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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

2021 STATUS REPORT
ACUTE LEUKEMIA WORKING COMMITTEE

Working Committee Leadership	
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INTRODUCTION

a. Minutes and overview plan from 2020 TCT meeting (Attachment 1)

PROPOSALS MOVING FORWARD FOR SCORING (click here to cast your score)

a. PROP 2009-13; 2010-08; 2010-10 Impact of *IDH1* and *IDH2* mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation (Francisco Andres Socola/ Hana Safah/ Saba Nakhle/ Antonio Martin Jimenez/ Trent Peng Wang/ Krishna Komanduri/ Namrata Chandhok/ Evan Chris Chen/ Yi-Bin Chen). (Attachment 2)

b. PROP 2010-27; 2010-147; 2010-197; 2010-258; 2010-298; 2010-332 Impact of measurable residual disease status on outcomes of acute myeloid leukemia and patients 18-65 years old in first complete remission undergoing allogeneic hematopoietic cell transplantation (Maria Queralt Salas/ Alberto Mussetti/ Roman M. Shapiro/ Asad Bashey/ Mukta Arora/ Rizwan Romee/ Hany Elmariah/ Nelli Bejanyan/ Joseph Pidala/ Firas El Chaer/ Christopher Hourigan/ Monzr Al Malki/ Stefan Ciurea/ Abu-Sayeef Mirza/ Rory M. Shallis/ Lohith Gowda/ Amer Zeidan). (Attachment 3)

PROPOSALS DROPPED BECAUSE THEY OVERLAP WITH EXISTING STUDIES OR ARE NOT FEASIBLE DUE TO LIMITATIONS OF AVAILABLE PATIENTS OR DATA

a. PROP 2010-15 Induction chemotherapy vs. hypomethylating agent therapy for older/frail AML patients undergoing allogeneic hematopoietic stem cell transplantation (Antonio M. Jimenez/ Trent P. Wang/ Krishna Komanduri/ Marcos de Lima).

b. PROP 2010-24 Comparison of reduced-intensity conditioning regimens for older patients with AML and MDS: a propensity score analysis (Stefan O. Ciurea/ Piyanuch Kongtim/ Monzr Al Malki/ Nelli Bejanyan/ Brenda Sandmaier).

c. PROP 2010-28 Outcome of adults treated with azacitidine and venetoclax followed by allogeneic stem cell transplantation (Maria Q. Salas/ Alberto Mussetti).

d. PROP 2010-37 Comparison of allogeneic hematopoietic cell transplantation following antibody-based salvage strategies for relapsed/refractory B-cell acute lymphoblastic leukemia (Ryan D. Cassaday/ Brenda M. Sandmaier).

e. PROP 2010-47 Outcome of allogenic hematopoietic stem cell transplantation in Philadelphia chromosome positive (Ph+) acute myeloid leukemia (AML) (Ayman Qasrawi/ Carolina Escobar/ Reinhold Munker).

f. PROP 2010-57 Comparison of second allogeneic hematopoietic cell transplantation vs. donor lymphocyte infusion in the treatment of first relapse after haploidentical transplants for ALL, AML and MDS (Najla El Jurdi/ Daniel Weisdorf/ Claudio Brunstein).

g. PROP 2010-74 Transplant related toxicities and predictors of toxicities in adult patients with B-ALL who were previously treated with blinatumomab and/or inotuzumab ozogamicin (Kitsada Wudhikarn/ Jae H. Park/ Miguel-Angel Perales).

h. PROP 2010-77 Real-world impact of incorporating CD19 CART therapy in salvage regimens in relapsed and refractory b-cell acute lymphoblastic leukemia prior to allogeneic hematopoietic cell transplantation (Mahmoud R. Gaballa/ Sajad J. Khazal/ Kris M. Mahadeo/ Partow Kebriaei).

i. PROP 2010-78 Maintenance therapy with hypomethylating agents after allogeneic stem cell transplantation (AlloHCT) in patients with myeloid malignancies may improve leukemia free survival (LFS)/ progression free survival (PFS) but not overall survival (OS) (Sunita Nathan/ Ankur Varma/ Celalettin Ustun).

j. PROP 2010-101 Impact of CD56 status on CBF AML following induction and allogeneic stem cell transplant (Nasheed M. Hossain/ Stephanie Berg/ Nicholas K. Torgerson).

k. PROP 2010-109 Does choice of induction intensity affect outcomes of allogeneic hematopoietic cell transplantation in acute myeloid leukemia? (Hemant Murthy/ Zaid H. Rahman/ James Foran/ Mohamed A. Kharfan-Dabaja).

l. PROP 2010-126 Allogeneic stem cell transplant outcomes based on initial anti-leukemia therapy intensity in older adults with acute myeloid leukemia (John L. Reagan/ Aryeh Pelcovits).

m. PROP 2010-151 Utilization and outcomes of second allogeneic hematopoietic stem cell transplantation for adult for acute lymphoblastic leukemia (Vaibhav Agrawal/ Lori Samantha Muffly).

n. PROP 2010-153 Comparison of FluMelTBI and FluCyTBI conditioning regimens for haploidentical hematopoietic cell transplant with post-transplant cyclophosphamide in patients with acute myeloid leukemia (Monzr M. Al Malki/ Shukaib Arslan/ Filippo Milano).

o. PROP 2010-168 Efficacy and survival of patients with relapsed/refractory acute lymphoblastic leukemia who receive a second CAR T-cell product infusion (Joanna C. Zurko/ Nirav N. Shah).

p. PROP 2010-186 Outcomes of allogeneic hematopoietic stem cell transplant in triple hit AML (concurrent DNMT3A, FLT3, and NPM1 mutations) (Sowjanya Vuyyala/ Shatha Farhan).

q. PROP 2010-187 The impact of sirolimus-based treatment for acute graft-versus-host disease on disease relapse in acute leukemia patients (Hyun-Don, Yun/ Sunita Nathan/ Celalettin Ustun).

r. PROP 2010-212 Transplant outcomes for acute myeloid leukemia in first complete remission after hypomethylating agent and venetoclax based therapy (Benjamin K. Tomlinson/ Marcos de Lima/ Amin Firoozmand).

s. PROP 2010-242 A necessary, contemporary analysis of patients with acute promyelocytic leukemia undergoing autologous and allogeneic hematopoietic stem cell transplantation in the ATRA/ATO era (Rory M Shallis/ Lohith Gowda/ Amer M. Zeidan).

t. PROP 2010-243 Allogeneic transplantation for acute myeloid leukemia in first complete remission after HMA-based therapy (Oren Pasvolsky/ Moshe Yeshurun/ Uri Rozovski/ Liat Shargian-Alon).

u. PROP 2010-244 Incidence, characteristics and outcomes of very late relapse in acute myeloid leukemia patients after allogeneic stem cell transplant (A Tomas, L Segundo, M Perales).

v. PROP 2010-245 Kinetics of measurable residual disease after allogeneic stem cell transplant for myelodysplastic syndromes and acute myeloid leukemia and the influence on provider practice patterns and patient outcomes (Rory Shallis/ Lohith Gowda/ Amer M. Zeidan/ Marcos de Lima).

w. PROP 2010-250 Predictors for overall survival after a second allogeneic transplant for acute myeloid leukemia (AML) in complete remission (CR/CRi) (Alexandra Gomez-Arteaga/ Boglarka Gyurkoza/ Koen van Besien).

x. PROP 2010-265 Impact of maintenance therapy on one year survival in acute myeloid leukemia patients undergoing allogenic transplant (Vamsi Kota/ Marcos de Lima).

y. PROP 2010-276 Hematopoietic cell transplant outcomes in adult patients with Philadelphia chromosome like acute lymphoblastic leukemia (Shivaprasad Manjappa/ Marcos de Lima/ Leland Metheny).

z. PROP 2010-305 Assessment of transplant indication, genetic mutation profiling, and minimal residual disease in secondary CBF AML (Pankit Vachhani/ Antonio Di Stasi/ Ayman Saad/ Celalettin Ustun/ Gautam Borthakur/ Gautam Marcucci/ Donna Salzman/ Ann-Kathrin Eisfeld).

aa. PROP 2010-328 Outcomes of B- acute lymphoblastic leukemia patients transplanted with prior exposure to novel agents (Sayeef Mirza/ Lohith Gowda/ Rory M. Shallis/ Amer Zeidan).

ab. PROP 2010-329 Outcomes of second or subsequent CAR-T infusion after relapse from prior CAR-T cell therapy (Sayeef Mirza/ Lohith Gowda).

