6, >6

Transplant-related:

- Graft source: peripheral blood, bone marrow
- Reduced-intensity conditioning regimen: Flu/Mel, other Mel-based, Flu/Bu, other Bu-based, other chemotherapy-based
- Conditioning regimen: TBI-based, No TBI
- T-cell depletion: ATG, Campath, none
- GVHD prophylaxis: Tacrolimus/CSA + MTX ± other(s) except MMF, post-Cy; Tacrolimus/CSA + MMF ± others except post-Cy; Tacrolimus/CSA ± other(s) except MTX, MMF, post-CY; Tacrolimus/CSA alone; post-transplant cyclophosphamide ± others; others, none
- T-cell depletion: ATG, Campath
- Total Campath dose received, mg: continuous, <80mg, ≥80mg
- Total ATG dose: continuous, 2.0-3.9mg/kg, 4.0-5.9mg/kg, 6.0-7.9mg/kg, ≥8mg/kg
- Type of donor: matched related donor, 8/8 HLA-matched unrelated donor
- HLA-C KIR ligand status: C1/1, C1/2, C2/2
- Donor age: continuous
- Sex match: M-M, M-F, F-M, F-F
- D/R CMV status: +/+, +/-, -/+, -/-
- Years of transplant: 2005-2010, 2011-2016
- Median follow up: months

Variable to be analyzed:

Main effect:

- In vivo T-cell depletion: yes vs no

Patient-related:

- Age, years: continuous/range
- Age, years: 65-69, 70-74, 75+
- 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, ($x10^9$/L): continuous and <50, ≥50
- Platelet count at diagnosis, ($x10^9$/L): continuous and <50, ≥50

- Prior MDS; yes, no
- Therapy-related disease: yes, no
- European LeukemiaNet prognostic classification (2017) at diagnosis: Favorable, Intermediate-I, Intermediate-II, Adverse
- FLT3 status at diagnosis: wild-type, FLT-ITD, FLT-TKD
- Persistent cytogenetic abnormality at transplant: yes , no
- Persistent molecular abnormality at transplant: yes, no
- Extramedullary disease at diagnosis: yes, no
- Time to documentation of CR1: ≤4 weeks, >4-8 weeks, >8 weeks
- Cycles of chemotherapy prior to transplantation: 1,2,3, >3
- Time from CR1 to transplantation, months: <3, 3-6, >6

Transplant-related:

- Graft source: peripheral blood, bone marrow
- Conditioning regimen: Flu/Mel, other Mel-based, Flu/Bu, other Bu-based, other chemotherapy-based
- Conditioning regimen: TBI-based/No TBI
- GVHD prophylaxis: Tacrolimus/CSA + MTX ± other(s) except MMF or post-Cy, Tacrolimus/CSA + MMF ± others except post-Cy, Tacrolimus/CSA + other(s) except MTX, MMF, or post-CY, Tacrolimus/CSA alone, post-transplant cyclophosphamide ± others, others, none
- T-cell depletion: ATG, Campath
- Total Campath dose received, mg: continuous, <80mg, ≥80mg
- Total ATG dose: continuous, 2.0-3.9mg/kg, 4.0-5.9mg/kg, 6.0-7.9mg/kg, ≥8mg/kg
- ATG type: rabbit, horse
- Type of donor: matched related donor, 8/8 HLA-matched unrelated donor
- Pre-emptive DLI received: yes (<6 months), yes(≥6 months), no
- DLI received for disease relapse: yes (<6 months), yes(≥6 months), no
- Donor age: continuous
- Sex match: M-M, M-F, F-M, F-F
- D/R CMV status: +/+, +/-, -/+, -/-
- HLA-C KIR ligand status: C1/1, C1/2, C2/2

Study design:

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[9]. Prognostic factors for OS, RFS, relapse, and NRM will be analyzed using the proportional hazards model with the competing-risk regression model[10].

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Table 1. Characteristics of adult older than 60 years receiving first RIC allo-HCT for AML in CR1 between 2000-2017, reported to CIBMTR

Characteristic	No in vivo T-cell depletion	in vivo T-cell depletion
Number of patients	446	282
Number of centers	86	81
Age at HCT		
Median (range)	66 (60-77)	66 (60-76)
60-64	197 (44)	131 (46)
65-69	181 (41)	113 (40)
70-74	63 (14)	35 (12)
≥ 75	5 (1)	3 (1)
Gender		
Male	274 (61)	173 (61)
Female	172 (39)	109 (39)
Race		
Caucasian	405 (91)	264 (94)
African-American	13 (3)	9 (3)
Asian	14 (3)	5 (2)
Pacific islander	3 (<1)	0
Native American	2 (<1)	0
More than one race	1 (<1)	0
Missing	8 (2)	4 (1)
HCT-CI		
0	53 (12)	45 (16)
1	50 (11)	21 (7)
2	59 (13)	23 (8)
3+	198 (44)	115 (41)
TBD	8 (2)	12 (4)
NA, f2400 (pre-TED) not completed	74 (17)	65 (23)
Missing	4 (<1)	1 (<1)
ATG/Campath		
ATG alone	0	247 (88)
CAMPATH alone	0	35 (12)
No ATG or CAMPATH	446	0
Donor type		
HLA-identical sibling	185 (41)	63 (22)
Well-matched unrelated	261 (59)	219 (78)

Characteristic	No in vivo T-cell depletion	in vivo T-cell depletion
Donor/recipient CMV serostatus		
+/+	142 (32)	84 (30)
+/-	48 (11)	35 (12)
-/+	149 (33)	101 (36)
-/-	94 (21)	59 (21)
Missing	13 (3)	3 (1)
Donor/recipient sex match		
M-M	173 (39)	126 (45)
M-F	105 (24)	63 (22)
F-M	98 (22)	47 (17)
F-F	66 (15)	46 (16)
Missing	4 (<1)	0
GVHD prophylaxis		
No GVHD prophylaxis	0	1 (<1)
TAC + MMF ± other(s) (except post-CY)	64 (14)	59 (21)
TAC + MTX ± other(s) (except MMF, post-CY)	260 (58)	148 (52)
TAC + other(s) (except MMF, MTX, post-CY)	36 (8)	12 (4)
TAC alone	8 (2)	14 (5)
CSA + MMF ± other(s) (except post-CY)	41 (9)	13 (5)
CSA + MTX ± other(s) (except MMF, post-CY)	30 (7)	14 (5)
CSA + other(s) (except MMF, MTX, post-CY)	2 (<1)	11 (4)
CSA alone	4 (<1)	6 (2)
Other(s)	1 (<1)	4 (1)
Graft type		
Bone marrow	23 (5)	22 (8)
Peripheral blood	423 (95)	260 (92)

