Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR CHRONIC LEUKEMIA
Salt Lake City, UT
Sunday, April 24, 2022, 12:15 pm – 1:45 pm

Co-Chair:	**Ryotaro Nakamura, MD, City of Hope**
	Phone: 626-256-4673; Email: rnakamura@coh.org
Co-Chair:	**Betul Oran, MD, MD Anderson Cancer Center**
	Phone: 713-145-3219; Email: boran@mdanderson.org
Co-Chair:	**Bart Scott, MD, Fred Hutchinson Cancer Research Center**
	Phone: 206-667-1990; Email: bscott@fredhutch.org
Statistical Director:	**Soyoung Kim, PhD, CIBMTR Statistical Center**
	Phone: 414-955-8271; Email: skim@mcw.edu
Scientific Director:	**Wael Saber, MD, MS, CIBMTR Statistical Center**
	Phone: 414-805-0677; Fax: 414-805-0714; Email: wsaber@mcw.edu
Statisticians:	**Noel Estrada-Merly, MS, CIBMTR Statistical Center**
	Phone: 414-805-0692; Fax: 414-805-0714; Email: nestrada@mcw.edu

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1. **Introduction**
   a. **Minutes and overview plan from February 2021 meeting** (Attachment 1)
   b. **Instructions for sign-in and voting**
2. **Accrual summary** (Attachment 2)

3. **Presentations, Published or Submitted Papers**

   a. **CK17-02** Oran B, Ahn KW, Fretham C, Beitinjaneh A, Bashey A, Pawarode A, Wirk B, Scott BL, Savani BN, Bredeson C, Weisdorf D, Marks DI, Rizzieri D, Copelan E, Hildebrandt GC, Hale GA, Murthy HS, Lazarus HM, Cerny J, Liesveld JL, Yared JA, Yves-Cahn J, Szer J, Verdonck LF, Aljurf M, van der Poel M, Litzow M, Kalaycio M, Grunwald MR, Diaz MA, Sabloff M, Kharfan-Dabaja MA, Majhail NS, Farhadfar N, Reshef R, Olsson RF, Gale RP, Nakamura R, Seo S, Chhabra S, Hashmi S, Farhan S, Ganguly S, Nathan S, Nishihori T, Jain T, Agrawal V, Bacher U, Popat U, Saber W. Fludarabine and melphalan compared with reduced doses of busulfan and fludarabine improve transplantation outcomes in older patients with myelodysplastic syndromes. ***Transplantation and Cellular Therapy. 2021 Nov 1; 27(11):921.e1-921.e10. doi:10.1016/j.jtct.2021.08.007. Epub 2021 Aug 14.***

   b. ***CK18-03*** *Guru* Murthy GS, Kim S, Hu Z-H, Estrada-Merly N, Abid MB, Aljurf M, Bacher U, Badawy SM, Beitinjaneh A, Bredeson C, Cahn J-Y, Cerny J, Diaz Perez MA, Farhadfar N, Gale RP, Ganguly S, Gergis U, Hildebrandt GC, Grunwald MR, Hashmi S, Hossain NM, Kalaycio M, Kamble RT, Kharfan-Dabaja MA, Hamilton B, Lazarus HM, Liesveld J, Litzow M, Marks DI, Murthy HS, Nathan S, Nazha A, Nishihori T, Patel SS, Pawaride A, Rizzieri D, Savani B, Seo S, Solh M, Ustun C, van der Poel M, Verdonck LF, Vij R, Wirk B, Oran B, Nakamura R, Scott B, Saber W. Relapse and disease-free survival in patients with myelodysplastic syndrome undergoing allogeneic hematopoietic

cell transplantation using older matched sibling donors vs younger matched unrelated donors. ***JAMA Oncology. 2022 Mar 1; 8(3):404-411. doi:10.1001/jamaoncol.2021.6846. Epub 2022 Jan 13. PMC8759031.***

c. **CK19-01a** Murthy HS, Ahn KW, Estrada-Merly N, Alkhateeb HB, Bal S, Kharfan-Dabaja MA, Dholaria B, Foss F, Gowda L, Jagadeesh D, Sauter C, Bilal Abid M, Aljurf M, Awan FT, Bacher U, Badawy SM, Battiwalla M, Bredeson C, Cerny J, Chhabra S, Deol A, Diaz MA, Farhadfar N, Freytes C, Gajewski J, Gandhi MJ, Ganguly S, Grunwald MR, Halter J, Hashmi S, Hildebrandt GC, Inamoto Y, Jimenez-Jimenez AM, Kalaycio M, Kamble R, Krem MM, Lazarus HM, Lazaryan A, Maakaron J, Pashna N. Munshi PN, Munker R, Nazha A, Nishihori T, Oluwole OO, Ortí G, Pan DC, Patel SS, Pawarode A, Rizzieri D, Saba NS, Savani B, Seo S, Ustun C, van der Poel M, Verdonck LF, Wagner JL, Wirk B, Oran B, Nakamura R, Scott B, Saber W. Outcomes of Allogeneic Hematopoietic Cell Transplantation in T Cell Prolymphocytic Leukemia: A Contemporary Analysis from the Center for International Blood and Marrow Transplant Research. ***Transplantation and Cellular Therapy. 2022 Apr 1; 28(4):187.e1-187.e10. doi:10.1016/j.jtct.2022.01.017. Epub 2022 Jan 23.***

d. **CK16-01** Identification of germline predisposition mutations in young myelodysplastic syndrome patients. (L Godley) ***Oral presentation, ASH 2021.***

e. **CK18-02** The impact of somatic mutations on allogeneic transplant in chronic myelomonocytic leukemia. (M Mei/ R Nakamura/ R Pillai) ***Oral presentation, ASH 2021.***

f. **CK20-01** Outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis based on the conditioning regimen. (G Murthy/ W Saber) ***Oral presentation, ASH 2021.***

g. **CK19-01b** Outcomes after HCT for rare chronic leukemias: Outcomes of chronic neutrophilic leukemia patients who underwent allogeneic hematopoietic cell transplantation. (B Dholaria/B Savani/M Kharfan-Dabaja) ***Oral presentation, EBMT 2022.***

4. Studies in Progress (Attachment 3)

a. **CK16-01** Identification of germline predisposition mutations in young myelodysplastic syndrome patients. (L Godley) **Submitted**

b. **CK17-01** Development of a prognostic scoring system predictive of outcomes in patients with myelofibrosis after allogeneic hematopoietic cell transplantation. (T Roni/SA Giralt/J Palmer) **Manuscript Preparation**

c. **CK18-02** The impact of somatic mutations on allogeneic transplant in chronic myelomonocytic leukemia. (M Mei/ R Nakamura/ R Pillai) **Accepted in *Haematologica***

d. **CK19-01a** Outcomes after HCT for rare chronic leukemias: Evaluating outcomes of Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemias. (H Murthy/B Dholaria/M Kharfan-Dabaja/ S Bal) **Published in *TCT***

e. **CK19-01b** Outcomes after HCT for rare chronic leukemias: Outcomes of chronic neutrophilic leukemia patients who underwent allogeneic hematopoietic cell transplantation. (B Dholaria/B Savani/M Kharfan-Dabaja) **Submitted**

f. **CK20-01** Outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis based on the conditioning regimen. (G Murthy/ W Saber) **Submitted**

g. **CK21-01** Outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis based on the conditioning regimen. (Tania Jain/ M Queralt Sala/V Gupta/ T Nishihori) **Datafile Preparation**

5. Future/Proposed Studies

a. **PROP 2110-259:** Allogeneic Hematopoietic Cell Transplantation (HCT) for the Treatment of Myelodysplastic Syndromes (MDS) in Younger Adults. (A Jimenez/T Wang) (Attachment 4)

b. **PROP 2110-308:** Impact of Somatic Mutations on Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Myelodysplastic Syndrome with Ring Sideroblasts (MDS-RS) and MDS/myeloproliferative neoplasm with RS and thrombocytosis. (MDS/MPN-RS-T) (S Arslan/R Nakamura) (Attachment 5)

c. **PROP 2110-163/PROP 2110-310** Combined proposal: Impact of Pre-Allogeneic Hematopoietic Stem Cell Transplantation Treatment on Outcomes of Patients with Higher-Risk MDS and CMML: A Propensity Score Analysis. (P Kongtim/S Ciurea/R Shallis/A Zeidan) (Attachment 6)
Impact of Pre-transplant Hypomethylating Treatment on Outcomes of Patients with High Risk MDS and CMML Receiving Allogeneic Hematopoietic Stem Cell Transplantation: A Propensity Score Analysis.
Exploring the Impact of Frontline Therapy Intensity in Higher-Risk Myelodysplastic Syndromes or Chronic Myelomonocytic Leukemia on Post-Allogeneic Stem Cell Transplant Outcomes.

d. **PROP 2110-195/PROP 2110-339** Combined proposal: Characteristics Associated with Improved Survival Following Allogeneic Hematopoietic Cell Transplant (HCT) for Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Syndromes. (H Elmariah/T Nishihori/L Gowda/ R Shallis) (Attachment 7)
Comparison of Haploidentical Donor Allogeneic Hematopoietic Cell Transplant (HCT) with Post-Transplant Cyclophosphamide to Matched Donor HCT for Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Syndromes.
Does Allografting help prolong remissions for MDS-MPN.)

e. **PROP 2110-287/PROP 2110-345** Combined proposal: Impact of TP53 Mutational Burden, Conditioning Regimen, and HLA Match on Cumulative Incidence of Relapse and Overall Survival after Allogeneic Stem Cell Transplant for TP53-Aberrant Myeloid Neoplasms. (S Patel/J Cerny/J Maakaron/M Juckett) (Attachment 8)
Impact of TP53 Mutational Subtype, Conditioning Regimen, and Stem Cell Donor Choice on Cumulative Incidence of Relapse and Overall Survival after Allogeneic Stem Cell Transplant for TP53-Aberrant Myeloid Neoplasms.
Matched vs. Mismatched Hematopoietic Stem Cell Transplantation (HCT) for TP53 mutated acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Future/proposed studies to be presented at the CIBMTR Collaborative Working Committee Study Proposals Session

f. **PROP 2110-217/PROP 2110-99** Combined proposal: Long-term Outcomes of AML/MDS Patients Receiving Allogeneic Stem Cell Transplantation using Reduced-Intensity Conditioning: A propensity score analysis. (A Portuguese/B Scott/P Kongtim/S Ciurea) (Attachment 9)
Does Melphalan Dose Prior to Allogeneic Transplant Affect Outcomes in Myeloid Malignancies.
Toxicity and Survival of AML/MDS Patients Receiving Allogeneic Stem Cell Transplantation using Reduced-Intensity Conditioning: A propensity score analysis.