PROPOSALS NOT ACCEPTED FOR CONSIDERATION AT THIS TIME DUE TO RELATIVE SCIENTIFIC IMPACT COMPARED TO ONGOING STUDIES AND/OR OTHER PROPOSALS

a. PROP 2008-05 Allogeneic hematopoietic cell transplantation for older adults with acute myeloid leukemia with nucleophosmin (NPM1) mutation (Vijaya Raj Bhatt).

b. PROP 2010-36 A comparison of outcomes following HLA-matched allogeneic hematopoietic cell transplantation for AML using sibling donors older than 50 years to unrelated donors younger than 50 years (David Allan/ Christopher Bredeson/ Mitchell Sabloff/ Wael Saber).

c. PROP 2010-83 Comparison of reduced intensity conditioning regimens in haploidentical donor transplant for acute leukemia and myelodysplastic syndrome (Dipenkumar Modi/Joseph Uberti/ Bipin Savani).

d. PROP 2010-113 Machine learning methods to better predict post-hematopoietic stem cell transplant (HSCT) relapse in patients with acute hematologic malignancies featuring post-transplant chimerism (David Chung-Chuan Shyr/ Simon C. Brewer).

e. PROP 2010-138 Outcomes of acute lymphoblastic leukemia in the setting of a prior malignancy (Trent P. Wang/ Antonio M. Jimenez).

f. PROP 2010-148 Identifying the risk factors for post-allogeneic stem cell transplant extramedullary relapse of acute myeloid leukemia in adult patients receiving TBI- and non-TBI-based myeloablative conditioning (Roman M. Shapiro/ Robert Soiffer).

g. PROP 2010-174 Clinical outcomes of adults with acute lymphoblastic leukemia undergoing allogeneic stem cell transplant by type of reduced intensity conditioning regimen (Rawan G. Faramand/ Nelli Bejanyan/ Partow Kebriaei).

h. PROP 2010-214 Outcomes with donor lymphocyte infusion after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia and myelodysplastic syndromes (Muhammad U. Mushtaq/ Sunil Abhyankar/ Joseph P. McGuirk).

i. PROP 2010-257 Comparison of outcomes between busulfan-based myeloablative conditioning regimens with cyclophosphamide (bu/cy) OR fludarabine (bu/flu) for acute myeloid leukemia (Evandro D. Bezerra/ Roland B. Walter/ Brenda M. Sandmaier/ Mark R. Litzow).

j. PROP 2010-293 Impact of pre-transplant extramedullary disease on allogeneic transplant outcomes in acute lymphoblastic leukemia (ALL) (Reshma Ramlal/ Gerhard Hildebrandt/ Partow Kebriaei).

k. PROP 2010-304 The effect of the prophylactic donor lymphocyte infusion on allogeneic hematopoietic cell transplantation outcomes in patients with acute myeloid leukemia (Nelli Bejanyan/ Wael Saber).

l. PROP 2010-319 Survival after post-allogeneic transplant relapse for patients with AML and MDS in the modern era (Sayeef Mirza/ Lohith Gowda/ Rory M. Shallis/ Amer Zeidan).

m. PROP 2010-323 Identification of risk factors and characteristics of patients who have late (>2 years) relapse of acute leukemia following allogeneic transplant (Aric C. Hall/ Ayesha Hassan).

Though many of these proposals address important clinical questions, we will unfortunately not be able to take them forward to the TCT meeting. These proposed studies are interesting, but given the unique circumstances of this year, as well as a larger backlog of unfinished existing studies, the working committees were directed only to select 0-2 total proposals from each committee to be considered by the overall CIBMTR this year. This change from prior years significantly limited our ability to accept proposals for consideration and we look forward accepting a broader portfolio of studies in future years.

STUDIES IN PROGRESS

a. **LK16-03** Allogeneic transplantation to treat therapy related acute myeloid leukemia and myelodysplastic syndromes. Status: Manuscript Preparation**.** An initial manuscript draft has been received and the plan is to submit by July 2021.

b. **LK18-01** Prognostic impact of the new European leukemia net genetic risk stratification categories in predicting outcomes for adults with acute myeloid leukemia undergoing allogeneic hematopoietic stem cell transplantation. Status: Manuscript Preparation. An initial manuscript draft has been received and the plan is to submit by July 2021.

c. **LK18-02** Comparison of outcomes of transplants with matched-related donor or matched-unrelated donor allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia. Status: Manuscript Preparation. An initial manuscript draft has been received and the plan is to submit by July 2021.

d. **LK19-01** Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm. Status: Data File Preparation. The data file is currently being prepared and the plan is to finalize the analysis and manuscript by July 2021.

e. **LK19-02** Evolving significance of philadelphia chromosome status on acute lymphoblastic leukemia prognosis in the TKI era. Status: Protocol Development. The protocol is currently being finalized and the plan is to complete the data file and analysis by July 2021.

f. **LK19-03** Outcomes of allogeneic transplants in acute myeloid leukemia patients who achieved first complete remission after two or more cycles of induction chemotherapy. Status: Data File Preparation. The data file is currently being prepared and the plan is to finalize the analysis by July 2021.

g. **LK20-01** Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation. Status: Protocol Development. The protocol is currently being prepared will be finalized by July 2021.

h. **LK20-02** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia. Status: Protocol Development. The study population has been finalized and the samples are currently being genotyped.

i. **LK20-03** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia. Status: Deferred. The plan is to begin working on the study protocol in July 2021.

j. **LK20-04** Impact of older age in allogeneic transplants for acute myeloid myelogenous leukemia in first complete remission. Status: Manuscript Preparation. A manuscript draft is currently being prepared and the plan is to submit by July 2021.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **LK16-02** Bejanyan N, Zhang M, Bo-Subait K, Brunstein C, Wang H, Warlick ED, Giralt SA, Nishihori T, Martino R, Passweg J, Dias A, Copelan E, Hale G, Gale RP, Solh M, Kharfan-Dabaja MA, Diaz MA, Ganguly S, Gore S, Verdonck LF, Hossain NM, Kekre N, Savani B, Byrne M, Kanakry C, Cairo MS, Ciurea S, Schouten HC, Bredeson C, Munker R, Lazarus H, Cahn J-Y, van Der Poel M, Rizzieri D, Yared JA, Freytes C, Cerny J, Aljurf M, Palmisiano N, Pawarode A, Bacher VU, Grunwald MR, Nathan S, Wirk B, Hildebrandt GC, Seo S, Olsson RF, George B, De Lima M, Hourigan CS, Sandmaier BM, Litzow M, Kebriaei P, Saber W, Weisdorf D. Myeloablative conditioning for allogeneic transplantation results in superior disease-free survival for acute myeloid leukemia and myelodysplastic syndromes with low/intermediate, but not high disease risk index: A CIBMTR study: Superior DFS with MAC compared to RIC HCT in AML/MDS with low/intermediate risk DRI. Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation. doi:10.1016/j.bbmt.2020.09.026. Epub 2020 Oct 1.

b. **LK16-01** Zhou Z, Nath R, Cerny J, Wang H-L, Zhang M-J, Abdel-Azim H, Agrawal V, Ahmed G, Al-Homsi AS, Aljurf M, Alkhateeb HB, Assal A, Bacher U, Bajel A, Bashir Q, Battiwalla M, Bhatt VR, Byrne M, Cahn J-Y, Cairo M, Choe H, Copelan E, Cutler C, Damlaj MB, DeFilipp Z, De Lima M, Diaz MA, Farhadfar N, Foran J, Freytes CO, Gerds AT, Gergis U, Grunwald MR, Gul Z, Hamadani M, Hashmi S, Hertzberg M, Hildebrandt GC, Hossain N, Inamoto Y, Isola L, Jain T, Kamble RT, Khan MW, Kharfan-Dabaja MA, Kebriaei P, Kekre N, Khera N, Lazarus HM, Liesveld JL, Litzow M, Liu H, Marks DI, Martino R, Mathews V, Mishra A, Murthy HS, Nagler A, Nakamura R, Nathan S, Nishihori T, Olin R, Olsson RF, Palmisiano N, Patel SS, Patnaik MM, Pawarode A, Perales M-A, Politikos I, Popat U, Rizzieri D, Sandmaier BM, Savani BN, Seo S, Shah NN, Uy GL, Valcárcel D, Verdonck LF, Waller EK, Wang Y, Weisdorf D, Wirk B, Wong E, Yared JA, Saber W. Reduced intensity conditioning for acute myeloid leukemia using melphalan- vs busulfan-based regimens: A CIBMTR report. Blood Advances. 2020 Jul 14; 4(13):3180-3190. doi:10.1182/bloodadvances.2019001266. Epub 2020 Jul 14. PMC7362362.

c. **LK17-01** Outcomes of acute myeloid leukemia patients who undergo allogeneic transplant stratified by depth of clinical response. *Submitted.*

d. **LK17-02** Allogeneic hematopoietic transplant outcomes in adult patients with MLL-rearranged acute myeloid leukemia. *Submitted.*

e. **LK15-03** Comparison of outcomes of older adolescents and young adults with philadelphia/BCR-ABL1-negative acute lymphoblastic leukemia receiving post-remission consolidation chemotherapy with pediatric-inspired chemotherapy on CALGB 10403 or myeloablative allogeneic hematopoietic cell transplantation. *Submitted.*

f. **LK18-01** Prognostic impact of the new european leukemia net genetic risk stratification categories in predicting outcomes for adults with acute myeloid leukemia undergoing allogeneic hematopoietic stem cell transplantation. *Poster presentation at the ASH 2020 Annual Meeting.*

g. **LK18-02** Comparison of outcomes of transplants with matched-related donor or matched-unrelated donor allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia. *Oral presentation at the ASH 2020 Annual Meeting.*

h. **LK20-04** Impact of older age in allogeneic transplants for acute myeloid myelogenous leukemia in first complete remission. *Poster presentation at the ASH 2020 Annual Meeting.*

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR ACUTE LEUKEMIA
Orlando, FL
Thursday, February 20th, 2020, 12:15 - 2:15 PM

Co-Chair:	**Partow Kebriaei, MD; M.D. Anderson Cancer Center, Houston, TX; Telephone: 713- 792-8750; E-mail: pkebriae@mdanderson.org**
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1. Introduction

Dr. Mark Litzow called the meeting to order at 12:15 PM, introduced the members of the LKWC leadership, and mentioned that Dr. Brenda Sandmaier was unable to attend the meeting. Dr. Litzow introduced the incoming Co-Chair, Dr. Christopher Hourigan, who will be replacing Dr. Sandmaier in the upcoming year. The attendees were reminded to have their badges scanned to be included in the working committee email list and to fill out the voting sheets and evaluations. Dr. Litzow explained the voting criteria and scoring, prioritization of accepted studies, rules for authorship on CIBMTR studies, and the advisory committee metrics. The differences between TED and CRF sources of data were briefly reviewed.