Characteristic	No in vivo T-cell depletion	in vivo T-cell depletion
Year of HCT		
2000	4 (<1)	0
2001	2 (<1)	3 (1)
2002	0	4 (1)
2003	5 (1)	6 (2)
2004	13 (3)	7 (2)
2005	18 (4)	11 (4)
2006	18 (4)	13 (5)
2007	18 (4)	27 (10)
2008	20 (4)	41 (15)
2009	28 (6)	20 (7)
2010	4 (<1)	13 (5)
2011	6 (1)	26 (9)
2012	15 (3)	4 (1)
2013	37 (8)	21 (7)
2014	75 (17)	35 (12)
2015	86 (19)	26 (9)
2016	71 (16)	19 (7)
2017	26 (6)	6 (2)
Median follow-up of survivors (range), months	36 (3-169)	63 (3-170)

Proposal: 1811-170

Title:
Survival Probabilities of Patients with Acute Leukemias, Myelodysplastic Syndromes and Myelofibrosis Undergoing Allogeneic Hematopoietic Cell Transplantation Conditional on Years Already Survived

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Hypothesis:
Overall survival projections for patients with acute leukemias (AL), myelodysplastic syndromes (MDS) and myelofibrosis (MF) at the time of transplantation is typically based on a combination of patient- (performance status, comorbidities), disease- (remission status, relapsed refractory disease, disease risk - cytogenetics and mutations) and transplant-related characteristics (type of transplant, intensity of conditioning regimen among others).[1-6] A question frequently posed by patients is whether having outlived the predicted survival time post-transplant means he or she will live longer. There is little data-driven evidence for physicians on how to counsel patients who wish to revisit the prognosis discussion. The ability to adjust survival estimates based on years already survived since transplant would be clinically meaningful. Conditional survival (CS), defined as the probability of surviving an additional amount of time after the patient has already survived a specific period of time, can provide this practical information. We hypothesize that the survival of AL, MDS and MF patients who are alive at least a year after allogeneic hematopoietic cell transplantation (HCT) steadily improves conditional on years already survived.

Specific aims:

- Aim 1: To assess 5-year CS in 1-5 year survivors after allogeneic HCT for AL, MDS and MF.
  Subgroup specific analyses will be performed to:
  - Generate 5-year CS estimates for each disease type.
  - Generate 5-year CS for therapy-related AML and MDS (t-AML and t-MDS)
  - Analyze the impact of patient, disease and HCT factors particularly conditioning regimen intensity on 5-year CS

- Aim 2: To assess mortality of AL, MDS, MF, t-AML and t-MDS patients relative to the general population adjusted for age, sex, ethnicity, and nationality.

Scientific impact:
CS is a simple and yet powerful measure that dynamically adjusts survival prognosis based on time already survived. Consideration of length of survivorship improves the accuracy of prognosis estimates and allows continual adjustment to surveillance plans. CS can provide more relevant prognostic information once a patient reaches or exceeds a specific landmark time of survival as it accounts for the length of survivorship and for the continuously changing hazard rates of death over time. CS can be easily incorporated in daily clinical practice to counsel patients and their families with up-to-date and more realistic survival estimates. Especially for this proposed cohort of patients who underwent potentially curative allogeneic HCT for their high-risk disease, improved CS estimates with increasing survivorship can generate optimism, help set realistic expectations about life expectancy and bring certain level of normalcy and well-being in the post-HCT period.

Scientific justification:
CS has been assessed in many solid tumor malignancies and in some hematologic malignancies, notably lymphoma and AML.[7-9] Findings from these studies showed substantial improvements in outcome with longer period survived from treatment intervention, and also showed dynamically improved survival even after adjustment for known adverse prognostic factors. An earlier CIBMTR study on adult ALL and AML survivors by Lee *et al.* reported most factors predictive of leukemia-free survival at the time of and after HCT lose their predictive value once patients survive without relapse for 2 or more years.[6] Subsequent high survival in 2-year HCT survivors has also been shown in AML and MDS patients in several other studies.[1-5] However, the applicability of these findings is limited to predominantly younger patient cohorts (median age ~ 30-40 years) who received MAC regimens with accumulated data ending in 2005. To the best of our knowledge, no CS data have been reported for MF patients and additionally, for patients receiving RIC/NMA regimens for any of these hematologic malignancies proposed in this study.
AML, MDS and MF disproportionately affects older patients (> 60 years) and in this group, there has been a steady increase in the number of HCTs performed in the last decade due to introduction of RIC regimens.[10, 11] Data obtained from CIBMTR (through custom data request) show that the number of HCTs performed in AL and MDS patients between the years 2008-2015 was 9005 and 1464 in the age groups 60-70 years and > 70 years, respectively. Approximately, 67% and 83% of patients in the corresponding age groups received RIC HCT. Moreover, the proportion of patients with t-MDS/t-AML in this demographic cohort has been steadily rising. This study proposes to provide comprehensive CS estimates of those treated with MAC as well as RIC/NMA regimens for AML, ALL, MDS and MF patients between the years 2000 – 2012, an era that has witnessed a sharp increase in HCTs performed in the elderly cohort. Additionally, this study will also provide CS estimates of t-AML/t-MDS patients, a unique cohort with steadily growing numbers for which prognosis remains poor. Considering CIBMTR collects data from transplant centers over the world, the findings will be generalizable.

Patient eligibility population:
Inclusion criteria: AL will include acute myeloid leukemias (AML) and acute lymphoblastic leukemias (ALL). All patients aged 18 years or older who had a first allogeneic HCT for AML, ALL, MDS and MF with related or unrelated donors of all ages between 2000 and 2012 and who were alive 1-year post-HCT with follow-up data reported to CIBMTR will be included. Follow up information regarding OS will be required. Both myeloablative conditioning (MAC) as well as reduced-intensity/nonmyeloablative conditioning (RIC/NMA) regimens will be included. Recipients of identical twin transplantations, umbilical cord blood transplants and haploidentical transplants will be excluded.