Dropped proposed studies

a. **PROP 2109-17:** A personalized, machine learning derived prediction model for outcomes after allogeneic stem cell transplantation in patients with myelodysplastic/myeloproliferative overlap syndromes. *Dropped due to low scientific impact among proposal*

b. **PROP 2110-64** Allogeneic stem cell transplantation for chronic myeloid leukemia 2010- 2020: How has the selection of patients and outcomes changed after the introduction of 2nd and 3rd generation TKIs? *Dropped-supplemental data needed*

c. **PROP 2110-76** Early platelet count recovery before white cell count recovery after allogeneic hematopoietic cell transplantation and effect on clinical outcome. *Dropped due to low scientific impact among proposal*
d. **PROP 2110-129** Outcomes of allogeneic hematopoietic cell transplantation for Myelofibrosis: PTCY vs ATG. *Dropped due to overlap with current study/publication*
e. **PROP 2110-138** Clinical outcomes and impact of somatic mutations on outcomes of allogeneic blood or marrow transplantation in atypical chronic myeloid leukemia. *Dropped due to small sample size*
f. **PROP 2110-194** Mutational Predictors of Outcomes following Allogeneic Blood or Marrow Transplantation (BMT) for Myelofibrosis (MF). *Dropped due to small sample size*
g. **PROP 2110-208** Effect of pre-transplant ferritin on survival and non-transplant mortality in alternative donor types after hematopoietic stem cell transplant for myelofibrosis. *Dropped-supplemental data needed*
h. **PROP 2110-210** Allogeneic Hematopoietic Cell Transplantation for Patients with Chronic Myelomonocytic Leukemia. *Dropped due to overlap with current study/publication*
i. **PROP 2110-213** Impact of Measurable Residual Disease After AlloHCT for Patients with Myelofibrosis. *Dropped-supplemental data needed*
j. **PROP 2110-224** Outcomes after Hematopoietic Stem Cell Transplant for Chronic Myeloid Leukemia in Blast Crisis when using Busulfan-based versus Total Body Irradiation-based Conditioning Regimens. *Dropped due to small sample size*
k. **PROP 2110-255** Impact of PTCY on Outcomes in Adults with Myelofibrosis. *Dropped due to overlap with current study/publication*
l. **PROP 2110-265** Sequential Allogeneic Hematopoietic Stem Cell Transplantation for Myelodisplastic Syndrome. *Dropped due to small sample size*
m. **PROP 2110-309** Optimal Donor Type for Allogeneic Hematopoietic Cell Transplant for Myelodysplastic Syndrome. *Dropped due to overlap with current study/publication*

MINUTES
CIBMTR WORKING COMMITTEE SESSION
Thursday, February 11, 2021, 1:00 - 4:00 pm
Co-Chair: Bronwen Shaw, MD, PhD; CIBMTR Statistical Center, Milwaukee, WI; E-mail: beshaw@mcw.edu
Co-Chair: John Wingard, MD; University of Florida, Gainesville, FL; E-mail: wingajr@ufl.edu

INTRODUCTION:

Dr. Wingard opened the virtual meeting at 1:00 pm by welcoming the working committee members and the presenters. He discussed the proposal selection and voting process. Though the pandemic amended the process for proposal selection, 368 working committee proposals were submitted and evaluated altogether by CIBMTR Working Committee Chairs and Scientific Directors. About 61% were screened out, 30% had less-relative scientific merit, and 3% were combined with overlapping proposals with relevant nature. 21 proposals (about 6%), were considered for advancing of further pro-development. The proposals were pre-recorded 5-minutes presentations of the 15 semi-finalists, which were presented by the principal investigators. Each presentation was followed by a 5-minute question and answer session, in which audience was invited to submit questions via live chat. For those not able to attend the live session, a link was posted with the session recording and voting was closed on Monday, February 15, 2021. Audience was also instructed on where to locate the scoring and voting links for the presentations. It was mentioned that over 1,000 Working Committee members voted on the first screening of these proposals. Dr. Shaw led the second part of the meeting starting with presentation #9.

GENERAL REMINDERS:

The following reminders were mentioned and posted via the chat option:

a. Thank you for participating in the CIBMTR Working Committee Session! Please cast your score here: https://mcwisc.co1.qualtrics.com/jfe/form/SV_7QwO1ZvzfPZV1NY to vote on the proposals that were presented during the session.
b. Several presenters provided their email addresses for any future communication.

PRESENTATIONS:

1. **Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.** This proposal was presented by Dr. Ana Alarcon Tomas. The primary objective of this proposal is to describe the incidence rate, risk factors, characteristics, and outcomes of subsequent neoplasms in patients receiving post-transplant cyclophosphamide (PTCy) and compare it with calcineurin inhibitors-based graft-versus-host disease prophylaxis and the general population. The CIBMTR identified 64,935 patients ≥18 years of age who underwent a first allogeneic for a malignant disease between 2008-2017. 5,771 (9%) of these patients developed a subsequent neoplasm. Currently, there are no published studies on the incidence of subsequent neoplasms in patients who received post-transplant cyclophosphamide. The following questions were answered during the Q&A:
    a. How are we going to prove that these secondary neoplasms are related to post-transplant cyclophosphamide or cyclophosphamide in conditioning and not due to "by chance" itself- as in general population? This is a case-controlled study. For example, for each patient received with a post-transplant cyclophosphamide will be matched with at least three patients who didn't receive post-transplant cyclophosphamide. Characteristics including primary disease, HLA complexity, survival, follow up time etc. would be used for matching and reviewing survival will also allow us to see that this is because of PTCy and not by coincidence.

b. What is the median follow up time from transplant and subsequent malignancy in post-transplant cyclophosphamide group? I assume it is much shorter than other cohort? Information is not available for each median follow up time cohort. What is available is the median follow up for all patients and some numbers related to the type of diseases for each group. Dr. Rachel Phelan included in the chat that the median follow-up for the PT-Cy group is 38.2 months, and for the proposed control population is 60.3 months.
c. How is this in comparison with matched unrelated donor and cord transplants? Cord transplants will be excluded from the analysis because we don't think we can match those patients.
d. Do we have adequate follow up to answer this important question? We have follow-up for mantle hematological diseases but less time for solid tumors. However, when we saw the numbers that we have (around 5,000 - 5,700) subsequent neoplasms, the majority of cases occurred after the 1st - 5th year of post- transplant and have a 5-year median follow up. We think we have enough numbers to address this question now and we should not wait because it hasn't been published before. This is a noble study and if we wait for a longer median follow up, we might lose that opportunity to have it published first.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix A.

2. **Outcomes of chimeric antigen receptor-T cell therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome)**. This proposal was presented by Dr. Farrukh Awan. The objective of this proposal is to assess outcomes in adult patients with chronic lymphocytic leukemia undergoing transformation to diffuse large B-cell lymphoma (Richter's Syndrome) and undergoing CAR-T therapy. The CIBMTR identified 36 patients underwent CAR-T for Richter's Syndrome from 2015-2019. The following questions were answered during the Q&A:
   a. I know that in the Ohio State paper have many patients that used concurrent Bruton Tyrosine Kinase (BTK) inhibitors. Will you be able to collect data on concurrent BTK inhibitors for these patients? Yes, this information is available through the CIBMTR dataset.
   b. Are you looking at diffuse large B-cell lymphoma derived Richter's Syndrome or chronic lymphocytic leukemia derived Richter's Syndrome? Yes, but it is difficult to determine a clonality between related and unrelated Richter's syndrome. Any studies that show similarities versus dissimilarities in the clone would be very helpful but unfortunately, previous studies have shown that this has been consistently difficult.
   c. You mentioned the opportunity of comparing to other treatment groups. Can you talk about that a little more? We can compare to patients with de novo diffuse large B-cell lymphoma. There are multiple approved and ongoing studies within CIBMTR of diffuse large B-cell lymphoma patients, who do undergo CAR-T therapy and look at toxicity outcomes and infectious outcomes, for example. There are efforts in place to look at outcomes of transplantation for patients with Richter's Syndrome, which can improve the impact of this project and be a competitor to those other ongoing studies.
   d. How many pts do we have? 36 patients
   e. How do you plan to deal with the very low patient numbers (n=36) to make meaningful conclusion? I agree that it is a small number, but it is substantial. Despite the small numbers, if the right competitors are used, such as those mentioned previously, this study can still provide an impactful dataset.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix B.