2. Accrual summary

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

3. Presentations, published or submitted papers

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

a. **LK15-02** Yeshurun, M., Weisdorf, D., Rowe, J. M., Tallman, M. S., Zhang, M. J., Wang, H. L., …, Bachanova, V. (2019). The impact of the graft-versus-leukemia effect on survival in acute lymphoblastic leukemia. *Blood Advances*, 3(4), 670-680.

b. **LK15-01** Ustun, C., Le-Rademacher, J., Wang, H. L., Othus, M., Sun, Z., Major, B., … Artz, A. S. (2019). Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older

acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): An alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. *Leukemia,* 33(11), 2599-2609.

c. **LK16-04** Rashidi, A., Hamadani, M., Zhang, M. J., Wang, H. L., Abdel-Azim, H., Aljurf, M., … Saber, W. (2019) Outcomes of haploidentical vs matched sibling transplantation for acute myeloid leukemia in first complete remission. *Blood Advances*, 3(12), 1826-1836.

d. **LK13-02** Lazaryan, A., Dolan, M., Zhang, M. J., Wang, H. L., Kharfan-Dabaja, M. A., Marks, D. I., … Weisdorf, D. (2019). Impact of cytogenetic abnormalities on outcomes of adult Philadelphia-negative acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation: A study by the Acute Leukemia Working Committee of the Center for International Blood and Marrow Transplant Research. *Haematologica*. Advance online publication.

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

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

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

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

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

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

4. Studies in progress

Dr. Litzow gave an overview of the status of currently active studies.

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

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

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

d. **LK19-01** Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm (H Murthy/M Kharfan-Dabaja) **Protocol development**

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

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

5. Future/proposed studies

Drs. Litzow and Partow Kebriaei led this session. Presenters were reminded to limit their presentations to 5 minutes to ensure time for discussion (5 minutes).

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

Dr. Stefan Ciurea presented the proposal. The main objective of the proposed study is to compare the progression-free survival of elderly patients with AML and MDS receiving allo-HCT using FM100 with other RIC and NMA conditioning regimens. A total of 3,649 patients aged 60 and older underwent first allo-HCT for AML/MDS in 2008-2018, with 89 receiving FM100 and 3560 receiving another type of RIC/NMA regimen.

Comments were received about potential confounding due to the effect of GVHD prophylaxis on toxicity of Flu/Mel and disease status on conditioning intensity choice. Suggestions were made to limit the patient population to MDS due to the small number of AML patients, to not include FM140 in the comparison to other RIC regimens, and to look at center effect for those receiving FM100 regimen.

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

Dr. Fevzi Yalniz presented the proposal. The primary objective of the proposed study is to assess the outcomes of adult patients who underwent a second allo-HCT for relapsed AML/MDS/ALL and to identify risk factors associated with survival. The secondary aim is to establish the impact of using haploidentical donors for second allo-HCT. There are 790 patients who received a second allo-HCT for relapsed AML, ALL, or MDS in 2000-2018.

The attendees made several suggestions including separating the AML/MDS and ALL populations, checking which patients had the same donor for the first and second transplants, and extending the population to include those transplanted after 2018. Concerns were raised about the feasibility of the second aim since very few patients received a second transplant from a haploidentical donor.

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

Dr. Madiha Iqbal presented the proposal. The study objectives are to describe clinical outcomes of patients with T-cell ALL undergoing allo-HCT and to evaluate the impact of patient, disease, and transplant related factors on these outcomes. There are 1144 patients who received first allo-HCT for T-cell ALL in 2000-2017.

Questions were asked about availability of the following data: MRD status, cytogenetics, nelarabine use, extramedullary involvement, and ATG use. An attendee suggested including T-cell lymphoblastic lymphoma patients in the study.

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

Dr. Jean Yared presented the proposal. The proposed study aims to identify patient, disease, and transplant related variables that can be predictors of outcomes in AML patients with chromosome

17 (ch17) abnormalities. There are 632 patients with ch17 abnormalities who received a first allo-HCT for AML in 2007-2018.
Questions were asked about the availability of post-HCT maintenance therapy data (particularly about venetoclax and IDH inhibitors), if it is possible to identify mono/bi-allelic TP53 mutations, if samples are available for TP53 typing, MRD data availability, and post-transplant maintenance therapy. Due to small number of patients with reliable TP53 typing, one attendee suggested comparing complex and/or monosomal karyotypes with and without 17p deletion.

e. **PROP 1911-73/1911-205** Comparison of outcomes of myeloablative versus reduced-intensity conditioning for allogeneic hematopoietic cell transplant in adults with B-cell acute lymphoblastic leukemia (M Schwartz/M Wieduwilt/M Mei/R Nakamura/I Aldoss)
Dr. Marc Schwartz presented the proposal. The proposed study aims to compare outcomes between ALL patients who received MAC and those who received RIC; within the RIC population, outcomes of patients receiving Flu/Mel vs FluBu2 will be compared. A total of 2526 adult patients undergoing first allo-HCT for ALL in 2000-2017 received either MAC (2276) or RIC (250) prior to transplant; out of the 250 RIC patients, 68 received FluBu2 and 117 received Flu/Mel.
Comments were made about taking age into account since the median age of patients in MAC and RIC groups differ greatly. Another commenter suggested accounting for year of transplant because therapy regimens have changed over the past decade.

f. **PROP 1911-078** Busulfan based conditioning in ALLO-HCT for acute myeloid leukemia or myelodysplastic syndromes from HLA matched related and unrelated donors (M Sobh/C Bredeson)
Dr. Christopher Bredeson presented the proposal. The primary objective of the study is to compare post-transplant outcomes of AML and MDS patients receiving different busulfan-based conditioning regimens, specifically in the dose ranges of 6.4 mg/kg, 9.6 mg/kg, and 12.8 mg/kg. A total of 873 patients undergoing first allo-HCT for AML or MDS in 2008-2017 received busulfan-based conditioning with doses in the described categories; specifically, 458 received 6.4 mg/kg, 49 received 9.6 mg/kg, and 366 received 12.8 mg/kg.
Questions were asked about the number of centers using the 9.6 mg/kg dose and about clarifying if the goal of the study is to determine if a higher busulfan dose can be used in older patients or if a lower dose can be used in younger patients. An attendee commented that a similar study was proposed in the EBMT working group. One suggestion was to include population based pharmacokinetic modeling for inference of busulfan exposure.

g. **PROP 1911-162/1911-194/1911-242** Outcomes of second allogeneic hematopoietic cell transplant vs donor lymphocyte infusion in patients with relapsed acute lymphoblastic leukemia relapse after the first allogeneic hematopoietic cell transplant (B Dholaria/A Jimenez/B Wirk/B Savani/K Komanduri/T Wang/M de Lima)
Dr. Bhagirathbhai Dholaria presented the proposal. The primary objective of the proposed study is to compare progression-free and overall survival of patients who received DLI vs. second allo-HCT for relapsed ALL. Out of 275 adult patients undergoing first allo-HCT for ALL in 2000-2018 and relapsed, 155 received a second allo-HCT and 120 received DLI.
Questions were asked about the number of patients receiving CAR T-cell therapy, availability of data on Ph status, how to address patients who received both treatments, and how to account for possible selection bias due differing disease status between patients receiving second allo-HCT and DLI. A suggestion was made to include relapsed patients who did not receive second allo-HCT or DLI for comparison.

h. **PROP 1911-190** Outcomes of allogeneic hematopoietic cell transplantation (HCT) among germline RUNX1 mutation carriers with acute myeloid leukemia (AML) (P Liu/W Saber/L Cunningham)

Dr. Wael Saber presented the proposal. The objective of the proposed study is to identify patient, disease, and transplant related factors that affect post-transplant outcomes in AML patients with germline RUNX1 mutations. There are 180 patients who received first allo-HCT for AML with a RUNX1 mutation in 2013-2019 and have samples available for typing in the CIBMTR biorepository.

Questions were asked about the availability of donor samples. Suggestions from the audience consisted of expanding the study to examine other germline mutations, including MDS patients, and including late effects as outcomes.

Proposed studies; not accepted for consideration at this time

Dr. Litzow mentioned that the committee received many proposals and briefly discussed common reasons for declining proposals such as feasibility issues, overlap with ongoing studies, and potential scientific impact.

a. **PROP 1906-01** Outcomes of allogeneic hematopoietic stem cell transplantation in Philadelphia chromosome positive acute myeloid leukemia
b. **PROP 1910-04** Compare outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) in patients with acute lymphoblastic leukemia (ALL) with or without central nervous system disease involvement
c. **PROP 1910-05** Evaluating outcomes of allogeneic hematopoietic cell transplantation in acute myeloid leukemia with central nervous system involvement
d. **PROP 1910-06** Outcomes and predictors of outcomes of adult patients with therapy-related acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation
e. **PROP 1910-08** Impact of donor lymphocyte infusion (DLI) on mixed chimerism and minimal residual disease (MRD) and association with the CD3+ cell dose
f. **PROP 1910-11** Impact of the intensity of the conditioning regimen in adults between 55-65 years diagnosed with high-risk acute myeloid leukemia
g. **PROP 1910-14** Clinical implication of morphologic complete remission following targeted therapy in AML patients undergoing allogeneic hematopoietic stem cell transplantation.
h. **PROP 1910-17** Hematopoietic stem cell transplantation (HCT) for patients with active acute leukemia
i. **PROP 1911-09** Comparison of Flu/2GY TBI vs. Flu/4GY TBI reduced-intensity conditioning regimen in Leukemia/MDS patients undergoing allogeneic HCT
j. **PROP 1911-48** Comparison of post-transplant outcomes for patients with acute myeloid leukemia treated with higher intensity chemotherapy versus lower intensity targeted therapy
k. **PROP 1911-64** Influence of molecular and cytogenetic risk factors in myeloid sarcoma
l. **PROP 1911-82** Transplant outcomes of myeloid/lymphoid neoplasms with 8p11 syndrome (8p11 chromosomal translocation; FGFR1 molecular rearrangement)
m. **PROP 1911-91** The impact of allogeneic stem cell transplantation on acute myeloid leukemia and myelodysplastic syndrome with chromosome 3 abnormalities
n. **PROP 1911-111** Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia: survival and outcomes in the modern era
o. **PROP 1911-112** Prophylactic CNS therapy after allogenic hematopoietic stem cell transplantation in adult acute lymphoblastic leukemia: A CIBMTR study
p. **PROP 1911-127** Impact of second cell therapy on the outcomes of patients with acute myeloid leukemia or myelodysplastic syndrome relapsed after a first allogeneic hematopoietic cell transplantation
q. **PROP 1911-131** Outcomes of patients with myeloid sarcoma and isolated CNS leukemia post-allogeneic stem cell transplant: a potential trans-Atlantic collaboration with EBMT