Data requirements:
Variables required for this study are as follows:
Patient-related:

- Age at HCT, year at diagnosis; gender; Karnofsky performance score; Race/ethnicity and Hematopoietic cell transplantation co-morbidity index

Disease-related:

- Date of diagnosis of AML, ALL, MDS and MF; Cytogenetic status at the time of diagnosis [AML– SWOG/ECOG and MRC classifications, MDS – MDS Comprehensive Cytogenetic Scoring System, ALL – lineage (T vs B vs other), Philadelphia chromosome or BCR-ABL positivity; MF – DIPSS prognosis score]; disease status at transplant; pre-transplantation therapy for MDS; Prior or first cancer (for t-MDS/and t-AML); time for diagnosis of prior disease to t-MDS/t-AML; prior therapy

for t-MDS/t-AML [radiation + chemotherapy, radiation alone (not chemotherapy), chemotherapy (not radiation) or others, prior autologous transplantation]; duration of CR1 (for t-AML patients in CR2 or beyond or in relapse at the time of HCT); time from diagnosis to HCT

Transplant-related variables:

- donor-recipient gender match; donor and recipient cytomegalovirus status; donor type; HLA matching; graft type; conditioning regimen (MAC vs RIC/NMA); use of TBI; GVHD prophylaxis; Acute GVHD (grades II to IV); Chronic GVHD; Year of transplant; Interval from diagnosis HCT; Median follow up of survivors

Study design:

This is an observational study of adult patients (> 18 years) with AML, ALL, MDS and MF who received first allogeneic HCT between the years 2000 and 2012. Overall survival will be defined as absence of death as a result of any cause. Patients who are alive will be censored at the time of last contact or end of study period whichever occurs earlier. The primary outcome is 5-year CS, defined as the probability of a patient surviving an additional 5 years, conditioned on the patient having already survived 1-5 years after HCT. Descriptive tables showing the baseline patient-, disease- and transplant-related factors will be prepared. The CS probabilities for each of the five specific disease categories (AML, ALL, MDS, MF, t-AML/t-MDS) will be generated separately. Association of CS with selected patient-, disease- and treatment-related variables will be assessed through multiple regression analyses.

Relative mortality will be defined as the relative or excess risk of death in the transplantation cohort compared to the general population matched on age, sex, country and ethnicity (for US population only) as done in prior CIBMTR studies using Andersen and Vaeth approach.[5,6,12] Tests of significance will be based on two-sided hypotheses at the 0.05 level. In addition, we will also compare mortality between the CIBMTR cohort with SEER cohort matched (1:4) by age-, gender-, disease type and race/ethnicity to assess differences in survival outcomes at specific landmark survival time-points (1, 3, 5 and 10 years) between transplanted cohort versus real-world patients.

We have the prior experience and the expertise to do all statistical work proposed in this study.

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Conflicts of interest:
None

Table 1. Characteristics of adult patients receiving first allo-HCT for AL, MDS, MF between 2000-2015, reported to CIBMTR

	AL	MDS	MF
Number of patients	9211	2676	532
Number of centers	284	192	124
Age at HCT			
Median (range)	46 (18-78)	60 (18-83)	56 (18-79)
18-29	1896 (21)	150 (6)	11 (2)
30-39	1543 (17)	149 (6)	23 (4)
40-49	2034 (22)	312 (12)	107 (20)
50-59	2187 (24)	753 (28)	225 (42)
60-69	1391 (15)	1080 (40)	151 (28)
≥70	160 (2)	232 (9)	15 (3)
Gender			
Male	5027 (55)	1667 (62)	318 (60)
Female	4184 (45)	1009 (38)	214 (40)
Race			
Caucasian	7798 (85)	2418 (90)	477 (90)
African-American	331 (4)	81 (3)	21 (4)
Asian	705 (8)	117 (4)	17 (3)
Pacific islander	23 (<1)	3 (<1)	2 (<1)
Native American	29 (<1)	6 (<1)	2 (<1)
Other	23 (<1)	0	1 (<1)
More than one race	27 (<1)	5 (<1)	1 (<1)
Missing	275 (3)	46 (2)	11 (2)
Karnofsky score			
<90	2626 (29)	935 (35)	182 (34)
≥90	6078 (66)	1645 (61)	329 (62)
Missing	507 (6)	96 (4)	21 (4)
HCT-CI			
0	1225 (13)	385 (14)	91 (17)
1	645 (7)	234 (9)	47 (9)
2	657 (7)	257 (10)	49 (9)
3+	1651 (18)	971 (36)	124 (23)
TBD	232 (3)	114 (4)	17 (3)
NA, f2400 (pre-TED) not completed	4686 (51)	697 (26)	193 (36)
Missing	115 (1)	18 (<1)	11 (2)

	AL	MDS	MF
Disease			
AML	6968 (76)	0	0
ALL	2243 (24)	0	0
MDS	0	2676	532
Disease status prior to HCT for MDS			
MDS			
MDS early		886 (33)	163 (31)
MDS advanced		1590 (59)	18 (3)
MDS Other		200 (7)	351 (66)
AML			
Primary induction failure	685 (7)		
CR1	4004 (43)		
CR2	1487 (16)		
≥CR3	106 (1)		
Relapse	630 (7)		
Missing	56 (<1)	0	0
ALL			
Primary induction failure	85 (<1)		
CR1	1418 (15)		
CR2	507 (6)		
≥CR3	68 (<1)		
Relapse	148 (2)		
Missing	17 (<1)	0	0
Donor type			
HLA-identical sibling	3168 (34)	862 (32)	197 (37)
Other related	652 (7)	147 (5)	21 (4)
Well-matched unrelated	3863 (42)	1356 (51)	248 (47)
Partially-matched unrelated	1172 (13)	257 (10)	52 (10)
Mis-matched unrelated	150 (2)	15 (<1)	8 (2)
Multi-donor	26 (<1)	7 (<1)	2 (<1)
Unrelated (matching TBD)	175 (2)	24 (<1)	4 (<1)
Cord blood	1 (<1)	0	0
Missing	4 (<1)	8 (<1)	0