3. **Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies**. This proposal was presented by Dr. Andrea Bauchat. The objectives of this proposal is to determine the impact of development of grade I-II acute graft versus host disease on relapse and leukemia-free survival, to assess the impact of development of grade III-IV acute graft versus host disease on relapse and leukemia-free survival, and to determine whether the impact of graft versus host disease on

relapse and leukemia-free survival is influenced by disease risk prior to HCT. The CIBMTR identified 1,345 children <18 years who received first HCT for acute lymphoblastic leukemia and acute myeloid leukemia receiving first allogeneic transplantation between 2008 - 2017. The following questions were answered during the Q&A:

a. What is the sample size of each sub-group: disease-risk index (DRI)-low, -intermediate, -high? Exact sample size not available but the high-risk group was less in comparison to others.
b. How will you factor in occurrence of chronic graft versus host disease in your analysis? Our main focus is on acute graft versus host disease because it will have more impact on our clinical practice. However, we will collect the data for the interactions of chronic graft versus host disease alone, and if the patient had a history of acute.
c. What is the biological basis for focusing this study on a pediatric population? The interest from our perspective is looking at the pediatric population compared to the adults. The literature on pediatric is severely lacking in comparison to adults and we need to expand on that for the patient population that we care for.
d. Are you going to separate acute myeloid leukemia and acute lymphoblastic leukemia numbers at DRI level? Yes, they are already divided from DRI protocol. Our acute lymphoblastic leukemia patients are about 1,300 and the acute myeloid leukemia are about 1,200.
e. Is the analysis going to be time dependent or landmark? Landmark
f. Do you have the date of this max acute graft versus host disease grade to take into account the time to event aspect of the effect? No
g. Do you have a plan to include/account for the various GVHD prophylaxis regimen "strengths?" We are taking into consideration of what GVHD prophylaxis regimen the patient uses. This data, which is already categorized, will show us the differences between trends.
h. What is the clinical benefit besides prognostic? This will help define a better foundation of which patients will benefit more from a little bit of graft versus host disease. If we can come up with a patient category that we see is beneficial to have exposure to a little bit of graft versus host disease, it can go forward with clinical trials and GVHD prophylaxis adjustment or manipulation to improve their Leukemia-free survival.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix C.

4. **Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant**. This proposal was presented by Dr. Christine Camacho-Bydume. The primary objective of this proposal is to determine if HLA evolutionary divergence (HED) of HLA class I alleles of HLA-A, -B, -C and HLA class II alleles of HLA-DR is associated with overall survival and relapse. The objective is to also evaluate association of HED with acute and chronic GVHD and treatment-related mortality (TRM). The CIBMTR identified pediatric and adult patients with acute myeloid leukemia, myelodysplastic syndromes, acute lymphoblastic leukemia, chronic myeloid leukemia, or lymphoma (non-Hodgkin or Hodgkin's lymphoma), who have received initial allogeneic 8/8 HLA-matched (HLA-A, -B, -C, -DR) transplant between 2008 - 2018. The following questions were answered during the Q&A:

   a. Could HLA diversity simply be a surrogate for race? How would you account for race in the study? Great question given there are particular HLA alleles that are more common in certain ethnic groups. We do think that evaluation of HED lows and highs within these different ethnicities can help to tease this out more, with potential to adjust for race more in this analysis. We think some of these differences in peptide binding grooves can help us to understand better the different peptides and how antigens are presented to T-cells.
   b. Extrapolating HLA data from solid tumors and checkpoint inhibitors and their antigen presentation is slightly challenging in context of allo donor T-cell interaction with antigen presented for bone marrow origin cancers. Yes, have to consider there could be some differences. Was a small previous study that

looked at this question, saw some signals there, larger population and different types of cancers, may be able to explore that more.

c. Leukemia (both lymphoblastic and myeloid) have low mutational burden as compared to melanoma and lung. Will the HED algorithm still work? Yes, we do expect to see differences in mutational burdens, and we do plan to look at the cohort at large to look at the disease subgroups to see more or less of this phenomenon in these groups. Do you have preliminary data in leukemias? There was a small study in Germany that looked at AML, to my knowledge only one that looked at leukemias. Mutational burden did see some differences, so we do expect it and also, besides the overall cohort, also plan to look at disease subgroups.
d. Given HED implications for infection surveillance, are you going to look at infectious sequelae differences? No, at the moment we have initially requested information in terms of tumor control, relapse, overall survival, graft versus host disease, and TRM. Not sure of availability of the other information but would be interesting to look at if available.
e. Would you please discuss the confounding effects of HLA mismatching for HLA-DRB3, 4, 5, DQ, and DP? Not known off the top of my head the percentages of mismatching differences in this cohort. For DR at least they will be matched, 8/8 matched, in terms of DP, don't have that info but if available it is something that can be looked at.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix D.

5. **Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Evan C. Chen. The primary objective of this proposal is to identify differences in survival outcomes between mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients and to assess the prognostic significance of disease features in mutIDH1/2 and wtIDH1/2 acute myeloid leukemia patients. The CIBMTR identified patients ≥ 18 years old with a diagnosis of normal karyotype acute myeloid leukemia, receiving first allogeneic HCT during CR1 in 2013 - 2019. The following questions were answered during the Q&A:
   a. Is there any concern that patients with IDH1/2 mutated acute myeloid leukemia would have received more intensive conditioning / therapy than IDH1/2 wild-type? Yes, and it's important to look at how conditioning intensity can be an important covariant, which is a variable captured in CIBMTR.
   b. Will you have registry information on the type and duration of use of IDH inhibitors before/after HCT? It's currently not available with CIBMTR.
   c. IDH mutations are usually seen in older subjects. How will you a priori adjust for this known association? Age will certainly be a covariant in our multi-variant analysis.
   d. How reliable are the wild-type patients as some may just not be tested for IDH mutations? It is double checked. There is a datapoint in the forms that indicate whether or not testing has been done, versus if testing was done and IDH was found to be absent.
   e. Do you have information what the numbers will be like when you divide your patient groups with concomitant mutations such FLT3 or p53 that may have an impact on outcomes? Yes, the numbers are about 20-40 for co-mutated for ITD and NPM1 patients. p53 not provided.
   f. Is there data in CIBMTR forms that collect use of IDH inhibitors pre transplant? Will you be able to study their impact on the transplant? I'm not aware of this data point being available in the forms but it is something that we should follow up on.
   g. How do you analyze its (or ITS?) with multiple mutations? With regards to double-mutated patients, IDH1, and IDH2 patients, which are generally rarely reported, we would look at the CIBMTR forms to ensure accurate data entry. In regard to analyzing IDH with other co-mutations, we would include co-mutations as a co-variant in a multi-variant analysis, should the sample size permit.

h. What about other mutations in Wild type IDH? We focus on NPM1 and FLT3-ITD because they are prevalent in the cytogenetic risk population. We will look at the other mutations to see if they have any relevance at all.
i. Do the data forms reliably collect information on use of IDH inhibitors pretransplant? Data point is not available.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix E.

6. **Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant**. This proposal was presented by Dr. Christin B. DeStefano. The primary objective of this proposal is to describe patient and disease related characteristics of adolescent and young adults (AYAs) with multiple myeloma treated with early high dose melphalan and AutoHCT and to characterize response to AutoHCT, survival outcomes, SPMs, and infections of AYA multiple myeloma patients and AutoHCT. The CIBMTR identified 1,142 AYA multiple myeloma patients who underwent autologous hematopoietic cell transplant) between 2008 -2018. The following questions were answered during the Q&A:
   a. What will differentiate this study from MM18-03 "To compare the outcomes in young patients with multiple myeloma at diagnosis undergoing upfront autologous hematopoietic stem cell transplant with older patients in the US: progression-free and overall survival"? There appears to be substantial population overlap. The Scientific Director clarified via the chat function that MM18-03 included the years 2013-2017 and excluded patients less than 40 years from the outcome analysis owing to small numbers.
   b. How do you plan to control for differences between your AYA group and older control group which would be attributable to age? In total, there are about 1,700 TED and CRF cases. We can adjust the critical variables of these cases, such as stage, treatment rendered, and cytogenetics, for example, to control for differences.
   c. Will results be stratified according to different induction regimens? Yes, we will adjust those critical variables amongst the CRF cases where this information is available.
   d. A cohort going back to 1995 seems too outdated. What was the N for a more recent group (since 2010)? There were 1,142 AYA cases between 2008-2018.
   e. This is a long cohort 1995-2019 with lots of changes in induction treatment, novel agents and time to bone marrow transplant. How will this be controlled for? We are going to study induction regimens, post-transplant treatment, use of tandem transplants in our analysis.
   f. Will you be also studying the effect of post-transplant maintenance therapy? Also, any effect of extramedullary plasmacytomas in this AYA group? We will for cases where this information is available. Extramedullary plasmacytomas are a good focus, as AYA patients may have a more aggressive presentation of myeloma.
   g. Are plasma cell leukemias included in this analysis? No

   Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix F.

7. **Impact of measurable residual disease status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT**. This proposal was presented by Dr. Firas El Chaer. The objectives of this proposal is to determine if acute myeloid leukemia measurable residual disease (MRD) analysis as currently performed has prognostic value when measured prior to AlloHCT, to explore factors that may modify the risk associated with detectable acute myeloid leukemia MRD pre-AlloHCT, and identification, using MRD combined with other clinical factors, of patients most at risk of post-AlloHCT relapse. The CIBMTR identified 753 MRD positive and 1986 MRD negative adult patients receiving first AlloHCT for de-novo AML in CR1 in 2007-2018. The following questions were answered during the Q&A:

a. What kind of MRD data is collected? Depending on the individual participating centers, the methodology uses molecular or immunotherapy? MRD
b. What is the rate of missing MRD status and are those patients different from those with MRD data available? The answer is not included in this study.
c. Are you going to also study the effect of post-transplant maintenance in AML FLT3, IHD mutations on relapse and overall survival? One of the aims of this study is to have future studies look at post-transplant maintenance from this study.
d. What do you mean by most "recent" pre-conditioning MRD assessment? Would testing need to be completed within a specific time frame before conditioning? All patients who will be receiving a stem cell transplant are required to get a bone marrow biopsy and peripheral blood aspiration before transplantation. Within a month before the transplant, we would look at data point.
e. What is your working definition of MRD? A combination of molecular testing as well as immunotherapy by NFC.
f. Are all mutations equivalent when thinking about MRD? Absolutely not.
g. How sure are you that the MRD patients are really MRD negative? We can never be absolutely sure.
h. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when? The way that CIBMTR reports the acute myeloid leukemia data is by reporting their cytogenetics and mutation analysis so we can calculate the data for this population. The point of this study is to look at the commercial availability of these tests and we can rely on it or if we should standardize one testing at all centers.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix G.