r. **PROP 1911-146** Outcomes of allogeneic hematopoietic cell transplantation for early T-precursor acute lymphoblastic leukemia
s. **PROP 1911-161** A new prognostic model for post-transplant AML outcomes
t. **PROP 1911-164** Impact of baseline absolute lymphocyte count on outcomes in patients with acute leukemia who underwent allo-HCT with anti-thymocyte globulin
u. **PROP 1911-179** Clinical outcomes in AML patients carrying isocitrate dehydrogenase (IDH1-2) mutations undergoing allogeneic hematopoietic stem cell transplantation
v. **PROP 1911-184** Allogeneic hematopoietic cell transplant outcomes in adult patients with Philadelphia chromosome like acute lymphoblastic leukemia
w. **PROP 1911-217** Comparison of reduced intensity conditioning regimens for allogeneic hematopoietic stem cell transplant with post-transplant cyclophosphamide
x. **PROP 1911-232** Impact of asparaginase containing versus non-asparaginase containing induction regimen on allogeneic transplantation outcomes for acute lymphoblastic leukemia
y. **PROP 1911-243** Comparison of graft failure rate between acute lymphoblastic leukemia vs myeloid neoplasm patients who undergo busulfan-based myeloablative haploidentical stem cell transplant
z. **PROP 1911-246** Exploring the impact of upfront induction therapy intensity in high risk myelodysplastic syndromes and acute myeloid leukemia on post-allogeneic stem cell transplant outcomes in older patients
aa. **PROP 1911-247** Incidence of therapy-related myelodysplastic syndrome and acute myeloid leukemia in the recipients of prior autologous hematopoietic cell transplantation (HCT) and their outcomes after allogeneic HCT
ab. **PROP 1911-263** Impact of systemic immunosuppressive therapy on recurrent malignancy following allogeneic hematopoietic cell transplantation in acute myeloid leukemia
ac. **PROP 1911-271** Mixed chimerism in post hematopoietic stem cell transplant high risk hematologic malignancies: incidence, management and outcomes
ad. **PROP 1912-05** The impact of HLA-B35 expression on the incidence and outcomes of acute myeloid leukemia with IDH2-R140Q mutation

6. Other business

- Dr. Kebriaei presented an updated definition of primary induction failure (PIF) based on recent publications and answered questions from the audience. The working definition of PIF is: No complete remission (CR) after 2 cycles of conventional combination chemotherapy or no CR after 4 cycles of hypomethylating based therapy.
- Advisory committee member Dr. Bart Scott attended the pre- and post-meetings, as well as the working committee meeting.
- It was suggested to clearly indicate the data source (TED or CRF) in the proposal demographic tables provided to presenters.
- 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 of relevant cases, and the impact of the study on the field, the following studies will move forward in the committee's research portfolio for the upcoming year:
  - **PROP 1910-20** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (H Murthy/M Iqbal/M Kharfan-Dabaja)
  - **PROP 1911-18/1911-83/1911-191/1911-224** Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (A Dias/J Yared/A Gomez-Arteaga/R Shallis/M Byrne/B McClune/A Rapoport/A Jakubowski/L Gowda/B Skikne/N Hardy/S Dahiya/T Lin/S Giralt/M Litzow)

- **PROP 1911-190** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia (P Liu/W Saber/L Cunningham)

- An additional proposal, **PROP 1912-04:** Impact of older age in allogeneic HCT for AML in CR1, was accepted based on the timeliness of the topic and the minimal amount of statistical hours required for completion.

Working Committee Overview Plan for 2020 – 2021

a. **LK17-03** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia
Analysis is underway. The goal is to complete the analysis and start manuscript preparation by July 2020 and have the manuscript submitted by July 2021. 130 statistical hours have been allocated to accomplish these goals.

b. **LK18-01** Prognostic impact of ELN risk group in alloHCT for adult AML in CR1/CR2
Data file preparation is underway. The goal is to complete the data file and analysis and begin manuscript preparation by July 2020. We expect to have the manuscript submitted by July 2021. 170 statistical hours have been allocated to accomplish these goals.

c. **LK18-02** Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia
Data file preparation is underway. The goal is to complete the data file and analysis and begin manuscript preparation by July 2020. We expect to have the manuscript submitted by July 2021. 150 statistical hours have been allocated to accomplish these goals.

d. **LK19-01** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020. We expect to finish the analysis and start manuscript preparation by July 2021. 260 statistical hours have been allocated to accomplish these goals.

e. **LK19-02** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020. We expect to finish the analysis and start manuscript preparation by July 2021. 260 statistical hours have been allocated to accomplish these goals.

f. **LK19-03** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy
Protocol development is underway. The goal is to finalize the protocol and start data file preparation by July 2020. We expect to finish the analysis and start manuscript preparation by July 2021. 210 statistical hours have been allocated to accomplish these goals.

g. **LK20-01** Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation (Ajoy Dias, Jean Yared, Alexandra Gomez-Artega et al.) The plan is to begin protocol development in July 2020 and finalize the protocol and begin data file preparation by July 2021. 120 statistical hours have been allocated to accomplish these goals.

h. **LK20-02** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia (Paul Liu, Wael Saber, Lea Cunningham)
The plan is to begin protocol development in July 2020 and finalize the population and begin sample typing by July 2021. 10 statistical hours have been allocated to accomplish these goals.

i. **LK20-03** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia (Hemant Murthy, Madiha Iqbal, Mohamed Kharfan-Dabaja)
The plan is to begin protocol development in July 2020, finalize the protocol, and begin data file preparation by July 2021. 100 statistical hours have been allocated to accomplish these goals.

j. **LK20-04** Impact of older age in allogeneic HCT for AML in CR1 (Joseph Maakaron, Daniel Weisdorf)
The goal is to begin manuscript preparation by July 2020 and have the manuscript submitted by July 2021. 70 statistical hours have been allocated to accomplish these goals.

Oversight Assignments for Working Committee Leadership (March 2020)

Partow Kebriaei	**LK18-02:** Comparison of outcomes of haploidentical hematopoietic cell transplantation (HCT) with matched-related donor or matched-unrelated donor allogeneic HCT for adults with Ph-negative acute lymphoblastic leukemia **LK19-02:** Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era **LK20-02:** Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia
Christopher Hourigan	**LK19-03:** Outcomes of alloHCT in AML patients who achieved complete remission after two or more cycles of induction chemotherapy **LK20-03:** Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia **LK20-04:** Impact of older age in allogeneic HCT for AML in CR1
Mark Litzow	**LK17-03:** Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia **LK18-01:** Prognostic Impact of the new European LeukemiaNet (ELN) Genetic Risk Stratification Categories in Predicting Outcomes for Adults with Acute Myeloid Leukemia undergoing Allogeneic Hematopoietic Stem Cell Transplantation **LK19-01:** Evaluating outcomes of Hematopoietic Cell Transplantation in Blastic Plasmacytoid Dendritic Cell Neoplasm **LK20-01:** Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation

Appendix: Overview Plan

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total Hours allocated
LK17-03: Impact of post-transplant maintenance therapy with BCR-ABL tyrosine kinase inhibitors on outcomes of Philadelphia chromosome-positive acute lymphoblastic leukemia	Analysis	Submitted - July 2021	130	130	60	70	130
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	Data File Preparation	Submitted - July 2021	170	170	100	70	170
LK18-02: Comparison of outcomes of HCT with matched-related donor or matched-unrelated donor alloHCT for adults with acute lymphoblastic leukemia	Data File Preparation	Submitted - July 2021	150	150	80	70	150
LK19-01: Evaluating outcomes of hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm	Protocol Development	Manuscript Preparation - July 2021	330	260	100	160	260

LK19-02: Evolving significance of Ph-chromosome status on ALL prognosis in the TKI era	Protocol Development	Manuscript Preparation - July 2021	330	260	100	160	260
LK19-03: Outcomes of alloHCT in AML patients who achieved first complete remission after two or more cycles of induction chemotherapy	Protocol Development	Manuscript Preparation - July 2021	280	210	50	160	210
LK20-01: Acute myeloid leukemia with chromosome 17 abnormalities with or without TP53 abnormalities and outcomes after hematopoietic stem cell transplantation	Protocol Pending	Data File Preparation – July 2021	350	120	0	120	120
LK20-02: Outcomes of allogeneic hematopoietic cell transplantation among germline RUNX1 mutation carriers with acute myeloid leukemia	Protocol Pending	Sample Typing – July 2021	340	10	0	10	10
LK20-03: Evaluating outcomes of allogeneic hematopoietic cell transplantation in T-cell acute lymphoblastic leukemia	Protocol Pending	Data File Preparation – July 2021	330	100	0	100	100
LK20-04: Impact of older age in allogeneic HCT for AML in CR1	Protocol Pending	Submitted – July 2021	130	70	0	70	70

Combined Proposal: 2009-13; 2010-08; 2010-10

Title:
Impact of *IDH1* and *IDH2* Mutations on Outcomes of Acute Myeloid Leukemia Patients undergoing Allogeneic Hematopoietic Cell Transplantation

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Research hypothesis:
Acute myeloid leukemia (AML) patients with normal karyotype and mutated *IDH1* or *IDH2* (mut*IDH1/2*) may have a higher risk of post-transplantation relapse, lower rate of disease-free survival (DFS), and lower rate of overall survival (OS) compared to patients with normal karyotype, wild-type *IDH1* and *IDH2* (wt*IDH1/2*) disease.