	AL	MDS	MF
Conditioning regimen intensity			
MAC	6281 (68)	1243 (46)	270 (51)
RIC	1747 (19)	1094 (41)	221 (42)
NMA	603 (7)	216 (8)	31 (6)
TBD	180 (2)	78 (3)	6 (1)
Missing	400 (4)	45 (2)	4 (<1)
GVHD prophylaxis			
No GVHD prophylaxis	43 (<1)	37 (1)	1 (<1)
Ex-vivo T-cell depletion	210 (2)	44 (2)	6 (1)
CD34 selection	213 (2)	68 (3)	8 (2)
Post-CY + other(s)	313 (3)	85 (3)	10 (2)
Post-CY alone	1 (<1)	0	0
TAC + MMF ± other(s) (except post-CY)	957 (10)	426 (16)	71 (13)
TAC + MTX ± other(s) (except MMF, post-CY)	3660 (40)	1155 (43)	239 (45)
TAC + other(s) (except MMF, MTX, post-CY)	401 (4)	187 (7)	18 (3)
TAC alone	216 (2)	63 (2)	9 (2)
CSA + MMF ± other(s) (except post-CY)	551 (6)	212 (8)	47 (9)
CSA + MTX ± other(s) (except MMF, post-CY)	1975 (21)	281 (11)	100 (19)
CSA + other(s) (except MMF, MTX, post-CY)	130 (1)	26 (<1)	6 (1)
CSA alone	192 (2)	42 (2)	10 (2)
Other(s)	57 (<1)	27 (1)	5 (<1)
Missing	292 (3)	23 (<1)	2 (<1)
Graft type			
Bone marrow	2043 (22)	410 (15)	69 (13)
Peripheral blood	7165 (78)	2261 (84)	463 (87)
PB + Other	1 (<1)	5 (<1)	0
UCB + Other	1 (<1)	0	0
BM + PB + Other	1 (<1)	0	0

	AL	MDS	MF
Year of HCT			
2000	384 (4)	52 (2)	17 (3)
2001	448 (5)	71 (3)	15 (3)
2002	509 (6)	63 (2)	26 (5)
2003	523 (6)	94 (4)	23 (4)
2004	660 (7)	100 (4)	20 (4)
2005	757 (8)	120 (4)	35 (7)
2006	767 (8)	100 (4)	30 (6)
2007	739 (8)	106 (4)	31 (6)
2008	801 (9)	136 (5)	48 (9)
2009	634 (7)	162 (6)	56 (11)
2010	475 (5)	120 (4)	24 (5)
2011	232 (3)	194 (7)	9 (2)
2012	233 (3)	239 (9)	8 (2)
2013	581 (6)	361 (13)	27 (5)
2014	763 (8)	382 (14)	83 (16)
2015	705 (8)	376 (14)	80 (15)
Median follow-up of survivors (range), months	89 (12-218)	61 (12-221)	72 (12-193)

Proposal 1809-02

Title:
Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm

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Hypothesis:
Hematopoietic Cell Transplantation (HCT) is associated with durable remissions in patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Specific aims:

- To evaluate outcomes of autologous HCT in BPDCN
  - Overall Survival
  - Progression Free Survival
  - Non-Relapse Mortality
  - Cumulative incidence of relapse
- To evaluate outcomes of allogeneic HCT in BPDCN
  - Overall Survival
  - Progression Free Survival
  - Non-Relapse Mortality
  - Cumulative incidence of relapse
  - Cumulative Incidence of acute and chronic GVHD
- To compare outcomes of autologous HSCT and allogeneic HCT in BPDCN
- To evaluate the impact of conditioning intensity on allogeneic HSCT outcomes (myeloablative vs reduced intensity)
- To identify the impact of pre-transplant markers on post-transplant outcomes in BPDCN

Scientific justification:
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy derived from the precursors of plasmacytoid dendritic cells. It is an exceedingly rare disorder, which accounts for approximately 0.4% of all hematologic malignancies. BPDCN diagnosis carries a very poor prognosis with a median survival of approximately 1 year and is essentially incurable with standard conventional induction therapy alone.
Limited retrospective studies have shown durable remissions in BPDCN; however, these studies are small, not exceeding50 cases. The European Society for Blood and Marrow Transplantation (EBMT) published outcomes of 34 BPDCN cases who received an allogeneic HCT, showing a 3-year disease-free survival (DFS) and overall survival (OS) of 33% and 41%, respectively while the Japanese Society for Hematopoietic Cell Transplantation reported 25 cases [allogeneic HCT = 14, autologous HCT) = 11], showing 4-year OS of 53% for allogeneic HCT and 82% for autologous HCT recipients, respectively. More

recently, Kharfan-Dabaja and colleagues reported a North American multicenter collaborative observational study of 45 cases [allogeneic HCT = 37, autologous HCT = 8] showing 3 year OS of 68% in allografted patients, but 1 year OS of 11% in patients receiving an autologous HCT.
No randomized controlled trials (RCTs) exist comparing the efficacy of HCT to chemotherapy alone. Due to the rare nature of BPDCN, it is unlikely that a RCT will ever be conducted. It is increasingly becoming a standard practice to offer an allogeneic HCT early in their treatment course. We believe that there is a unmet need for larger observational studies to help guide and better inform clinical decision making regarding the role of HCT in BPDCN. The most feasible way to evaluate transplant outcomes in these rare diseases is by using registry-based data. Thus we propose to utilize the Center for International Blood and Marrow Transplantation Research (CIBMTR) database to evaluate outcomes of autologous and allogeneic HCT recipients with the diagnosis of BPDCN.

Study population:
Inclusion Criteria:

- Adult patients age 18 or older with BPDCN who underwent HSCT from 2000-2017

Data requirements:
The following CIBMTR forms will be used:

- Recipient baseline data: Form 2000
- Pre-transplant Essential Data: Form 2400; Form 2402
- Post-HSCT data: Form 2100
- Recipient death data: Form 2900

Variables to be analyzed:
Patient-related:

- Age at HCT, years
- Sex: male vs female
- Karnofsky performance score
- HCT-CI
- Race (Caucasian vs African American vs others)

Disease-related:

- Disease state at time of transplant: CR1 vs CR2 vs PR vs SD vs PD
- Time from diagnosis to HSCT
- Number of pre-transplant lines of therapy

Transplant-related:

- Stem cell source: bone marrow vs. peripheral blood
- Time period transplant was performed: Continuous
- Conditioning intensity: myeloablative vs reduced intensity/ non-myeloablative
- GVHD prophylaxis
- Time from disease diagnosis to transplant

- Conditioning regimen intensity: Myeloablative vs. reduced intensity vs. non-myeloablative
- Source of hematopoietic stem cells: bone marrow vs. peripheral stem cell vs. cord blood
- Donor source: HLA-matched related donor, matched-unrelated donor, HLA-mismatched donor, haploidentical donor
- Donor-recipient gender
- Donor-recipient CMV status
- Graft-versus-host disease (GVHD) prophylaxis
- Year of transplant

Study design:

This retrospective study will investigate the efficacy of HCT in patients with BPDCN who received either an autologous or an allogeneic HCT between 2000 and 2017 and were reported to Center for International Blood and Marrow Transplantation (CIBMTR).

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 transplant to date of death or last follow up. Cumulative incidence of relapse/progression and NRM will be calculated using the Fine and Gray competing risk regression model

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.