8. **Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.** This proposal was presented by Dr. Nosha Farhadfar. The objectives of this proposal are to determine whether clinical manifestations and severity of chronic GVHD differ based on racial/ethnic and socioeconomical status (SES) differences, to determine whether treatment patterns of chronic GVHD differ based on racial/ethnic and SES differences, and to evaluate whether chronic GVHD treatment outcomes differ based on racial/ethnic and SES differences. The CIBMTR identified 17,665 patients, age 18 years or older, who have received first allogeneic transplant for hematologic malignancy (acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome) between 2008 - 2019. The following questions were answered during the Q&A:
   a. I like the idea for looking at outcomes based on race/ethnicity/SES but not sure if incidence should be a primary outcome because it will be dependent on donor type which is very different amongst the groups. The primary outcome of this study is to look at the outcome of patients who develop chronic graft versus host disease. We need to look at the whole cohort, report the incidence, and then focus on chronic graft versus host disease cohort as the primary endpoint of this study.
   b. How will you correct for the impact of race on HLA mismatch between recipients and donors due to the lower chance of identifying a fully matched donor in non-Hispanic white patients? For the same reason, should cord blood recipients be excluded? We are going to include both the donor type, graft source and degree of HLA matching as covariables in a multi-variable analysis. Cord blood recipients should not be excluded, as there was near 14% of Non-Hispanic black, 14% Hispanic, and 15% Asian who received cord transplant. Approximately 7-8% of cord transplants were received by Non-Hispanic whites. We do have the number to look into cords but if a statistician reviews and determines we don't have the power, then we can eliminate the cords.
   c. Is it possible to access constitutional DNA to look at ancestry information markers in this population? This information is not available for the population. The analysis will focus on self-reported race/ethnicity.
   d. All patients in your cohort from 2008 were not reported with NIH consensus criteria for chronic GVHD. Since you have large numbers, should you limit this to more recent time period? We do have all of the

information on graft versus host disease and whether it was limited or extensive. There is information on whether graft versus host disease is progressive, de-novo or interrupted. We have organ involvement and maximum grade of chronic graft versus host disease. NIH scoring is available for at least the past 4 years and maybe we can look at that group separately. Within the past 4 years, the population limited to NIH grading only in about 1,500 non-Hispanic white, 270 non-Hispanic black, and 200 Hispanic, who have developed chronic graft versus host disease.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix H.

9. **Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity**. This proposal was presented by Dr. Lohith Gowda. The objectives of this proposal are to identify density and types of early and late infections (bacterial, viral and fungal) in patients that went to transplant a) <6 months b) between 6- 12 months and c) > 12 months from diagnosis; to identify T cell lymphocyte absolute numbers at days 100 and 180 and CD4/CD8 ratio for the timeline cohorts examining individual donor types; to evaluate the impact of bacterial, viral or fungal infections by day 100 and day 180 on 1-year post-transplant outcomes (relapse, non-relapse mortality, disease free survival, acute and chronic graft versus host disease); and to evaluate quantitative immunoglobulin levels at D+ 100 and + 180 if available. The CIBMTR identified 6,877 ≥ 18 years old patients who underwent first allogeneic transplants for AML in CR1, ALL in CR1 or MDS in the United States from 2012 to 2019. The following questions were answered during the Q&A:
    a. How many patients in the registry have the immune parameters you wish to assess? >2100
    b. How will you account for the type of treatment used prior to transplant? For example, treatments such as hypomethylating agents may require months of treatment before transplant versus induction chemo that works more quickly. We do have some variables that are available, such as types of therapy, and we can analyze levels of intensity of therapy (low to high) and post-transplantation outcomes. The exact number of how many patients who have had different intensities of therapies is not available.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix I.

10. **Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement**. This proposal was presented by Dr. Hamza Hashmi. The primary objective of this proposal. The CIBMTR identified 55 adult patients (age ≥ 18) who received CD19 CAR T-cell therapy for B-cell NHL with secondary central nervous system (CNS) involvement. The following questions were answered during the Q&A:
    a. How will you differentiate between immune effector cell-associated neurotoxicity syndrome (ICANS) and CNS relapse? ICANS will be documented as a neurotoxicity and CNS relapse will be when the form is filled out.
    b. Is this active CNS disease or previously treated CNS disease? The data received from CIBMTR looks at CNS disease at the time of diagnosis and the CNS disease that is present at the time of cellular therapy.
    c. Do you have any registry information on concomitant CNS therapy (chemo/radiation) pre, peri and post transplantation? Answer was not available at this time.
    d. How many patients are in your study? How will you define whether the patients have cleared their CNS involvement? There are currently 60 patients in the history of this data. Of the 60, 40 had this disease at the time of diagnosis and 20 had this disease at the time of cellular therapy. Whether the patients have cleared their CNS involvement, this information is not available at the time.
    e. Since this is your primary endpoint, how will you account for the differences of frequency of CRS and ICANS across different products (e.g. high in Yescarta, lower in Kymriah, low in Breyanzi)? If you look at the toxicity profile of CD19 therapy, they seem to be relatively similar.

f. Could you please include other agents such as anakinra, siltuximab, and other agents? Dasatinib for this populations for ICANS? Also, was CNS disease under control at CAR-T therapy? As for Anakinra, siltuximab, and other agents, I'm not sure if CIBMTR is capturing this data. As for dasatinib, I'm not sure if this information is available as well. Per Dr. Pasquini of CIBMTR in the live chat, he commented "we capture treatment of ICANS, like siltuximab, dasatinib has been reported as other treatment."
g. Will you have detail on the nature and extender features of secondary CNS involvement to associate with the toxicity and outcome? I only have the essential data with me but am hopeful that this comprehensive research will have further detail.
h. Will all the patients included have active CNS disease at the time of CAR-T or, are treated CNS disease are also included? They are both included, and we are able to tell who has had active disease with a prior history at the time they got the CAR-T therapy.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix J.

11. **Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis**. This proposal was presented by Dr. Tania Jain. The primary objective of this proposal is to explore the impact of donor type on overall survival of patients undergoing HCT for myelofibrosis. The CIBMTR identified 1,640 patients ≥18 years old diagnosed with primary, post-ET or post-PV myelofibrosis and undergoing first HCT between 2013 and 2019. The following questions were answered during the Q&A:
    a. Are you also going to compare the effect of pretransplant Ruxo in haplo vs MUD/MRD? Also, are you going to look for graft failures as well in these patient populations? Yes, this will be included. We also do look at graft failures in these populations.
    b. Is there a difference in time from diagnosis to HCT across the groups? The median time from diagnosis to transplant for haploidentical patients was 38 months, while for HLA- identical sibling and URD 8/8 was 21 and 24 months, respectively.
    c. Are you including all conditioning regimens types: MAC, RIC and NMA? Yes, and they will be looked at for comparison in the univariable and may be taken to the multivariable analysis as well.
    d. For the graft failure or rejection analysis are you going to include spleen size? Ideally it should be included but the spleen size measurement has many variables and it may not be a clean assessment. We don't collect precise spleen size in our forms, but it can be analyzed as spleen size as splenomegaly, no splenomegaly or splenectomy.
    e. Can you comment on the bone marrow vs peripheral blood in the three groups? Peripheral blood is more common in the donor source (about 80%).

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix K.

12. **Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL**. This proposal was presented by Dr. Arushi Khurana. The objective of this proposal is to enhance our understanding of sex- and race-based differences in utilization of CAR-T vs AutoHCT and outcomes after CAR-T. The CIBMTR identified 1,133 patients to compare sex and race/ethnicity rates for first cellular infusion (AutoHCT vs. CAR-T) for relapsed/refractory non-hodgkins lymphoma patients from 2017 – 2019 (aim 1a). The CIBMTR identified 619 non-hodgkins lymphoma patients who relapse after first AutoHCT to describe subsequent treatment patterns (e.g. CAR-T, second AutoHCT, AlloHCT, other treatment, no treatment) by sex and race/ethnicity (aim 1b). The CIBMTR identified 1,253 patients to identify sex-and race-based differences in response to CD19 CAR-T in aggressive lymphomas (aim 2). The following questions were answered during the Q&A:
    a. Is there gender and race-based difference in SEER data with or without treatment for diffuse large B-cell lymphoma even before CAR T? Yes, that data does exist.

b. Can this be stratified by center/geography (private/public, large urban/rural)? Yes, it will be shown based on zip code (of patient and of recorded center), which will allow us to differentiate from urban/rural as well.
c. We saw almost no neurotoxicity in women so would you be plotting CRS and ICANS based on gender and race? Yes, and we believe CIBMTR is the best resource for this because of the larger numbers
d. How do you differentiate between larger trial centers vs less resourced centers? The information is reported based on the center type. Basing on academic or zip code, or city versus rural center, that will also be a way to differentiate the centers.
e. Would disease response status prior to cellular therapy be taken into account for analysis? Yes, that is one of the co-variants that will be included.
f. How reliable is the data you will get to study "access", as there are many factors, depending on patient specific factors (education, resource, finances, mobility, support, performance, etc.), center specific (criteria), and also access depends on the hematologist/oncologist who sees these patients in the community? Access to a center is not one of the main issues in this study. It is more about why some of these minorities receiving other treatments when they should be receiving cellular therapy at the time of indication.
g. Is there any way to take into account insurance issues? We do look at the insurance statuses as one of the co-variants.
h. Would it be possible to look at differences in access based on commercial CAR T vs. clinical trials? The majority of the patients from the forms received are from commercial CAR T.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix L.