Specific aims:
- Aim 1. To identify differences in the following post-transplant outcomes between mut*IDH1, mutIDH2* and wt*IDH1/2* patients:
  - Disease free survival (DFS)
  - Overall survival (OS)
  - Cumulative incidence of relapse
- Aim 2. To describe the following prognostic factors associated with worse post-transplant outcomes in patients with mut*IDH1/2* AML
  - CR1 vs. >CR2
  - Pre-transplant measurable residual disease (MRD, positive vs. negative)
  - Conditioning intensity (reduced intensity/non-myeloablative vs. myeloablative)
  - Mutation isoform (IDH1 vs. IDH2)
  - Concurrent mutations (*FLT3*-ITD, *NPM1*, *DNMT3A*) or cytogenetic abnormalities

Scientific justification:
Mutations within genes for the isocitrate dehydrogenase enzymes, *IDH1* and *IDH2* (mut*IDH1/2*) are reported in ~20% of patients with acute myeloid leukemia (6–16% for IDH1 and 8–19% for IDH2

mutations).[1] *IDH1/2* mutations result in impairment of normal hematopoietic differentiation and promote leukemogenesis through competitive inhibition of αKG-dependent enzymatic activities.[2,3] mut*IDH1/2* AML has distinctive clinicopathologic features. These mutations are frequently reported in elderly patients and those with intermediate-risk cytogenetics.[4] They are typically associated with high blast burden at diagnosis, higher platelet count, and co-occurrence of *FLT3*-ITD and *NPM1* mutations.[5-7] The prognostic impact of mut*IDH1/2* in AML remains controversial.[8] Several studies suggest an association with inferior outcomes,[9-11] whereas others did not identify any clear impact on response rates or survival;[12-14] still others report improved survival, particularly for patients with concurrent *NPM1*-mutated disease.[15-16] Assuming no adverse co-occurring genomic abnormalities or high-risk clinical features are present, *IDH1/2* mutation carriers are typically classified as intermediate-risk.[17] Allogeneic transplant consolidation is offered if a suitable donor is identified, the patient has an adequate performance status/HCT-CI, and acceptable disease control is achieved.

Clinical trials investigating the role of IDH inhibitors as maintenance therapy are underway (e.g. NCT03564821, NCT03515512). However, clinical outcomes of mut*IDH1/2* AML patients who undergo allogeneic HCT compared to wt*IDH1/2* AML patients has not been well described, and are important for informing the design and interpretation of maintenance therapy trials. To date, there has been only one published study on post-HCT outcomes for *IDH1/2*-mutated AML involving 23 *IDH* mutated patients.[18] The study reported 1-year OS and relapse rates of 68% and 29%, respectively, and a statistically significant association between *IDH1/2* mutation and increased 1-year relapse (HR 2.78, 95% CI 1.02-7.60) when compared to a historical control group of wt*IDH* AML patients.

We propose to evaluate the prognostic impact of *IDH1/2* mutations on the outcomes of normal karyotype AML patients who receive hematopoietic stem cell transplantation. To our knowledge, no large multicenter studies have addressed this important question.

Patient eligibility population:

Inclusion criteria

- Patients with a diagnosis of normal karyotype AML transplanted in CR1
- Ages 18 and older
- First allogeneic transplantation
- Transplantation dates: 2013 to 2019
- Available cytogenetic and molecular mutational status prior to transplant.

Study outcomes:

- Relapse: Cumulative incidence of disease relapse, with NRM as competing event.
- Disease-free survival (DFS): Time to relapse or death from any cause. Patients are censored at last follow-up.
- Overall survival (OS): Time to death. Death from any cause will be considered an event. Surviving patients are censored at time of last follow-up.
- Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse. Relapse is competing event.
- Incidence of acute and chronic GVHD: cumulative incidence of acute and chronic GVHD, with death as competing risk. Patients are censored at subsequent HCT or last follow-up.

Variables to be described:

Study main effect:

- IDH 1/2 mutational status: yes/no

Patient-related (CIBMTR form 2040):

- Age at transplant: 18-39 vs. 40-59 vs. 60+
- Patient sex: male vs. female
- Race: White vs. Others
- Karnofsky performance status at transplant: ≥ 90 vs. < 90
- HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3

Disease-related (CIBMTR forms 2010-2402):

- Clinical onset of AML: De novo vs. Transformed from MDS or MPN vs. Therapy-related
- Measurable residual disease (MRD) status: Positive vs. Negative
- Genetic risk category*: Favorable vs. intermediate vs. adverse
- CR status: CR1 vs. >CR2
- IDH mutation: IDH1 vs. IDH2
- FLT3-ITD status: Mutated/wild-type
- NPM1 status: Mutated/wild-type
- DNMT3A status: Mutated/wild-type
- Type of pre-HCT induction therapy: 7+3-based vs. high dose cytarabine (HIDAC) vs. HMA vs. other

*Per ELN2017 criteria

Transplant-related (CIBMTR forms 2005, 2006, 2400):

- Graft source: bone marrow vs. peripheral blood vs. cord blood
- Conditioning intensity: myeloablative (MAC) vs. reduced intensity (RIC)/non-myeloablative (NMA)
- Donor type: HLA-identical sibling vs. haploidentical vs. matched-unrelated vs. mismatched unrelated vs. cord blood
- Donor-recipient HLA match
- GVHD prophylaxis: Tacrolimus-based vs. CsA-based vs. other
- In vivo T-cell depletion: ATG/Alemtuzumab vs none
- IDH inhibitor maintenance post-transplant (i.e: ivosidenib, enasidenib, indirect inhibitors, investigational agents, or other): Yes/No

Study design:

This is a retrospective cohort analysis to evaluate the impact of IDH mutational status on transplantation outcomes. Patient data will be abstracted based on available molecular information.

Continuous variables will be described as median and ranges and categorical variables will be reported as absolute numbers and percentage. The primary endpoint is DFS. The secondary endpoints are OS, NRM, and relapse. All outcomes will be measured from time of transplant.

Univariate analysis will be performed using Kaplan-Meier Method and will be compared using log-rank test for OS and LFS, while NRM, and relapse will be calculated using the cumulative incidence method considering competing risks, with comparisons performed using Gray's method.

Multivariate analysis will also be performed using Cox proportional hazard model for OS, DFS, NRM and relapse. The assumption of proportional hazards for each factor in the Cox model will be tested by adding time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), models will be constructed breaking the post-transplant time course into two periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions will be further tested. A backward stepwise model selection approach will be used to identify all significant risk factors. Factors which are significant at a 5% level will be kept in the final model. Potential interaction between main effect and significant co-variates will be tested.
Adjusted probabilities of DFS and OS, and adjusted cumulative incidence functions of NRM and relapse will be calculated using the multivariate models, stratified on main effect and weighted by the pooled sample proportion value for each prognostic factor. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors.

Conflicts of interest:
None

References:
1. Im AP, Sehgal AR, Carroll MP, et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: Associations with prognosis and potential treatment strategies. Leukemia. 2014;28:1774–1783.
2. Wise DR, Ward PS, Shay JE, et al. Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of alpha-ketoglutarate to citrate to support cell growth and viability. Proc Natl Acad Sci USA. 2011;108:19611–19616.
3. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012;483:474–478.
4. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am J Hematol*. 2015;90:732–736.
5. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol. 2010;28:3636–3643
6. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: A Cancer and Leukemia Group B study. J Clin Oncol. 2010;28:2348–2355. Epub 2010/04/07.
7. Zhou KG, Jiang LJ, Shang Z, et al. Potential application of IDH1 and IDH2 mutations as prognostic indicators in non-promyelocytic acute myeloid leukemia: A meta-analysis. Leuk Lymphoma. 2012;53:2423–2429.
8. DiNardo CD, Propert KJ, Loren AW, et al. Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. Blood. 2013;121:4917–4924.
9. Aref S, Kamel Areida el S, Abdel Aaal MF, Adam OM, El-Ghonemy MS, El-Baiomy MA et al. Prevalence and clinical effect of IDH1 and IDH2 mutations among cytogenetically normal acute myeloid leukemia patients. Clin Lymphoma Myeloma Leuk 2015; 15: 550–555.
10. Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Kronke J, Bullinger L et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol 2010; 28: 3636–3643.

11. Feng JH, Guo XP, Chen YY, Wang ZJ, Cheng YP, Tang YM. Prognostic significance of IDH1 mutations in acute myeloid leukemia: a meta-analysis. Am J Blood Res 2012; 2: 254–264.
12. DiNardo CD, Ravandi F, Agresta S, Konopleva M, Takahashi K, Kadia T et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol 2015; 90: 732–736.
13. Chotirat S, Thongnoppakhun W, Promsuwicha O, et al. Molecular alterations of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) metabolic genes and additional genetic mutations in newly diagnosed acute myeloid leukemia patients. J Hematol Oncol 2012; 5: 5.
14. Abbas S, Lugthart S, Kavelaars FG, Schelen A, Koenders JE, Zeilemaker A et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood 2010; 116: 2122–2126.
15. Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366:1079–1089.
16. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016; 374: 2209–2221. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016; 374: 2209–2221. Green CL, Evans CM, Zhao L, et al. The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. Blood. 2011;118:409–412.
17. Estey EH. Acute myeloid leukemia: 2019 update on risk stratification and management. Am J Hematol. 2018;93(10):1267–91.
18. Salhotra A, Afkhami M, Yang D, et al. Allogeneic Hematopoietic Cell Transplantation Outcomes in Patients Carrying Isocitrate Dehydrogenase Mutations. Clin Lymphoma Myeloma Leuk. 2019;19(7):e400-e405.