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Table 1. Characteristics of adult patients receiving first HCT for BPDCN between 2000-2017, registered with CIBMTR

	Allogeneic	Autologous
Number of patients	181	19
Number of centers	92	13
Age at HCT		
Median (range)	58 (18-78)	66 (27-77)
18-29	14 (8)	1 (5)
30-39	27 (15)	0
40-49	17 (9)	2 (11)
50-59	47 (26)	3 (16)
60-69	57 (31)	7 (37)
≥70	19 (10)	6 (32)
Gender		
Male	137 (76)	15 (79)
Female	44 (24)	4 (21)
Race		
Caucasian	125 (69)	18 (95)
African-American	18 (10)	0
Asian	6 (3)	1 (5)
Missing	32 (18)	0
Disease status prior to HCT		
PIF	17 (9)	0
CR1	119 (66)	14 (74)
CR2	10 (6)	0
Relapse	7 (4)	0
Missing	28 (15)	5 (26)
HCT-CI		
0	52 (29)	5 (26)
1	25 (14)	0
2	28 (15)	1 (5)
3+	63 (35)	12 (63)
TBD	5 (3)	1 (5)
Missing	8 (4)	0
GVHD prophylaxis		
No GVHD prophylaxis	0	19
Ex-vivo T-cell depletion	1 (<1)	0
CD34 selection	4 (2)	0
Post-CY	25 (14)	0

	Allogeneic	Autologous
TAC based	98 (54)	0
CSA based	51 (28)	0
Other	1 (<1)	0
Missing	1 (<1)	0
Conditioning as repoted by center		
MAC	91 (50)	0
RIC/NMA	88 (49)	0
Auto-only	0	19
Missing	2 (1)	0
Conditioning regimen		
MAC		
TBI/Cy	38 (21)	
TBI/Cy/TT	1 (<1)	
TBI/other(s)	13 (7)	
Bu/Cy	13 (7)	
Mel alone	1 (<1)	
Mel/other(s)	2 (1)	
Other(s)	21 (12)	
Missing	2 (1)	0
RIC/NMA		
TBI/Cy	14 (8)	
TBI/Cy/TT	1 (<1)	
TBI/Mel	2 (1)	
TBI/other(s)	14 (8)	
Bu/Cy	2 (1)	
Cy alone	5 (3)	
Mel alone	27 (15)	
Mel/other(s)	4 (2)	
TLI	1 (<1)	
Other(s)	18 (10)	
Missing		0
Auto-only		
TBI/Cy		2 (11)
Bu/Cy		3 (16)
Bu/Mel		1 (5)
BEAM like		11 (58)
Mel/other(s)		1 (5)
Other(s)		1 (5)

	Allogeneic	Autologous
Missing	0	
Missing		
TBI/other(s)	1 (<1)	
Missing	1 (<1)	0
Graft type		
Bone marrow	21 (12)	0
Peripheral blood	146 (81)	19
Umbilical cord blood	14 (8)	0
Year of HCT		
2007	2 (1)	0
2009	7 (4)	2 (11)
2010	6 (3)	0
2011	16 (9)	1 (5)
2012	15 (8)	1 (5)
2013	22 (12)	0
2014	20 (11)	1 (5)
2015	27 (15)	4 (21)
2016	34 (19)	8 (42)
2017	32 (18)	2 (11)
Median follow-up of survivors (range), months	26 (3-95)	22 (3-97)

Proposal: **1811-86**

Title:
10 year survival after allogeneic hematopoietic cell transplantation for AML in adults 60 years and above: frequency and success factors

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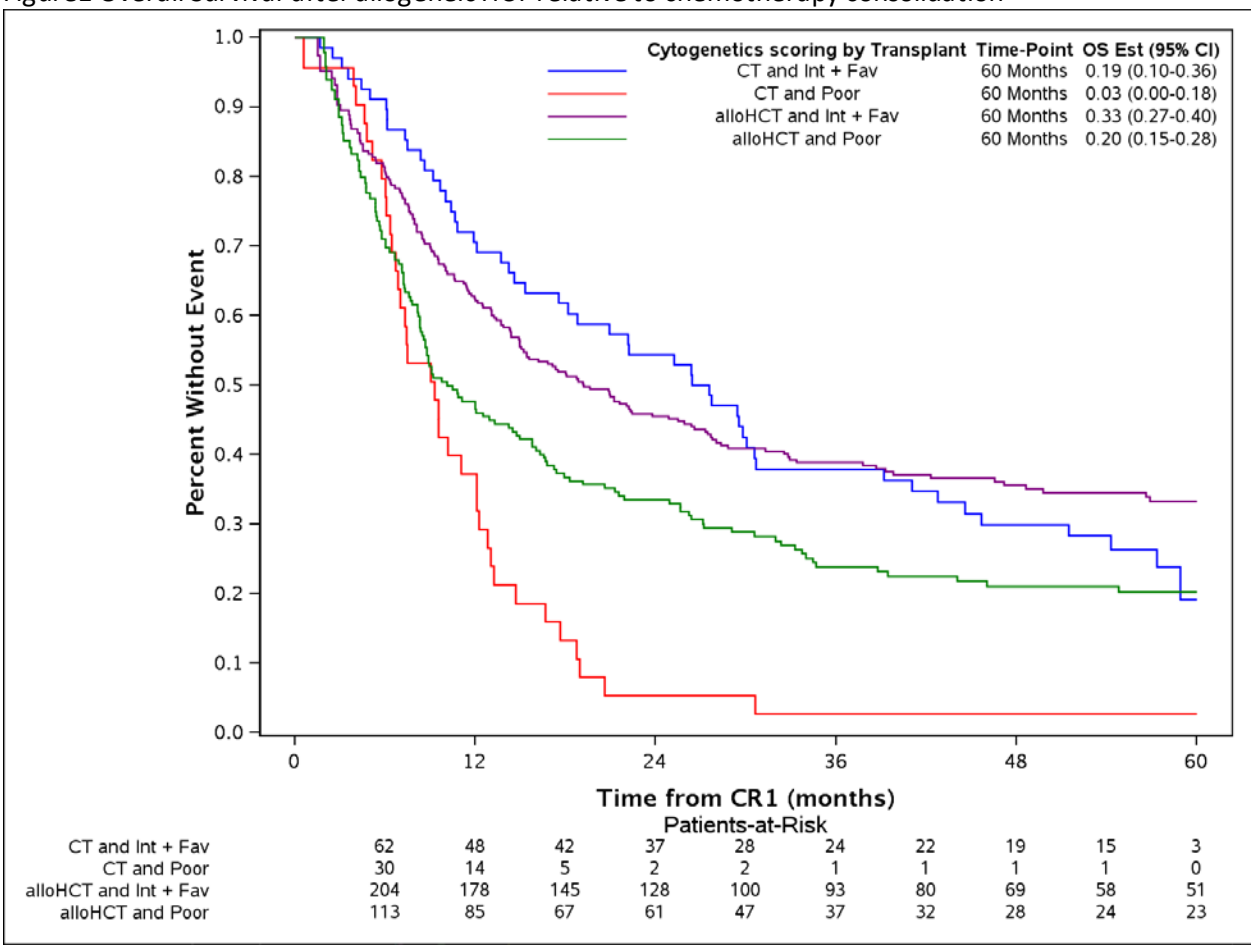
Hypothesis:
Allogeneic transplant for older AML patients enables long-term survival.