13. **Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation**. This proposal was presented by Dr. Richard J. Lin. The primary objective of this proposal is to compare CRFS among patients ≥ 60 years old undergoing myeloablative conditioned, allogeneic hematopoietic cell transplantation with following graft versus host disease prophylaxis in 2 matched-pair analysis and to compare other transplant outcomes in the above 2 matched-pair analysis. The CIBMTR identified 1,301 patients at ≥ 60 years old at the time of first allo-HCT between 2010 and 2019, with any myeloablative conditioning defined by CIBMTR, 8/8 matched related or unrelated donor only, graft versus host disease prophylaxis (ex-vivo TCD/CD34+ selection versus PTCy-based versus Tac/MTX). The following questions were answered during the Q&A:
    a. What do you mean by "robust?" Is it based on KPS, HCT-CI, or just the fact that someone got MA. regimen? We use the definition of a patient getting a myelo-conditioning as a way of saying that they are robust by their transplant centers.
    b. Are patients with In-vivo T cell depletion (Campath or ATG) excluded from this analysis? T cell depletion and CD34 selection does include ATG and does not include Campath.
    c. Why do you pool post-CY and ex vivoCD34+ selection? Can we still consider ex vivoCD34 selection to be a promising transplant modality in 2021? We wanted to compare a 2-match pair analysis and not a direct comparison between CD34 selection and post-CY. We do know which will be better for an older patient.
    d. Why exclude TBI? For older patients, we don't consider TBI to be a conditioning regimen.
    e. How many patients with Tac/methotrexate prophylaxis had ATG? Answer was not available at the time of Q&A.
    f. Do we know GFR (creatinine) coming into allo in these groups? In this study, we didn't include the GFR (creatinine) as a variable but we have some evidence in older patients that does play a major role. I can discuss with our statistician on whether we can include this as a variable.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix M.

14. **Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas**. This proposal was presented by Dr. Sayeef Mirza. The primary objectives of this proposal to evaluate cumulative incidence grades, duration and median time to onset of CRS and CRES/ICANS in patients > 65 years of age receiving CD-19 directed CAR-T therapy, describe post CAR-T clinical outcomes and resource utilization in elderly, and identify disease biology, comorbidities and other clinical predictive markers of toxicity, response, and survival in elderly patients. The CIBMTR identified 1,036 patients (<65y,n=612; 65-74y, n=348; >75y, n=76) with the diagnosis of any B-cell lymphoid malignancy (indolent or aggressive lymphoma) receiving CAR-T cell product (CD19 target). The following questions were answered during the Q&A:
    a. Would you please also look at Incidence of pancytopenia, hypogammaglobulinemia and HLH in elderly versus younger in 3 cohorts <60, 60-75 ,>75? I think it's very important to look at this as the data becomes available to us. We are primarily looking at different age groups. We have 81 patients over the age of 75 and five patients over the age of 85. Overall, there are 435 (40 %) of the group are over 65 years old.
    b. How does this defer from the data presented by Dr. Pasquini last year in older patients? This data will be more helpful in including both CAR-T products.
    c. In case of CAR T was used for post-alloHCT relapse, would the donor age of the CART source be analyzed? This is something that we should include in our analysis.
    d. Are data on baseline geriatric scores or HCT-CI available for all? The answer was not available at the time of the Q&A.
    e. Do we have registry information on whether CAR-T production succeeded or not, when attempted? The answer was not available at the time of the Q&A but the moderator did state that on behalf of CIBMTR, this information is not captured.

    Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix N.

15. **Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation**. This proposal was presented by Dr. Joseph Pidala. The primary objective of this proposal is to validate prediction models for immune suppression discontinuation (ISD) and ISD failure developed in prior DISCIS-defined population, explore ISD and ISD failure in a new population inclusive of full range of diversity in current HCT practices, construct and validate dynamic prediction models of ISD and ISD failure in the expanded population. The CIBMTR identified 20,031 patients with a hematologic malignancy who received an allogeneic HCT from matched sibling donor, matched or mismatched unrelated donor, umbilical cord blood or haploidentical donor between 2009-2018. The following questions were answered during the Q&A:
    a. Can you explain how the ISD data information was made feasible? We used CIBMTR follow up data in the previous analysis that led to the development of the prediction model for ISD that we intend to validate in this study.
    b. Can you provide more granularity on how the time of discontinuation of immune suppression will be defined? In the CIBMTR data, there is a hard stop date for a complete discontinuation of immune suppression. That granular data is available, and it was the data we used for the prior project. We used that hard stop of all systemic immune suppression because that's an unambiguous measure of success.
    c. Many with PTCY may be discontinuing by days 100 or 60- likely based on center practice rather than patient response, how will this be addressed? Our prior project was successfully addressed this issue, specifically within that study population. The first step in this project is to validate those findings. We will definitely be studying how immune suppression was performed and what are the subsequent outcomes.
    d. Do you plan to use age as one of the variables regarding likelihood to discontinue IST, or will you have a separate pediatric specific model? Yes, we will consider age as a variable and evaluate the need for a pediatric specific model.

Additional questions and comments posted via the chat but were unanswered due to limited time can be found in Appendix O.

CLOSING:

Dr. Shaw, on behalf of herself and co-chair, Dr. John Wingard, did thank presenters, conference organizers, and the CIBMTR staff for having coordinated this virtual session. She did mention that this session was recorded and encouraged attendees to take survey, as access would be available until Monday, February 15, 2021.

APPENDICES:

A. Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis.

1. How will authorship work for these studies? The same as usual, there are fewer studies being accepted but the process otherwise is the same
2. What if a higher risk of cancer is related to the almost uniform use of 2GyTBI in these patients rather than PTCY?
3. What is the breakdown of haploidentical versus matched sib/MUD in the post-transplant cyclophosphamide group?
4. How can we r/o genetic predisposition on samples and variables of TBI based conditioning therapies?
5. What is your sample size and follow-up period?
6. How long post BMT you will follow up? From where will you receive the SN data?
7. Will you be adjusting for chronic GVHD when looking at your outcome of SN?
8. Is this study statistically powered to detect a difference between PTCY and above a certain threshold? What is the threshold?
9. Will analysis be conducted separately for TBI/non-TBI and MAC/RIC conditioning? Are you evaluating all malignancies?
10. Since the total CY exposure is likely not that different in PTCY vs. BU/CY or CY/TBI, is your hypothesis that the timing of exposure to CY may lead to a difference in risk? And if so, why?
11. Information on skin cancers - ssc, bcc available?
12. Matching for HLA matching could be a limitation because the PTCY patients are more likely to receive haploidentical grafts.

B. Outcomes of chimeric antigen receptor-T cell (CAR-T) therapy for patients with antecedent chronic lymphocytic leukemia (Richter's Syndrome).

1. If patients had failed an auto or allo, how do you plan to compare to the results of auto? Isn't it a different group?
2. Can you please provide your thoughts if the small n will be able to generate meaningful results at this time?
3. Would you include both transformed lymphoma from other low-grade lymphoma and Richter's transformation?
4. Are there concerns about underreporting Richter's?
5. Since the numbers are small, can we go back to centers to establish clonality?

C. Impact of graft versus host disease following allogeneic hematopoietic cell transplantation on leukemia free survival in hematologic malignancies. *No additional questions*

D. Effect of HLA evolutionary divergence on survival and relapse following allogeneic hematopoietic cell transplant.

1. Does the HED algorithm take into account variations outside the peptide binding groove?

2. What is the size of the cohort you are looking at?

E. Impact of IDH1 and IDH2 mutations on outcomes of acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplantation. *No additional questions*

F. Characteristics and outcomes of adolescent and young adults with multiple myeloma treated with autologous hematopoietic cell transplant.

1. How do you plan to control for differences between your AYA group and older control group?

G. Impact of MRD status on outcomes of AML in patients 18-65 years old in CR1 undergoing Allo-HCT.

1. How are you going to account for the different sensitivity of methods used to determine MRD? Are ELN risk available at CIBMTR, since when?
2. Hi Firas, How are defining the MRD?
3. The methods for MRD assessment may be quite heterogeneous, including the threshold of detection. How will you deal with the high likelihood of false MRD negative assessments from using inadequately sensitive quantification?
4. MRD test is different from different centers. How can you control for this?
5. How do you account for different MRD- cut-offs?
6. To clarify, if AML-MRD is to become a "precision medicine tool", does that mean is will be used to guide treatment decisions in addition to being prognostic?
7. How will control for the various methods for detecting MRD as different techniques have different sensitivities/accuracy?
8. if both multiparameter flow and NGS are available and are discordant on the same patient, how will that be analyzed?
9. is the MRD before alloSCT is the one to be analyzed?
10. Will this require more data from centers to answer some of the questions above?

H. Racial, ethnicity and socioeconomic disparity in outcome of patients with chronic graft versus host disease.

1. Is age significantly different in your Hispanic cohort? How do you adjust for it?
2. Was the MMUD recipient cohort limited to single antigen mismatch? Or all mismatches (understanding most MMUD will likely be single antigen MM)?
3. Do you have information on health insurance? Why not to study this question in a more homogeneous patient population to avoid the complexity and interactions in different factors?
4. Are there any other sociodemographic variables available that could be used to adjust for socioeconomic status, or is median income in the patient's ZIP code the only one?
5. Baker et al 2009 demonstrated no impact of household income on GVHD (acute or chronic) and only minimal impact of race on Grade III-IV aGVHD (none of cGVHD). Why do you think this null relationship should be pursued again?
6. Is there a plan to study as per continent distribution?
7. Is there a better index to gauge SES or poverty level?
8. Are Native American/Hawaiian/Pacific islanders being grouped elsewhere?