Table 1. Characteristics of adult patients receiving first allo-HCT for AML with normal karyotype and transplanted in CR1 in 2013-2019, CRF track

Characteristic	mut IDH1	mut IDH2	mut IDH1 & IDH2	WT IDH1 & IDH2
No. of patients	82	146	19	2312
No. of centers	43	59	16	154
Age at HCT				
Median (min-max)	62 (24-78)	61 (19-76)	61 (26-70)	57 (18-81)
18-29	3 (4)	6 (4)	2 (11)	222 (10)
30-39	5 (6)	6 (4)	0 (0)	238 (10)
40-49	8 (10)	13 (9)	2 (11)	333 (14)
50-59	18 (22)	45 (31)	5 (26)	587 (25)
60-69	36 (44)	52 (36)	10 (53)	757 (33)
>=70	12 (15)	24 (16)	0 (0)	175 (8)
Recipient sex				
Male	43 (52)	73 (50)	10 (53)	1228 (53)
Female	39 (48)	73 (50)	9 (47)	1084 (47)
Karnofsky score				
<90	39 (48)	65 (45)	12 (63)	919 (40)
>=90	42 (51)	80 (55)	7 (37)	1362 (59)
Missing	1 (1)	1 (1)	0 (0)	31 (1)
HCT-CI				
0	16 (20)	28 (19)	1 (5)	413 (18)
1	14 (17)	20 (14)	2 (11)	352 (15)
2	13 (16)	27 (18)	1 (5)	371 (16)
3+	38 (46)	71 (49)	15 (79)	1114 (48)
TBD	1 (1)	0 (0)	0 (0)	50 (2)
Missing	0 (0)	0 (0)	0 (0)	12 (1)
MRD at time of HCT				
Negative	33 (40)	59 (40)	7 (37)	1581 (68)
Positive	45 (55)	81 (55)	12 (63)	609 (26)
Missing	4 (5)	6 (4)	0 (0)	122 (5)
Donor type				
HLA-identical sibling	10 (12)	30 (21)	2 (11)	492 (21)
Other related	28 (34)	43 (29)	8 (42)	490 (21)
Well-matched unrelated (8/8)	21 (26)	45 (31)	7 (37)	812 (35)
Partially-matched unrelated (7/8)	3 (4)	6 (4)	2 (11)	131 (6)
Mis-matched unrelated (<= 6/8)	1 (1)	1 (1)	0 (0)	14 (1)
Multi-donor	0 (0)	0 (0)	0 (0)	7 (0)
Unrelated (matching TBD)	4 (5)	2 (1)	0 (0)	41 (2)

Characteristic	mut IDH1	mut IDH2	mut IDH1 & IDH2	WT IDH1 & IDH2
Cord blood	15 (18)	19 (13)	0 (0)	325 (14)
Graft type				
Bone marrow	16 (20)	25 (17)	4 (21)	391 (17)
Peripheral blood	51 (62)	102 (70)	15 (79)	1596 (69)
Cord blood	15 (18)	19 (13)	0 (0)	325 (14)
Conditioning regimen intensity				
MAC	37 (45)	58 (40)	6 (32)	1066 (46)
RIC	23 (28)	50 (34)	6 (32)	775 (34)
NMA	18 (22)	33 (23)	5 (26)	386 (17)
TBD	2 (2)	0 (0)	0 (0)	37 (2)
Missing	2 (2)	5 (3)	2 (11)	48 (2)
GVHD prophylaxis				
Ex-vivo T-cell depletion	0 (0)	1 (1)	0 (0)	18 (1)
CD34 selection	5 (6)	3 (2)	0 (0)	103 (4)
Post-CY + other(s)	29 (35)	45 (31)	8 (42)	504 (22)
Post-CY alone	0 (0)	1 (1)	1 (5)	24 (1)
TAC + MMF +- other(s) (except post-CY)	9 (11)	21 (14)	1 (5)	296 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	21 (26)	50 (34)	5 (26)	835 (36)
TAC + other(s) (except MMF, MTX, post-CY)	2 (2)	7 (5)	3 (16)	105 (5)
TAC alone	3 (4)	2 (1)	0 (0)	44 (2)
CSA + MMF +- other(s) (except post-CY)	8 (10)	12 (8)	0 (0)	210 (9)
CSA + MTX +- other(s) (except MMF, post-CY)	2 (2)	1 (1)	0 (0)	114 (5)
CSA + other(s) (except MMF, MTX, post-CY)	0 (0)	0 (0)	0 (0)	5 (0)
CSA alone	0 (0)	0 (0)	0 (0)	7 (0)
Other(s)	2 (2)	0 (0)	0 (0)	21 (1)
Missing	1 (1)	3 (2)	1 (5)	26 (1)
Year of HCT				
2013	2 (2)	4 (3)	1 (5)	342 (15)
2014	6 (7)	5 (3)	2 (11)	431 (19)
2015	6 (7)	17 (12)	0 (0)	432 (19)
2016	16 (20)	27 (18)	3 (16)	350 (15)
2017	10 (12)	27 (18)	6 (32)	284 (12)
2018	18 (22)	35 (24)	5 (26)	264 (11)
2019	24 (29)	31 (21)	2 (11)	209 (9)

Characteristic	mut IDH1	mut IDH2	mut IDH1 & IDH2	WT IDH1 & IDH2
Median follow-up of survivors (range), months	24 (3-73)	24 (3-72)	24 (6-57)	46 (2-81)

Abbreviations: Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine

Table 2a. Cross-tabulation of donor type and GVHD prophylaxis for bone marrow and peripheral blood graft recipients

GVHD prophylaxis	HLA-identical sibling	Other related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<= 6/8)	Multi-donor	Unrelated (matching TBD)
Bone marrow graft							
Ex-vivo T-cell depletion	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
CD34 selection	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Post-CY + other(s)	3 (1)	143 (25)	6 (1)	12 (8)	10 (63)	3 (43)	2 (4)
Post-CY alone	10 (2)	0 (0)	16 (2)	0 (0)	0 (0)	0 (0)	0 (0)
TAC + MMF +- other(s) (except post-CY)	2 (0)	7 (1)	7 (1)	6 (4)	1 (6)	0 (0)	0 (0)
TAC + MTX +- other(s) (except MMF, post-CY)	28 (5)	6 (1)	114 (13)	16 (11)	0 (0)	0 (0)	2 (4)
TAC + other(s) (except MMF, MTX, post-CY)	0 (0)	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
TAC alone	1 (0)	3 (1)	2 (0)	1 (1)	0 (0)	0 (0)	0 (0)
CSA + MMF +- other(s) (except post-CY)	4 (1)	0 (0)	4 (0)	2 (1)	0 (0)	0 (0)	0 (0)
CSA + MTX +- other(s) (except MMF, post-CY)	7 (1)	1 (0)	4 (0)	0 (0)	0 (0)	1 (14)	2 (4)
Missing	1 (0)	1 (0)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Peripheral blood graft							
Ex-vivo T-cell depletion	5 (1)	7 (1)	6 (1)	0 (0)	0 (0)	0 (0)	0 (0)
CD34 selection	18 (3)	8 (1)	28 (3)	0 (0)	0 (0)	1 (14)	1 (2)
Post-CY + other(s)	28 (5)	309 (54)	43 (5)	20 (14)	1 (6)	0 (0)	6 (13)
TAC + MMF +- other(s) (except post-CY)	58 (11)	22 (4)	95 (11)	12 (8)	0 (0)	0 (0)	8 (17)
TAC + MTX +- other(s) (except MMF, post-CY)	248 (46)	38 (7)	392 (44)	47 (33)	0 (0)	2 (29)	17 (36)
TAC + other(s) (except MMF, MTX, post-CY)	20 (4)	4 (1)	67 (8)	10 (7)	0 (0)	0 (0)	0 (0)
TAC alone	8 (1)	3 (1)	16 (2)	4 (3)	0 (0)	0 (0)	2 (4)
CSA + MMF +- other(s) (except post-CY)	20 (4)	3 (1)	37 (4)	4 (3)	2 (13)	0 (0)	2 (4)

GVHD prophylaxis	HLA-identical sibling	Other related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<= 6/8)	Multi-donor	Unrelated (matching TBD)
CSA + MTX +- other(s) (except MMF, post-CY)	62 (12)	9 (2)	25 (3)	2 (1)	1 (6)	0 (0)	3 (6)
CSA + other(s) (except MMF, MTX, post-CY)	1 (0)	0 (0)	4 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CSA alone	4 (1)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (2)
Other(s)	1 (0)	1 (0)	4 (0)	2 (1)	1 (6)	0 (0)	0 (0)
Missing	4 (1)	2 (0)	11 (1)	1 (1)	0 (0)	0 (0)	1 (2)

Table 2b. GVHD prophylaxis given for cord blood recipients

	N (%)
CD34 selection	53 (15)
TAC + MMF +- other(s) (except post-CY)	109 (30)
TAC + MTX +- other(s) (except MMF, post-CY)	1 (0)
TAC + other(s) (except MMF, MTX, post-CY)	14 (4)
TAC alone	9 (3)
CSA + MMF +- other(s) (except post-CY)	152 (42)
Other(s)	14 (4)
Missing	7 (2)

Combined Proposal: 2010-27; 2010-147; 2010-197; 2010-258; 2010-298; 2010-332

Title:
Impact of Measurable Residual Disease Status on Outcomes of Acute Myeloid Leukemia and Patients 18-65 Years Old in First Complete Remission Undergoing Allogeneic Hematopoietic Cell Transplantation

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Research hypothesis:
Measurable residual disease (MRD) test status before allogeneic hematopoietic cell transplantation (allo-HCT) of patients >18 & ≤65 years of age (y) with de novo acute myeloid leukemia (AML) in first complete remission (CR1) will predict the cumulative incidence of 1y relapse (CIR) & 3y overall survival (OS).