Specific aims:
1. To describe outcomes at 10 years for AML patients 60 years and older receiving allogeneic hematopoietic cell transplantation (HCT)
2. To evaluate success factors for long-term survival
3. To determine late risk factors after 5 years that impair 10 year survivorship.

Scientific impact:
This would be the first study to our knowledge to document the long-term 10 year survival rate after allogeneic transplant for older AML patients. In light of the rarity of 10 year survival without allogeneic HCT, this would offer evidence of a sustained benefit. Describing factors for success may further encourage HCT in appropriate patients. Finally, describing factors impairing success between year 5 and 10 for transplant would inform survivorship in older adults.

Scientific justification:
Older age, usually classified as 60 years and older, represents one of the strongest adverse risk factors for AML outcomes. [1] [2] Most patients with AML are older as the median age of diagnosis for AML is 67 years (seer.cancer.gov/statfacts/html/amyl.html) and survival is generally poor. [3]
Allogeneic transplant has an established role for AML in first complete remission in improving disease free and overall survival for younger adults, particularly with intermediate and high-risk disease in studies comparing patients with a matched donor against those without. [4] [5] Numerous advances may have promoted more widespread application of allogeneic transplant to older adults including better HLA matching of unrelated donors, reduced intensity regimens, better supportive care, insurance coverage, and better health and longevity of older adults. Still the proportion of older AML patients undergoing transplant remains low. [6]
Observational studies have suggested reasonable outcomes among older adults with AML in remission relative to chemotherapy alone consolidation. [7, 8] Non-randomized data suggest improvement in relapse free if not overall survival for allogeneic transplant although large prospective studies are limited. [9] [10]
Five year survival after allografting for all diseases was reported by Sorror after non-myeloablative HLA identical grafts as follows: 38% for those 60-64, 33% for those aged 65 through 69, and 25% for those 70 years or older. [11]
We recently compared 5 year survival for AML patients 60 years and older undergoing consolidation for CR1 on cooperative group trials versus allogeneic transplant results from the CIBMTR (LK1501) suggesting allogeneic HCT affords a benefit. Paradoxically, the relatively poor 5 year survival of 20% for adverse cytogenetics after allogeneic HCT appeared to produce the greatest benefit when considered the estimated 3% survival for similar karyotype patients receiving consolidation. (Ustun C, ASH abstract 2018)

Figure1 Overall Survival after allogeneic HCT relative to chemotherapy consolidation



In older adults, the ability to achieve long-term disease control remains unknown with or without transplant. One recent of 944 AML patients 60 years and older treated with chemotherapy through the CALGB showed only 23 (2.4%) were disease free at 10 years. [12] Among the 60% who achieved CR1, disease free survival by cytogenetic categories was as follows: 18% for core binding factor-AML, 3.6% for cytogenetically normally patients and 2.2% of those with other abnormal karyotypes. Allogeneic HCT as rescue was not mentioned although may have occurred in some of these patients. Allogeneic HCT may enable long-term survival although data on late disease relapse and GVHD complications are not known beyond 5 remains sparse. However, as a growing number of older adults undergo transplant, the implications of late survivorship and acceleration of the normal aging processes must be considered. We propose reviewing CIBMTR data for patients 60 and older with AML who underwent allogeneic transplant to describe long-term outcomes and prognostic factors.

To our knowledge, there are no studies detailing long-term survival for older AML patients. This study may well delineate a group of older AML patients without remission where acceptable long-term success justifies early referral for allogeneic transplant consideration. For risk groups with poor long-term outcomes, the study will provide estimates to council patients and to formulate future clinical trials.

Limitations:

Many patients status will be unknown. We will not have granular data of molecular mutations and many will not have HCT-CI scores. More recent approaches in transplant such as haploidentical grafts will not

be represented well. An alternative is to this approach is to evaluate 5 year and 10 year survival to better reflect modern practice.

Patient eligibility population:
Inclusion Criteria:

- Age 60 years or greater at time of transplant
- First allogeneic transplant (any donor source)
- AML as transplant indication
- Transplant year 2009 or earlier (assume study occurs in 2019)

Data requirements:
No new data requirements although if patients are lost to follow-up, the centers may be queried.

Study design:
Outcomes:

- Non-Relapse Mortality: time to death without evidence of disease relapse. Relapse is the competing risk, and patients surviving in continuous complete remission are censored at last follow up.
- Cumulative Incidence of Relapse: time to onset of leukemia or MDS or antecedent hematologic malignancy recurrence). NRM is the competing risk, and patients surviving in continuous complete remission will be censored at last contact.
- Leukemia-Free survival: Time to treatment failure (death or relapse). Patients surviving in continuous complete remission are censored at time of last follow-up.
- Overall Survival: Time to death from any cause. Surviving patients are censored at time of last follow-up.
- Chronic graft-versus-host disease: Time to onset of cGvHD, death is a competing risk.

Variables to be analyzed:

- Patient-related:
    - Age at HCT (60-64, 65-69, 70+)
    - Sex
    - Karnofsky Performance scores: <90 vs ≥90
    - Hematopoietic cell transplant-comorbidity index (HCT-CI) (available since 2008) (0, 1-2, 3+)

- Disease-related:
    - Type of AML: de-novo versus, therapy related, or secondary AML with antecedent hematologic disorder
    - Disease status at transplant
    - Disease risk index (may not be able to calculate)
    - Cytogenetic Category: favorable risk vs. intermediate vs. unfavorable risk

- Transplant-related:
    - Time to transplant from diagnosis of AML
    - Conditioning regimen: MAC vs. RIC vs. NMA.
    - Donor type (matched related, matched unrelated, mismatched unrelated, haplo-identical, cord, other)

- CMV status of donor and recipient: (+/+ vs. +/- vs. -/+ vs. -/-)
- Donor type (matched related, matched unrelated, mismatched unrelated, haplo related, cord or cord plus other, and other)
- Source of hematopoietic cells: BM vs. PBSC (among matched related and matched unrelated)
- GVHD prophylaxis: Calcineurin inhibitor (CNI) + MTX vs. CNI + MMF vs CNI plus cyclophosphamide after transplant vs others
- T-cell depletion with ATG or alemtuzumab (yes/no)

Statistical analysis:

Baseline characteristics of the entire cohort will be summarized. Kaplan-Meier curves will be used to estimate the probability of OS and LFS, cumulative incidence will be used to estimate probability of neutrophil recovery, TRM/NRM, chronic GVHD and relapse. Relapse will be summarized by the cumulative incidence estimate with treatment related mortality as a competing risk. For time to e vent analysis, patients will be censored at the time of last follow-up.