I. Time from diagnosis to transplant as an important contributor for post allogeneic stem cell transplant infections, immune reconstitution and its associated mortality/morbidity.

1. Do you plan to address the confounding influence of different factors leading to delay in transplant timing?
2. How are you going to account for number of cycles of chemotherapy versus no

chemotherapy as a confounder in the time delay?

J. Efficacy and safety of CD19 directed CAR T-cell therapy for non-Hodgkin B-cell lymphomas with secondary central nervous system involvement.

1. Is site-specific response (CNS vs. other lesions) and pattern of relapse/progression (CNS vs. systemic) available?
2. Why not to consider a comparative group?
3. Will you stratify patients according if they received IT chemo vs radiation therapy?

K. Haploidentical donor versus matched donor allogeneic hematopoietic cell transplantation in patients with myelofibrosis.

1. Availability of somatic mutations?
2. Is pretransplant Splenectomy data available? Are you going to factor this in the outcomes?
3. At least look at splenectomies?
4. What risk stratification is being used? DIPSS or DIPSS+?

L. Assessing utilization and clinical outcome differences by sex and race in CAR-T for relapsed/refractory NHL. *No additional questions*

M. Optimal GVHD prevention strategy in older, robust patients with acute leukemias and myeloid malignancies undergoing myeloablative, matched donor hematopoietic cell transplantation. *No additional questions*

N. Outcomes of elderly patients receiving CD-19 directed CAR-T therapy for B-cell lymphomas. *No additional questions*

O. Determinants of successful discontinuation of immune suppression following allogeneic hematopoietic cell transplantation.

1. How is immune suppression stop defined in the CIBMTR database?
2. How long after HCT do you expect data regarding ongoing IST usage to be reliable since many patients leave the transplant center and are managed elsewhere long-term?
3. How long will you deal with restart IST?

Accrual Summary for the Chronic Leukemia Working Committee

Characteristics of recipients undergoing allogeneic HCT for MDS reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
No. of patients	8252	1358	7679	5848
No. of centers	190	156	197	265
Age, median (range) - median (min-max)	62 (0-83)	45 (0-77)	57 (0-81)	52 (0-80)
Age, years - no. (%)				
< 10	248 (3)	115 (8)	233 (3)	249 (4)
10-19	284 (3)	115 (8)	326 (4)	340 (6)
20-29	227 (3)	140 (10)	306 (4)	425 (7)
30-39	355 (4)	194 (14)	513 (7)	614 (10)
40-49	740 (9)	265 (20)	1054 (14)	1058 (18)
50-59	1872 (23)	316 (23)	2288 (30)	1513 (26)
60-69	3458 (42)	191 (14)	2419 (32)	1474 (25)
>= 70	1068 (13)	22 (2)	536 (7)	174 (3)
Missing	0 (0)	0 (0)	4 (0)	1 (0)
Sex - no. (%)				
Male	5147 (62)	822 (61)	4594 (60)	3558 (61)
Female	3105 (38)	535 (39)	3085 (40)	2284 (39)
Missing	0 (0)	1 (0)	0 (0)	6 (0)
Disease at diagnosis - no. (%)				
MDS unclassifiable, NOS	1314 (16)	144 (11)	1684 (22)	987 (17)
Refractory anemia (RA)	775 (9)	288 (21)	630 (8)	696 (12)
Refractory anemia excess blasts (RAEB)	3575 (43)	586 (43)	3176 (41)	2520 (43)
Chronic myelomonocytic leukemia (CMML)	789 (10)	133 (10)	777 (10)	513 (9)
Acquired idiopathic sideroblastic anemia (RARS)	325 (4)	39 (3)	221 (3)	137 (2)
Refactory anemia with multilineage dysplasia (RCMD)	1051 (13)	105 (8)	948 (12)	742 (13)
Refactory anemia with dysplasia and ringed sideroblasts (RCMD/RS)	54 (1)	1 (0)	33 (0)	28 (0)
5q- syndrome	105 (1)	4 (0)	125 (2)	58 (1)
Other MDS, specified	264 (3)	58 (4)	85 (1)	167 (3)

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
Graft source - no. (%)				
Bone marrow	1605 (19)	420 (31)	1426 (19)	1259 (22)
Peripheral blood	6086 (74)	851 (63)	5930 (77)	4365 (75)
Cord blood	543 (7)	87 (6)	242 (3)	123 (2)
Missing	18 (0)	0 (0)	81 (1)	101 (2)
Donor type - no. (%)				
HLA-identical sibling	1878 (23)	577 (42)	2638 (34)	2604 (45)
Haplo	558 (7)	67 (5)	619 (8)	136 (2)
Unrelated donor	5007 (61)	464 (34)	3736 (49)	2654 (45)
Cord blood	543 (7)	87 (6)	242 (3)	123 (2)
Other/missing	266 (3)	163 (12)	444 (6)	331 (6)
Year of transplant - no. (%)				
1995-1996	153 (2)	82 (6)	174 (2)	196 (3)
1997-1998	179 (2)	93 (7)	199 (3)	259 (4)
1999-2000	195 (2)	147 (11)	202 (3)	322 (6)
2001-2002	288 (3)	145 (11)	225 (3)	348 (6)
2003-2004	353 (4)	149 (11)	274 (4)	399 (7)
2005-2006	467 (6)	169 (12)	303 (4)	382 (7)
2007-2008	558 (7)	85 (6)	330 (4)	354 (6)
2009-2010	565 (7)	78 (6)	599 (8)	543 (9)
2011-2012	801 (10)	27 (2)	738 (10)	655 (11)
2013-2014	1217 (15)	122 (9)	631 (8)	527 (9)
2015-2016	1349 (16)	128 (9)	675 (9)	490 (8)
2017-2018	1293 (16)	91 (7)	952 (12)	644 (11)
2019-2020	694 (8)	42 (3)	1564 (20)	522 (9)
2021	140 (2)	0 (0)	813 (11)	207 (4)

Characteristics of recipients undergoing allogeneic HCT for myelofibrosis reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
No. of patients	2583	415	1437	1475
No. of centers	134	92	136	170
Age, median (range) - median (min-max)	61 (1-79)	54 (2-74)	58 (0-79)	56 (2-75)
Age, years - no. (%)				
< 10	11 (0)	3 (1)	16 (1)	12 (1)
10-19	12 (0)	7 (2)	11 (1)	25 (2)
20-29	12 (0)	11 (3)	20 (1)	35 (2)
30-39	60 (2)	26 (6)	52 (4)	111 (8)
40-49	299 (12)	98 (24)	212 (15)	271 (18)
50-59	784 (30)	156 (38)	529 (37)	537 (36)
60-69	1143 (44)	111 (27)	537 (37)	456 (31)
>= 70	262 (10)	3 (1)	60 (4)	28 (2)
Sex - no. (%)				
Male	1491 (58)	268 (65)	860 (60)	920 (62)
Female	1092 (42)	147 (35)	577 (40)	555 (38)
Disease at diagnosis - no. (%)				
Polycythemia vera (PV)	345 (13)	46 (11)	186 (13)	125 (8)
Essential or primary thrombocythemia (ET)	425 (16)	46 (11)	207 (14)	172 (12)
Chronic myelofibrosis	1813 (70)	323 (78)	1044 (73)	1178 (80)
Graft source - no. (%)				
Bone marrow	208 (8)	83 (20)	135 (9)	201 (14)
Peripheral blood	2309 (89)	323 (78)	1276 (89)	1253 (85)
Cord blood	54 (2)	9 (2)	17 (1)	10 (1)
Missing	12 (0)	0 (0)	9 (1)	11 (1)
Donor type - no. (%)				
HLA-identical sibling	628 (24)	165 (40)	611 (43)	634 (43)
Haplo	240 (9)	18 (4)	60 (4)	34 (2)
Unrelated donor	1592 (62)	200 (48)	678 (47)	732 (50)
Cord blood	54 (2)	9 (2)	17 (1)	10 (1)
Other/missing	69 (3)	23 (6)	71 (5)	65 (4)
Year of transplant - no. (%)				

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
1995-1996	15 (1)	8 (2)	11 (1)	19 (1)
1997-1998	22 (1)	11 (3)	13 (1)	36 (2)
1999-2000	30 (1)	22 (5)	18 (1)	44 (3)
2001-2002	52 (2)	21 (5)	33 (2)	81 (5)
2003-2004	54 (2)	30 (7)	45 (3)	99 (7)
2005-2006	75 (3)	43 (10)	76 (5)	100 (7)
2007-2008	124 (5)	38 (9)	73 (5)	116 (8)
2009-2010	126 (5)	30 (7)	172 (12)	188 (13)
2011-2012	38 (1)	5 (1)	302 (21)	159 (11)
2013-2014	191 (7)	45 (11)	227 (16)	132 (9)
2015-2016	292 (11)	45 (11)	225 (16)	104 (7)
2017-2018	573 (22)	82 (20)	106 (7)	172 (12)
2019-2020	712 (28)	35 (8)	92 (6)	143 (10)
2021	279 (11)	0 (0)	44 (3)	82 (6)