Specific aims:
- **Primary:** AML MRD test status before allo-HCT has been shown to be prognostic in retrospective analyses when using consistent methodology (1-3). In the current study, we will try to confirm this observation in real-world practice with the non-standardized testing approaches currently in use. **The prognostic impact of test positivity prior to allo-HCT** will be studied for all methods combined, and for each method individually: flow cytometry, molecular testing (combined and for individual mutations), next generation sequencing, karyotype, and FISH analysis. Patients receiving post-HCT maintenance therapy will be considered separately. We will determine if pre-HCT MRD test status adds additional prognostic information beyond that from ELN risk group at initial diagnosis. Prognosis will be also evaluated for patient subgroups above and below the median age.
- **Secondary:** High-quality randomized data has shown that higher intensity allo-HCT conditioning regimens in patients with AML who test positive for MRD is associated with reduced relapse and

improved survival (4). In a prior registry analysis of 2292 patients with AML from the European Society of Blood and Marrow Transplantation, in multivariate analysis RIC and non-myeloablative regimen were inferior to MAC for patients in the <50y MRD positive group; patients ≥50y, whether MRD positive or MRD negative, derived no additional benefit from being treated with MAC regimens (5). In a single-center non-randomized observation study however this association was unable to be detected (6). For those testing MRD positive or negative, we will therefore **assess the interaction between clinical outcomes and conditioning type and intensity, GVHD prophylaxis (PTCy vs. non-PTCy) and donor type** (MRD, MUD, haplo, cord) for all patients, and for those above and below the median age. These variables will be considered both in isolation, and in combination.

Scientific impact:

The purpose of allo-HCT in patients with AML in complete remission (CR) is to prevent relapse. However, despite CR, AML MRD status before allo-HCT has been shown to be prognostic for CIR and OS (1-3). To date, despite testing for pre-allo-HCT AML MRD status, patients undergo allo-HCT even with persistence of MRD positive disease and conversion to AML MRD negative status is not yet standard of care.

Furthermore, the ideal conditioning regimen prior to HCT is unknown and clinical practice differs by institution according to experience. Myeloablative conditioning (MAC) regimen is superior to reduced intensity conditioning (RIC) regimen in preventing relapse in patients with acute myeloid leukemia (AML) in morphologic CR with evidence of measurable residual disease (MRD) either by flow cytometric or molecular methods. However, transplantation-related mortality is higher with MAC regimen. Given that MAC is not a viable conditioning option for many patients with AML because of age or comorbidity, this study will help to focus efforts on those at highest risk of post-transplantation relapse who will benefit the most from a MAC regimen.

In this study proposal we aim to show that pre-allo-HCT AML MRD negative disease in patients 18-65y with de novo AML in CR1 will have a better 1y CIR and 3y OS compared to patients with MRD positive disease. In addition, we aim to show that RIC conditioning regimen could be sufficient for patients 18-65y with AML in CR1 with MRD negative disease, saving them the MAC transplant related mortality (TRM) while providing them with a similar survival benefit.

Scientific justification:

Pretreatment characteristics, such as age, karyotype, and genomic alterations, are well established factors associated with clinical outcomes of patients with newly diagnosed AML receiving first-line therapy (7, 8). Further refinement of prognosis may be accomplished through evaluation of MRD, which refers to low levels of residual leukemia that cannot be detected by morphologic assessment alone.

Despite the effectiveness of allo-HCT, the major cause of transplant failure remains disease relapse. To use MRD information to guide clinical decision-making in AML and support its use as a meaningful clinical end point, it is necessary to understand the strength of the association of MRD with survival outcomes and the consistency of this association across patient-related, disease-related, and methodologic variables (1-3).

RIC regimens substantially reduce TRM and have permitted allo-HCT to be safely delivered in patients up to the age of 75 years, but they are associated with an increased risk of disease relapse compared with recipients of a MAC regimen. Therefore, one of the most important questions in the management of adults with AML who are deemed to be appropriate candidates for allo-HCT is whether to use a RIC regimen with its attendant reduction in TRM or instead to prioritize the increased anti-leukemic activity of a MAC regimen. Hourigan et al conducted ultra-deep, error-corrected sequencing of 13 commonly

mutated genes in AML on preconditioning blood from patients treated in a phase 3 clinical trial that randomly assigned patients with AML to MAC or RIC regimen (4). The investigators found that MAC rather than RIC in patients with AML with genomic evidence of MRD before allo-HCT can result in improved survival. However, patients with AML without genomic evidence of MRD (MRD negative) had similar survival with either MAC or RIC regimen. These observations have been duplicated in patients with MDS (9). Furthermore, in a registry analysis of 2292 patients with AML from the European Society of Blood and Marrow Transplantation, in multivariate analysis RIC and non-myeloablative regimen were only inferior to MAC for patients in the <50y MRD positive group; patients ≥50y, whether MRD positive or MRD negative, derived no additional benefit from being treated with MAC regimens (5).
Moreover, the administration of high doses of post-transplant cyclophosphamide (PTCy) has proven to be a potent intervention to prevent GVHD and allow for safe HCT even when using HLA haplo donors.(10) Multiple studies have shown that haplo HCT with PTCy results in low rates of GVHD, NRM, and comparable survival compared to outcomes with more traditional HCT platforms. (10-14) A recent CIBMTR analysis suggested that haplo HCT with PTCy in patients with AML may result in lower GVHD and otherwise similar survival to matched sibling donor transplant. (15)
While mounting data supports the use of MAC regimens with haplo HCT with PTCy for AML for fit patients, the optimal regimen to use this in this setting has not been identified. Similarly, for patients unfit for MAC, the optimal RIC regimen in this setting has not been identified. (16, 17)

Patient eligibility population:
Adult patients ≥18 years old and ≤65 years old with AML who underwent allo-HCT and for whom data on the most recent preconditioning allo-HCT bone marrow aspiration or blood flow cytometry. Next generation sequencing, molecular testing (by polymerase chain reaction), karyotypes and FISH were available.

- de novo Acute Myeloid Leukemia on comprehensive reporting tract in CR1
- Age ≥ 18 years old and ≤65 years old
- First allogeneic hematopoietic cell transplant
- Exclude ≥ 2 allogeneic transplants
- Years of transplant 2007 – 2018
- At least one year of follow up data reported to CIBMTR (unless death before 1 year).
- Patient consented to participate in CIBMTR database research study

Data requirements:
Preconditioning MRD status by MFC from either preconditioning bone marrow aspiration or blood.
Preconditioning myeloid mutations status by NGS from either preconditioning bone marrow aspiration or blood.

- Data Collection Forms
  - Pre-Transplant Essential Data
  - Recipient Baseline Data
  - Disease Classification
  - Post-Transplant Essential Data
  - Form 2010 AML Pre-Infusion Data
  - Form 2110 AML Post-Infusion Data
  - Post-HCT Follow Up Data (2100)

  - Recipient Death Data
  - Six Month to Two Year Post HSCT Data (2200)
  - Yearly Follow up for Greater than Two Years Post HSCT Data (2300)
- Supplemental data: None
- Combining CIBMTR data: No
- Variables Needed:
  - Patient demographics: age, race, sex, performance status, comorbidities
  - Disease-related variables: AML classification, transformed from MDS, therapy related, predisposing syndrome, cytogenetics (Karyotype / FISH), molecular markers, MRD by flow, MRD by NGS, CNS involvement
  - Induction chemotherapy (type, number of cycles)
  - Consolidation chemotherapy (type, number of cycles)
  - Immunotherapy received (yes/no)
  - Radiation therapy received (yes/no)
  - Best disease status after transplant
  - Donor type
  - In-vivo T-cell depletion
  - D/R CMV serostatus
  - D/R sex matching
  - Post-transplant therapy
  - Time from diagnosis to transplant
  - Median follow up
  - Acute GvHD (organ involvement, grade, stage)
  - Chronic GvHD (organ involvement, grade, limited, extensive)
  - GvHD treatments
  - Relapse date
  - Death date
  - Cause of death

Sample requirements:
None

Non-CIBMTR data source:
None

Study design:
Retrospective cohort study of all consecutive patients with AML who underwent allo-HCT and for whom data on the most recent preconditioning allo-HCT bone marrow aspiration or blood MRD status is available either by flow cytometry, karyotype, FISH, molecular studies and next generation sequencing were available.