The outcomes of 10 year OS, LFS, relapse, NRM and chronic GVHD will also be presented by patients in remission or not in remission at transplant and by age groups of 60-64, 65-69 and 70 years plus.

Multivariate models for OS, LFS, NRM and relapse will be generated. Chronic GVHD will be included as time dependent variable. Success Factors will be defined as those retained in multivariate models from the above.

Finally, to determine late risk factors, OS will be summarized at 5 years and 10 years. Cumulative incidence curves for TRM and relapse will be generated from year 5 to year 10. Similar to above, multivariate models will be created for prognostic factors for death, relapse or TRM between year 5 and 10.

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Table 1. Characteristics of patients older than 60 years receiving first allo-HCT for AML between 2000-2009, reported to CIBMTR

	Total
Number of patients	1580
Number of centers	163
Age at HCT	
Median (range)	64 (60-83)
60-64	919 (58)
65-69	534 (34)
70+	127 (8)
Gender	
Male	963 (61)
Female	617 (39)
Karnofsky score	
<90	181 (11)
≥90	1321 (84)
Missing	78 (5)
Disease status prior to HCT	
Primary induction failure	299 (19)
CR1	691 (44)
CR2	266 (17)
≥CR3	30 (2)
Relapse	281 (18)
Missing	13 (<1)
Clinical onset of AML	
De-novo	932 (59)
Transformed from MDS/MPS	563 (36)
Therapy linked	85 (5)
Donor type	
HLA-identical sibling	433 (27)
Twin	4 (<1)
Other related	54 (3)
Well-matched unrelated	722 (46)
Partially-matched unrelated	219 (14)
Mis-matched unrelated	40 (3)
Multi-donor	4 (<1)
Unrelated (matching TBD)	9 (<1)
Cord blood	95 (6)

	Total
Graft type	
Bone marrow	191 (12)
Peripheral blood	1293 (82)
Umbilical cord blood	95 (6)
BM + PB + Other	1 (<1)
Year of HCT	
2000	42 (3)
2001	72 (5)
2002	74 (5)
2003	108 (7)
2004	163 (10)
2005	184 (12)
2006	201 (13)
2007	226 (14)
2008	279 (18)
2009	231 (15)
Median follow-up of survivors (range), months	118 (3-193)

Proposal: 1811-96

Title:
10 yr relapse-free survival in Acute myeloid leukemia in patients who underwent HCT in CR1.

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Hypothesis:
10-yr disease –free survival in patients with denovo AML who did not receive an allogeneic transplant in first complete remission is known. However, 10-yr disease –free survival and overall survival in patients with de novo (stratified by ELN), secondary or therapy-related AML is not known. Most studies report 3 yr or 5 yr survival, but 10 yr survival is not reported.

Specific aims:
To evaluate 10 yr disease-free and overall survival in AML patients(De novo stratified by 2017 European Leukemia Net classification, Secondary AML and therapy-related AML) who underwent an allogeneic transplant in first complete remission

Scientific impact:
- With the rise of targeted therapies in AML, it is important to establish the enduring and long term disease free survival post allogeneic transplantation. Establishing 10 yr survival in patients stratified by ELN classification will harmonize evaluation of outcomes, since AML studies primarily use ELN for risk stratification and clinical trial participation. In addition, the recent ELN 2017 classification incorporates molecular markers and cytogenetic studies. This will allow evaluation of outcomes post allogeneic transplant taking into account the significant molecular heterogeneity in AML and adding prognostic information that what is available in the disease-risk index.
- Adding measurable residual disease to the analysis variables will assess role of MRD in long term survival.

Scientific justification:
Ongoing improvements are noted in non-relapse mortality following allogeneic transplantation (Gooley et al). Studies evaluating at outcomes following transplantation have reported 3 yr and 5 yr outcomes. Recently, Wingard et al reported on long-term survival, however they only looked at patients who survived at least 2 yrs post transplantation. Given that relapses and complications related to GVHD continue to occur up to 2 yrs, we seek to evaluate 10 yr disease free and overall survival for patients who underwent an allogeneic transplant in first complete remission. Recently 10 yr DFS was reported in a large cohort of patients (Vasu et al). 2551 AML patients (1607 aged <60 years, and 944 aged ≥60 years) enrolled in Cancer and Leukemia Group B treatment protocols and the cytogenetics companion protocol 8461 between 1983 and 2004 were evaluated for long-term DFS. At 10 years, 267 (16.6%) of patients aged <60 years and 23 (2.4%) of those aged ≥60 years were alive and disease-free. These data provide evidence that the frequency of long-term cure of AML is low among younger and especially older patients in the absence of Allo-HCT in CR1.
Given increasing utilization of allogeneic HCT in younger and older patients due to near-universal donor availability and reduced-intensity regimens, it would be imperative to know the 10 yr. DFS and OS in patients who received an allogeneic transplant in CR1. Currently the accepted system for classification of AML is the ELN a consensus document from investigators in AML globally (Dohner et al). It now includes the understanding about additional prognostic molecular markers in AML that have led to development

of targeted therapies. The disease risk index commonly used in BMT trials does not capture molecular prognostic markers. Hence evaluating transplant outcomes using the same classifications system adopted by the leukemia community allows us to harmonize risk stratification and allow comparability in evaluating outcomes of transplant and non-transplant therapies.