Characteristics of recipients undergoing allogeneic HCT for myelofibrosis reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (Excluding CRF) / US	TED (Excluding CRF) / non-US
No. of patients	2583	415	1437	1475
No. of centers	134	92	136	170
Age, median (range) - median (min-max)	61 (1-79)	54 (2-74)	58 (0-79)	56 (2-75)
Age, years - no. (%)				
< 10	11 (0)	3 (1)	16 (1)	12 (1)
10-19	12 (0)	7 (2)	11 (1)	25 (2)
20-29	12 (0)	11 (3)	20 (1)	35 (2)
30-39	60 (2)	26 (6)	52 (4)	111 (8)
40-49	299 (12)	98 (24)	212 (15)	271 (18)
50-59	784 (30)	156 (38)	529 (37)	537 (36)
60-69	1143 (44)	111 (27)	537 (37)	456 (31)
>= 70	262 (10)	3 (1)	60 (4)	28 (2)
Sex - no. (%)				
Male	1491 (58)	268 (65)	860 (60)	920 (62)
Female	1092 (42)	147 (35)	577 (40)	555 (38)
Disease at diagnosis - no. (%)				
Polycythemia vera (PV)	345 (13)	46 (11)	186 (13)	125 (8)
Essential or primary thrombocythemia (ET)	425 (16)	46 (11)	207 (14)	172 (12)
Chronic myelofibrosis	1813 (70)	323 (78)	1044 (73)	1178 (80)
Graft source - no. (%)				
Bone marrow	208 (8)	83 (20)	135 (9)	201 (14)
Peripheral blood	2309 (89)	323 (78)	1276 (89)	1253 (85)
Cord blood	54 (2)	9 (2)	17 (1)	10 (1)
Missing	12 (0)	0 (0)	9 (1)	11 (1)
Donor type - no. (%)				
HLA-identical sibling	628 (24)	165 (40)	611 (43)	634 (43)
Haplo	240 (9)	18 (4)	60 (4)	34 (2)
Unrelated donor	1592 (62)	200 (48)	678 (47)	732 (50)
Cord blood	54 (2)	9 (2)	17 (1)	10 (1)
Other/missing	69 (3)	23 (6)	71 (5)	65 (4)
Year of transplant - no. (%)				

Characteristic	CRF / US	CRF / non-US	TED (Excluding CRF) / US	TED (Excluding CRF) / non-US
1995-1996	15 (1)	8 (2)	11 (1)	19 (1)
1997-1998	22 (1)	11 (3)	13 (1)	36 (2)
1999-2000	30 (1)	22 (5)	18 (1)	44 (3)
2001-2002	52 (2)	21 (5)	33 (2)	81 (5)
2003-2004	54 (2)	30 (7)	45 (3)	99 (7)
2005-2006	75 (3)	43 (10)	76 (5)	100 (7)
2007-2008	124 (5)	38 (9)	73 (5)	116 (8)
2009-2010	126 (5)	30 (7)	172 (12)	188 (13)
2011-2012	38 (1)	5 (1)	302 (21)	159 (11)
2013-2014	191 (7)	45 (11)	227 (16)	132 (9)
2015-2016	292 (11)	45 (11)	225 (16)	104 (7)
2017-2018	573 (22)	82 (20)	106 (7)	172 (12)
2019-2020	712 (28)	35 (8)	92 (6)	143 (10)
2021	279 (11)	0 (0)	44 (3)	82 (6)

Characteristics of recipients undergoing allogeneic HCT for CML reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
No. of patients	4086	2952	4799	8628
No. of centers	179	195	204	284
Age, median (range) - median (min-max)	40 (1-77)	36 (1-76)	43 (0-76)	37 (0-75)
Age, years - no. (%)				
< 10	85 (2)	70 (2)	72 (2)	200 (2)
10-19	366 (9)	309 (10)	299 (6)	682 (8)
20-29	581 (14)	619 (21)	558 (12)	1707 (20)
30-39	1008 (25)	880 (30)	1082 (23)	2542 (29)
40-49	1164 (28)	700 (24)	1368 (29)	2303 (27)
50-59	714 (17)	319 (11)	999 (21)	1018 (12)
60-69	151 (4)	53 (2)	379 (8)	165 (2)
>= 70	17 (0)	1 (0)	33 (1)	4 (0)
Missing	0 (0)	1 (0)	9 (0)	7 (0)
Sex - no. (%)				
Male	2385 (58)	1807 (61)	2827 (59)	5174 (60)
Female	1701 (42)	1145 (39)	1965 (41)	3417 (40)
Missing	0 (0)	0 (0)	7 (0)	37 (0)
Graft source - no. (%)				
Bone marrow	2541 (62)	1705 (58)	2066 (43)	4688 (54)
Peripheral blood	1359 (33)	1168 (40)	2500 (52)	3533 (41)
Cord blood	184 (5)	74 (3)	148 (3)	105 (1)
Missing	2 (0)	5 (0)	85 (2)	302 (4)
Donor type - no. (%)				
HLA-identical sibling	869 (21)	1613 (55)	2674 (56)	5503 (64)
Haplo	76 (2)	18 (1)	211 (4)	44 (1)
Unrelated donor	2807 (69)	967 (33)	1290 (27)	2431 (28)
Cord blood	184 (5)	74 (3)	148 (3)	105 (1)
Other/missing	150 (4)	280 (9)	476 (10)	545 (6)
Year of transplant - no. (%)				
1995-1996	705 (17)	498 (17)	641 (13)	1344 (16)
1997-1998	749 (18)	546 (18)	712 (15)	1742 (20)

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
1999-2000	667 (16)	629 (21)	601 (13)	1775 (21)
2001-2002	351 (9)	391 (13)	276 (6)	1204 (14)
2003-2004	407 (10)	370 (13)	250 (5)	742 (9)
2005-2006	317 (8)	270 (9)	172 (4)	428 (5)
2007-2008	233 (6)	54 (2)	129 (3)	215 (2)
2009-2010	240 (6)	54 (2)	158 (3)	273 (3)
2011-2012	51 (1)	14 (0)	382 (8)	259 (3)
2013-2014	126 (3)	43 (1)	321 (7)	163 (2)
2015-2016	114 (3)	40 (1)	324 (7)	112 (1)
2017-2018	68 (2)	23 (1)	332 (7)	128 (1)
2019-2020	50 (1)	18 (1)	357 (7)	162 (2)
2021	8 (0)	2 (0)	144 (3)	81 (1)

Characteristics of recipients undergoing allogeneic HCT for CLL reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
No. of patients	1483	390	1939	1482
No. of centers	125	85	136	150
Age, median (range) - median (min-max)	55 (12-75)	53 (2-71)	57 (7-80)	54 (4-75)
Age, years - no. (%)				
< 10	0 (0)	1 (0)	2 (0)	3 (0)
10-19	3 (0)	1 (0)	2 (0)	0 (0)
20-29	11 (1)	1 (0)	15 (1)	22 (1)
30-39	63 (4)	34 (9)	83 (4)	78 (5)
40-49	331 (22)	101 (26)	355 (18)	387 (26)
50-59	639 (43)	166 (43)	841 (43)	675 (46)
60-69	400 (27)	84 (22)	586 (30)	304 (21)
>= 70	36 (2)	2 (1)	55 (3)	13 (1)
Sex - no. (%)				
Male	1099 (74)	285 (73)	1405 (72)	1077 (73)
Female	383 (26)	105 (27)	533 (27)	403 (27)
Missing	1 (0)	0 (0)	1 (0)	2 (0)
Disease at diagnosis - no. (%)				
Chronic lymphocytic leukemia, NOS	700 (47)	130 (33)	574 (30)	627 (42)
Chronic lymphocytic leukemia, B-cell	779 (53)	260 (67)	1354 (70)	849 (57)
Chronic lymphocytic leukemia, T-cell	4 (0)	0 (0)	11 (1)	6 (0)
Graft source - no. (%)				
Bone marrow	299 (20)	60 (15)	259 (13)	163 (11)
Peripheral blood	1099 (74)	316 (81)	1640 (85)	1267 (85)
Cord blood	84 (6)	13 (3)	33 (2)	17 (1)
Missing	1 (0)	1 (0)	7 (0)	35 (2)
Donor type - no. (%)				
HLA-identical sibling	409 (28)	221 (57)	972 (50)	801 (54)
Haplo	50 (3)	4 (1)	77 (4)	6 (0)
Unrelated donor	880 (59)	138 (35)	737 (38)	587 (40)
Cord blood	84 (6)	13 (3)	33 (2)	17 (1)
Other/missing	60 (4)	14 (4)	120 (6)	71 (5)

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
Year of transplant - no. (%)				
1995-1996	61 (4)	29 (7)	46 (2)	34 (2)
1997-1998	56 (4)	22 (6)	63 (3)	41 (3)
1999-2000	83 (6)	36 (9)	87 (4)	101 (7)
2001-2002	107 (7)	44 (11)	123 (6)	163 (11)
2003-2004	174 (12)	49 (13)	120 (6)	164 (11)
2005-2006	208 (14)	55 (14)	163 (8)	184 (12)
2007-2008	253 (17)	32 (8)	174 (9)	147 (10)
2009-2010	112 (8)	24 (6)	383 (20)	186 (13)
2011-2012	55 (4)	14 (4)	413 (21)	233 (16)
2013-2014	174 (12)	46 (12)	151 (8)	103 (7)
2015-2016	94 (6)	20 (5)	58 (3)	41 (3)
2017-2018	86 (6)	16 (4)	75 (4)	34 (2)
2019-2020	17 (1)	2 (1)	56 (3)	35 (2)
2021	3 (0)	1 (0)	27 (1)	16 (1)

Characteristics of recipients undergoing autologous HCT for CLL reported to the CIBMTR between 1995 and 2021