Conflicts of interest:
None

References:

1. Freeman SD, Hills RK, Virgo P, Khan N, Couzens S, Dillon R, et al. Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without NPM1 Mutations. J Clin Oncol. 2018;36(15):1486-97.
2. Short NJ, Zhou S, Fu C, Berry DA, Walter RB, Freeman SD, et al. Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA Oncol. 2020.
3. Buckley SA, Wood BL, Othus M, Hourigan CS, Ustun C, Linden MA, et al. Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis. Haematologica. 2017;102(5):865-73.
4. Hourigan CS, Dillon LW, Gui G, Logan BR, Fei M, Ghannam J, et al. Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease. J Clin Oncol. 2020;38(12):1273-83.
5. Gilleece MH, Labopin M, Yakoub-Agha I, Volin L, Socié G, Ljungman P, et al. Measurable residual disease, conditioning regimen intensity, and age predict outcome of allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first remission: A registry analysis of 2292 patients by the Acute Leukemia Working Party European Society of Blood and Marrow Transplantation. Am J Hematol. 2018;93(9):1142-52.
6. Morsink LM, Sandmaier BM, Othus M, Palmieri R, Granot N, Bezerra ED, et al. Conditioning Intensity, Pre-Transplant Flow Cytometric Measurable Residual Disease, and Outcome in Adults with Acute Myeloid Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation. Cancers (Basel). 2020;12(9).
7. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med. 2016;374(23):2209-21.
8. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116(3):354-65.
9. Dillon LW, Gui G, Logan BR, Fei M, Ghannam J, Li Y, et al. IMPACT OF CONDITIONING INTENSITY AND GENOMICS ON RELAPSE AFTER ALLOGENEIC TRANSPLANTATION FOR PATIENTS WITH MYELODYSPLASTIC SYNDROME. medRxiv. 2020:2020.08.25.20138461.
10. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641-50.
11. Elmariah H, Pratz KW. Role of Alternative Donor Allogeneic Transplants in the Therapy of Acute Myeloid Leukemia. J Natl Compr Canc Netw. 2017;15(7):959-66.
12. McCurdy SR, Kanakry JA, Showel MM, Tsai HL, Bolaños-Meade J, Rosner GL, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. Blood. 2015;125(19):3024-31.
13. McCurdy SR, Kasamon YL, Kanakry CG, Bolaños-Meade J, Tsai HL, Showel MM, et al. Comparable composite endpoints after HLA-matched and HLA-haploidentical transplantation with post-transplantation cyclophosphamide. Haematologica. 2017;102(2):391-400.

14. Ciurea SO, Zhang MJ, Bacigalupo AA, Bashey A, Appelbaum FR, Aljitawi OS, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015;126(8):1033-40.
15. Rashidi A, Hamadani M, Zhang MJ, Wang HL, Abdel-Azim H, Aljurf M, et al. Outcomes of haploidentical vs matched sibling transplantation for acute myeloid leukemia in first complete remission. Blood Adv. 2019;3(12):1826-36.
16. Solomon SR, St Martin A, Shah NN, Fatobene G, Al Malki MM, Ballen KK, et al. Myeloablative vs reduced intensity T-cell-replete haploidentical transplantation for hematologic malignancy. Blood Adv. 2019;3(19):2836-44.
17. Bolaños-Meade J, Reshef R, Fraser R, Fei M, Abhyankar S, Al-Kadhimi Z, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematol. 2019;6(3):e132-e43.

Table 1. Characteristics of adult patients receiving first allo-HCT for de-novo AML in CR1 in 2007-2018, CRF track

Characteristic	MRD pos	MRD neg
No. of patients	753	1968
No. of centers	137	165
Age at HCT		
Median (min-max)	51.9 (18.05-64.96)	49.82 (18.02-64.98)
18-29	93 (12)	276 (14)
30-39	88 (12)	289 (15)
40-49	155 (21)	432 (22)
50-59	261 (35)	652 (33)
60-69	156 (21)	319 (16)
Recipient sex		
Male	406 (54)	993 (50)
Female	347 (46)	975 (50)
Karnofsky score		
<90	261 (35)	617 (31)
≥90	484 (64)	1320 (67)
Missing	8 (1)	31 (2)
HCT-CI		
0	168 (22)	540 (27)
1	143 (19)	308 (16)
2	132 (18)	293 (15)
3+	276 (37)	660 (34)
TBD	18 (2)	78 (4)
Missing	16 (2)	89 (4)
Donor type		
HLA-identical sibling	191 (25)	616 (31)
Other related	107 (14)	233 (12)
Well-matched unrelated (8/8)	261 (35)	682 (35)
Partially-matched unrelated (7/8)	45 (6)	152 (8)
Mis-matched unrelated (≤ 6/8)	11 (1)	7 (0)
Multi-donor	1 (0)	4 (0)
Unrelated (matching TBD)	7 (1)	8 (0)
Cord blood	130 (17)	266 (14)
Graft type		
Bone marrow	145 (19)	326 (17)
Peripheral blood	478 (63)	1376 (70)

Characteristic	MRD pos	MRD neg
Cord blood	130 (17)	266 (14)
Conditioning regimen intensity		
MAC	467 (62)	1323 (67)
RIC	175 (23)	378 (19)
NMA	89 (12)	221 (11)
TBD	10 (1)	29 (1)
Missing	12 (2)	17 (1)
GVHD prophylaxis		
Ex-vivo T-cell depletion	8 (1)	24 (1)
CD34 selection	22 (3)	59 (3)
Post-CY + other(s)	110 (15)	214 (11)
Post-CY alone	10 (1)	12 (1)
TAC + MMF ± other(s) (except post-CY)	95 (13)	287 (15)
TAC + MTX ± other(s) (except MMF, post-CY)	296 (39)	835 (42)
TAC + other(s) (except MMF, MTX, post-CY)	29 (4)	110 (6)
TAC alone	17 (2)	31 (2)
CSA + MMF ± other(s) (except post-CY)	79 (10)	194 (10)
CSA + MTX ± other(s) (except MMF, post-CY)	43 (6)	142 (7)
CSA + other(s) (except MMF, MTX, post-CY)	7 (1)	10 (1)
CSA alone	8 (1)	6 (0)
Other(s)	9 (1)	18 (1)
Missing	20 (3)	26 (1)
Year of HCT		
2007	13 (2)	87 (4)
2008	45 (6)	246 (13)
2009	34 (5)	227 (12)
2010	28 (4)	229 (12)
2011	19 (3)	100 (5)
2012	19 (3)	91 (5)
2013	59 (8)	181 (9)
2014	115 (15)	193 (10)
2015	125 (17)	182 (9)
2016	134 (18)	158 (8)
2017	103 (14)	155 (8)
2018	59 (8)	119 (6)
Median follow-up of survivors (range), months	48.29 (12.01-144.93)	69.01 (12.01-149.74)

Abbreviations: Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine

Table 2a. Cross-tabulation of donor type and GVHD prophylaxis for bone marrow and peripheral blood graft recipients

GVHD prophylaxis	HLA-identical sibling	Other related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<= 6/8)	Multi-donor	Unrelated (matching TBD)
Bone marrow							
Ex-vivo T-cell depletion	1 (0)	0	1 (0)	0	0	0	0
CD34 selection	0	1 (0)	0	0	0	0	0
Post-CY + other(s)	5 (1)	100 (29)	10 (1)	7 (4)	8 (44)	2 (40)	0
Post-CY alone	9 (1)	1 (0)	12 (1)	0	0	0	0
TAC + MMF ± other(s) (except post-CY)	4 (0)	5 (1)	14 (1)	9 (5)	1 (6)	0	0
TAC + MTX ± other(s) (except MMF, post-CY)	31 (4)	4 (1)	144 (15)	21 (11)	0	0	2 (13)
TAC + other(s) (except MMF, MTX, post-CY)	0	1 (0)	4 (0)	2 (1)	0	0	0
TAC alone	2 (0)	2 (1)	2 (0)	0	0	0	0
CSA + MMF ± other(s) (except post-CY)	4 (0)	0	2 (0)	1 (1)	0	0	0
CSA + MTX ± other(s) (except MMF, post-CY)	22 (3)	2 (1)	13 (1)	5 (3)	0	0	3 (20)
CSA alone	0	0	1 (0)	0	0	0	0
Other(s)	1 (0)	0	3 (0)	1 (1)	0	0	0
Missing	2 (0)	1 (0)	2 (0)	2 (1)	1 (6)	0	0
Peripheral blood							
Ex-vivo T-cell depletion	13 (2)	10 (3)	5 (1)	0	2 (11)	0	0
CD34 selection	19 (2)	8 (2)	25 (3)	0	1 (6)	0	0
Post-CY + other(s)	20 (2)	145 (43)	15 (2)	10 (5)	1 (6)	0	1 (7)
TAC + MMF ± other(s) (except post-CY)	95 (12)	12 (4)	108 (11)	23 (12)	0	0	2 (13)
TAC + MTX ± other(s) (except MMF, post-CY)	378 (47)	23 (7)	435 (46)	83 (42)	1 (6)	2 (40)	1 (7)
TAC + other(s) (except MMF, MTX, post-CY)	46 (6)	3 (1)	57 (6)	11 (6)	0	0	0

GVHD prophylaxis	HLA-identical sibling	Other related	Well-matched unrelated (8/8)	Partially-matched unrelated (7/8)	Mis-matched unrelated (<= 6/8)	Multi-donor	Unrelated (matching TBD)
TAC alone	11 (1)	3 (1)	14 (1)	2 (1)	0	0	0
CSA + MMF ± other(s) (except post-CY)	31 (4)	2 (1)	24 (3)	10 (5)	1 (6)	1 (20)	2 (13)
CSA + MTX ± other(s) (except MMF, post-CY)	86 (11)	8 (2)	34 (4)	5 (3)	0	0	4 (27)
CSA + other(s) (except MMF, MTX, post-CY)	7 (1)	0	5 (1)	2 (1)	0	0	0
CSA alone	6 (1)	1 (0)	3 (0)	0	1 (6)	0	0
Other(s)	5 (1)	1 (0)	4 (0)	2 (1)	1 (6)	0	0
Missing	9 (1)	7 (2)	6 (1)	1 (1)	0	0	0

Table 2b. GVHD prophylaxis given for cord blood graft recipients

	N (%)
CD34 selection	27 (7)
TAC + MMF ± other(s) (except post-CY)	109 (28)
TAC + MTX ± other(s) (except MMF, post-CY)	6 (2)
TAC + other(s) (except MMF, MTX, post-CY)	15 (4)
TAC alone	12 (3)
CSA + MMF ± other(s) (except post-CY)	195 (49)
CSA + MTX ± other(s) (except MMF, post-CY)	3 (1)
CSA + other(s) (except MMF, MTX, post-CY)	3 (1)
CSA alone	2 (1)
Other(s)	9 (2)
Missing	15 (4)