Patient eligibility population:

Patient related:

- Age at HCT: continuous to find the appropriate cut point for the survival model
- Gender: male vs. female
- HCT comorbidity index
- Karnofsky performance score: ≥90 vs. <90

Disease related:

- Therapy related/secondary AML: (Yes vs. No)
- Cytogenetics category (Normal vs. Favorable vs. Intermediate vs. Poor)
- ELN Risk (2017)
- Disease status prior to transplant (Primary induction failure vs. CR1 vs. CR2 or greater vs. relapse)
- Time from diagnosis to CR1 (only for patients in CR1 at HCT)
- Measurable/minimal residual disease positivity pre-transplant

Transplant-related:

- Describe median (range) dose of Mel
- Dose of Mel: High vs. Low
- Dose of Bu: High vs. Low
- Describe median (range) dose of Flu
- Year of Transplant (adjust for time effect)
- Donor relationship and HLA-matching: HLA-identical sibling, Other relatives, Well-matched unrelated, Partially-matched unrelated ,Mismatched unrelated, Unrelated (matching unknown)
- Graft type: bone marrow vs peripheral blood
- Donor age (URD)
- Donor & recipient (D/R) ABO blood type: (Matched, Minor mismatch, Major mismatch, Bi-directional)
- GVHD prophylaxis regimen: Tac based vs. CSA based vs. PT-Cy
- Donor/Recipient gender: (F/F vs. M/M vs. F/M vs. M/F)
- Donor/Recipient CMV status: (-/+ vs. others)
- In vivo T-cell depletion (ATG/Alemtuzumab): Yes vs No

Data requirements:

- Pre-HCT Essential data 2400
- Pre-HCT Essential data : Disease classification 2402
- Post-HCT essential data: 2450R4.0
- Pre-Infusion data (2010)
- MDS/MPD 2014 Pre-HCT data
- 2006: HCT Infusion
- Form 2110 R4.0: AML Post-infusion data

- Post-HCT Follow up data

Study design (scientific plan):

- The goal of this study is to establish 10 yr survival of AML patients transplanted in CR1. We can then compare the disease free survival with the already known DFS of patients who did not receive an allograft in CR1.
- Patient-, disease- and transplant-related factors will be compared between treatment groups using the Chi-square test for categorical variables and the Wilcoxon two sample test for continuous variables.

Data Source:

CIBMTR Research Database

References:

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Conflicts of interest:

None

Table 1. Characteristics of adult patients receiving first allo-HCT for AML between 2000-2009, reported to CIBMTR

	TED	CRF	Total
Number of patients	5865	6610	12475
Number of centers	181	169	201
Age at HCT			
Median (range)	49 (18-83)	50 (18-83)	49 (18-83)
18-29	774 (13)	984 (15)	1758 (14)
30-39	836 (14)	864 (13)	1700 (14)
40-49	1428 (24)	1531 (23)	2959 (24)
50-59	1706 (29)	1952 (30)	3658 (29)
60-69	1044 (18)	1169 (18)	2213 (18)
≥70	77 (1)	110 (2)	187 (1)
Gender			
Male	3043 (52)	3485 (53)	6528 (52)
Female	2822 (48)	3125 (47)	5947 (48)
Race			
Caucasian	4555 (78)	5918 (90)	10473 (84)
African-American	280 (5)	297 (4)	577 (5)
Asian	209 (4)	133 (2)	342 (3)
Pacific islander	7 (<1)	4 (<1)	11 (<1)
Native American	12 (<1)	23 (<1)	35 (<1)
Other	154 (3)	12 (<1)	166 (1)
More than one race	3 (<1)	27 (<1)	30 (<1)
Missing	645 (11)	196 (3)	841 (7)
Karnofsky score at HCT [a]			
<90	825 (14)	1771 (27)	2596 (21)
≥90	986 (17)	3067 (46)	4053 (32)
Missing	4054 (69)	1772 (27)	5826 (47)
Karnofsky score at HCT [a]			
<80	825 (14)	1771 (27)	2596 (21)
≥ 80	3264 (56)	3713 (56)	6977 (56)
Missing	1776 (30)	1126 (17)	2902 (23)

	TED	CRF	Total
Disease status prior to HCT			
PIF	849 (14)	960 (15)	1809 (15)
CR1	2653 (45)	2876 (44)	5529 (44)
CR2	1050 (18)	1399 (21)	2449 (20)
≥CR3	47 (<1)	102 (2)	149 (1)
Relapse	861 (15)	1124 (17)	1985 (16)
Missing	405 (7)	149 (2)	554 (4)
Clinical onset of AML			
De-novo	5817 (99)	4908 (74)	10725 (86)
Transformed from MDS/MPS	37 (<1)	1329 (20)	1366 (11)
Therapy linked	11 (<1)	373 (6)	384 (3)
Cytogenetic score [b]			
Favorable	150 (3)	452 (7)	602 (5)
Intermediate	217 (4)	3228 (49)	3445 (28)
Poor	39 (<1)	1492 (23)	1531 (12)
TBD	15 (<1)	630 (10)	645 (5)
Not tested	3 (<1)	229 (3)	232 (2)
Missing	5441 (93)	579 (9)	6020 (48)
Donor type			
HLA-identical sibling	3723 (63)	1622 (25)	5345 (43)
Other related	537 (9)	248 (4)	785 (6)
Well-matched unrelated	496 (8)	2833 (43)	3329 (27)
Partially-matched unrelated	147 (3)	1028 (16)	1175 (9)
Mis-matched unrelated	23 (<1)	250 (4)	273 (2)
Multi-donor	61 (1)	34 (<1)	95 (<1)
Unrelated (matching TBD)	655 (11)	48 (<1)	703 (6)
Cord blood	164 (3)	511 (8)	675 (5)
Missing	59 (1)	36 (<1)	95 (<1)
Graft type			
Bone marrow	967 (16)	1488 (23)	2455 (20)
Peripheral blood	4722 (81)	4610 (70)	9332 (75)
Umbilical cord blood	164 (3)	511 (8)	675 (5)
Other, specify	9 (<1)	0	9 (<1)
BM + Other	2 (<1)	0	2 (<1)
PB + Other	1 (<1)	1 (<1)	2 (<1)

	TED	CRF	Total
Year of HCT			
2000	431 (7)	357 (5)	788 (6)
2001	400 (7)	421 (6)	821 (7)
2002	488 (8)	423 (6)	911 (7)
2003	540 (9)	476 (7)	1016 (8)
2004	535 (9)	675 (10)	1210 (10)
2005	603 (10)	727 (11)	1330 (11)
2006	646 (11)	770 (12)	1416 (11)
2007	733 (12)	838 (13)	1571 (13)
2008	664 (11)	997 (15)	1661 (13)
2009	825 (14)	926 (14)	1751 (14)
Median follow-up of survivors (range), months	117 (<1-219)	120 (1-218)	119 (<1-219)

[a] KPS score before 2007 is only collected dichotomous, using as cut off 80 or more

[b] Cytogenetic information only collected on CRF track before 2013