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
No. of patients	84	41	271	244
No. of centers	42	14	65	58
Age, median (range) - median (min-max)	52 (33-73)	50 (38-67)	53 (19-81)	52 (27-72)
Age, years - no. (%)				
10-19	0 (0)	0 (0)	1 (0)	0 (0)
20-29	0 (0)	0 (0)	2 (1)	4 (2)
30-39	12 (14)	3 (7)	14 (5)	12 (5)
40-49	25 (30)	18 (44)	80 (30)	76 (31)
50-59	26 (31)	18 (44)	112 (41)	114 (47)
60-69	19 (23)	2 (5)	57 (21)	37 (15)
>= 70	2 (2)	0 (0)	5 (2)	1 (0)
Sex - no. (%)				
Male	61 (73)	33 (80)	189 (70)	194 (80)
Female	23 (27)	8 (20)	82 (30)	49 (20)
Missing	0 (0)	0 (0)	0 (0)	1 (0)
Disease at diagnosis - no. (%)				
Chronic lymphocytic leukemia, NOS	21 (25)	24 (59)	85 (31)	48 (20)
Chronic lymphocytic leukemia, B-cell	62 (74)	17 (41)	181 (67)	195 (80)
Chronic lymphocytic leukemia, T-cell	1 (1)	0 (0)	5 (2)	1 (0)
Graft source - no. (%)				
Bone marrow	15 (18)	1 (2)	113 (42)	5 (2)
Peripheral blood	66 (79)	39 (95)	152 (56)	208 (85)
Missing	3 (4)	1 (2)	6 (2)	31 (13)
Year of transplant - no. (%)				
1995-1996	15 (18)	3 (7)	43 (16)	14 (6)
1997-1998	26 (31)	28 (68)	54 (20)	36 (15)
1999-2000	18 (21)	6 (15)	72 (27)	90 (37)
2001-2002	6 (7)	2 (5)	36 (13)	40 (16)
2003-2004	4 (5)	1 (2)	27 (10)	22 (9)
2005-2006	9 (11)	0 (0)	6 (2)	23 (9)
2007-2008	3 (4)	0 (0)	5 (2)	4 (2)

Characteristic	CRF / US	CRF / non-US	TED (excluding CRF) / US	TED (excluding CRF) / non-US
2009-2010	2 (2)	0 (0)	4 (1)	8 (3)
2011-2012	0 (0)	0 (0)	9 (3)	5 (2)
2013-2014	1 (1)	0 (0)	5 (2)	1 (0)
2015-2016	0 (0)	1 (2)	2 (1)	0 (0)
2017-2018	0 (0)	0 (0)	4 (1)	1 (0)
2019-2020	0 (0)	0 (0)	2 (1)	0 (0)
2021	0 (0)	0 (0)	2 (1)	0 (0)

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, 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	12610	4731	2220
Source of data			
CRF	8350 (66)	2694 (57)	1323 (60)
TED	4260 (34)	2037 (43)	897 (40)
Number of centers	234	197	268
Disease at transplant			
Other leukemia	1408 (11)	385 (8)	249 (11)
CML	3509 (28)	1045 (22)	695 (31)
MDS	6346 (50)	2568 (54)	1072 (48)
MPN	1347 (11)	733 (15)	204 (9)
MDS Disease status at transplant			
Early	1380 (22)	488 (19)	256 (24)
Advanced	4003 (63)	1854 (72)	592 (55)
Missing	963 (15)	226 (9)	224 (21)
Recipient age at transplant			
0-9 years	417 (3)	96 (2)	104 (5)
10-19 years	556 (4)	165 (3)	159 (7)
20-29 years	844 (7)	229 (5)	192 (9)
30-39 years	1432 (11)	404 (9)	257 (12)
40-49 years	2098 (17)	637 (13)	405 (18)
50-59 years	3027 (24)	1054 (22)	500 (23)
60-69 years	3444 (27)	1637 (35)	497 (22)
70+ years	792 (6)	509 (11)	106 (5)
Median (Range)	53 (0-83)	58 (1-79)	50 (1-81)
Recipient race/ethnicity			
Caucasian, non-Hispanic	10951 (87)	4125 (87)	1680 (76)
African-American, non-Hispanic	539 (4)	158 (3)	96 (4)
Asian, non-Hispanic	216 (2)	113 (2)	72 (3)
Pacific islander, non-Hispanic	15 (<1)	10 (<1)	6 (<1)
Native American, non-Hispanic	37 (<1)	18 (<1)	8 (<1)
Hispanic	446 (4)	156 (3)	66 (3)
Missing	406 (3)	151 (3)	292 (13)
Recipient sex			
Male	7698 (61)	2929 (62)	1344 (61)
Female	4912 (39)	1802 (38)	876 (39)
Karnofsky score			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
10-80	4353 (35)	1815 (38)	684 (31)
90-100	7817 (62)	2787 (59)	1401 (63)
Missing	440 (3)	129 (3)	135 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	5 (<1)	7 (<1)	1 (<1)
4/6	93 (1)	34 (1)	12 (1)
5/6	1620 (13)	476 (11)	293 (14)
6/6	10670 (86)	3793 (88)	1726 (85)
Unknown	222 (N/A)	421 (N/A)	188 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	319 (3)	23 (1)	8 (1)
6/8	520 (4)	28 (1)	37 (3)
7/8	2218 (18)	436 (13)	251 (18)
8/8	9036 (75)	2815 (85)	1065 (78)
Unknown	517 (N/A)	1429 (N/A)	859 (N/A)
HLA-DPB1 Match			
Double allele mismatch	3092 (29)	358 (21)	138 (24)
Single allele mismatch	5778 (54)	901 (52)	294 (52)
Full allele matched	1771 (17)	467 (27)	132 (23)
Unknown	1969 (N/A)	3005 (N/A)	1656 (N/A)
High resolution release score			
No	2333 (19)	4701 (99)	2174 (98)
Yes	10277 (81)	30 (1)	46 (2)
KIR typing available			
No	9265 (73)	4720 (>99)	2211 (>99)
Yes	3345 (27)	11 (<1)	9 (<1)
Graft type			
Marrow	4495 (36)	1322 (28)	872 (39)
PBSC	8099 (64)	3372 (71)	1329 (60)
BM+PBSC	3 (<1)	0	1 (<1)
PBSC+UCB	6 (<1)	36 (1)	1 (<1)
Others	7 (<1)	1 (<1)	17 (1)
Conditioning regimen			
Myeloablative	7515 (60)	2372 (50)	1351 (61)
RIC/Nonmyeloablative	5057 (40)	2347 (50)	837 (38)
TBD	38 (<1)	12 (<1)	32 (1)
Donor age at donation			
To Be Determined/NA	102 (1)	341 (7)	29 (1)
0-9 years	0	10 (<1)	2 (<1)
10-19 years	320 (3)	160 (3)	40 (2)
20-29 years	5515 (44)	2165 (46)	850 (38)
30-39 years	3717 (29)	1198 (25)	687 (31)
40-49 years	2252 (18)	641 (14)	465 (21)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
50+ years	704 (6)	216 (5)	147 (7)
Median (Range)	31 (13-62)	29 (1-109)	33 (0-60)
Donor/Recipient CMV serostatus			
+/+	2953 (23)	1210 (26)	543 (24)
+/-	1593 (13)	673 (14)	265 (12)
-/+	3891 (31)	1292 (27)	660 (30)
-/-	4034 (32)	1456 (31)	640 (29)
CB - recipient +	0	5 (<1)	0
CB - recipient -	1 (<1)	2 (<1)	0
Missing	138 (1)	93 (2)	112 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	31 (<1)	17 (<1)	11 (<1)
TDEPLETION alone	22 (<1)	9 (<1)	3 (<1)
TDEPLETION +- other	263 (2)	65 (1)	54 (2)
CD34 select alone	60 (<1)	34 (1)	17 (1)
CD34 select +- other	248 (2)	189 (4)	35 (2)
Cyclophosphamide alone	219 (2)	198 (4)	66 (3)
Cyclophosphamide +- others	591 (5)	425 (9)	110 (5)
FK506 + MMF +- others	1463 (12)	438 (9)	185 (8)
FK506 + MTX +- others(not MMF)	5151 (41)	1952 (41)	619 (28)
FK506 +- others(not MMF,MTX)	633 (5)	304 (6)	73 (3)
FK506 alone	240 (2)	80 (2)	32 (1)
CSA + MMF +- others(not FK506)	719 (6)	194 (4)	164 (7)
CSA + MTX +- others(not MMF,FK506)	2333 (19)	625 (13)	665 (30)
CSA +- others(not FK506,MMF,MTX)	263 (2)	73 (2)	75 (3)
CSA alone	103 (1)	30 (1)	63 (3)
Other GVHD Prophylaxis	216 (2)	69 (1)	24 (1)
Missing	55 (<1)	29 (1)	24 (1)
Donor/Recipient sex match			
Male-Male	5429 (43)	1995 (42)	926 (42)
Male-Female	2900 (23)	1042 (22)	471 (21)
Female-Male	2201 (17)	823 (17)	400 (18)
Female-Female	1975 (16)	683 (14)	390 (18)
CB - recipient M	4 (<1)	26 (1)	0
CB - recipient F	2 (<1)	11 (<1)	1 (<1)
Missing	99 (1)	151 (3)	32 (1)
Year of transplant			
1986-1990	193 (2)	26 (1)	21 (1)
1991-1995	912 (7)	199 (4)	213 (10)
1996-2000	1358 (11)	527 (11)	261 (12)
2001-2005	1349 (11)	250 (5)	395 (18)
2006-2010	2261 (18)	455 (10)	321 (14)
2011-2015	3377 (27)	918 (19)	412 (19)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2016-2020	2875 (23)	2075 (44)	535 (24)
2021	285 (2)	281 (6)	62 (3)
Follow-up among survivors, Months			
N Eval	4848	2156	871
Median (Range)	69 (0-385)	35 (0-339)	48 (0-362)

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	790	229	198
Source of data			
CRF	605 (77)	173 (76)	118 (60)
TED	185 (23)	56 (24)	80 (40)
Number of centers	120	75	97
Disease at transplant			
Other leukemia	93 (12)	30 (13)	27 (14)
CML	128 (16)	35 (15)	38 (19)
MDS	523 (66)	151 (66)	119 (60)
MPN	46 (6)	13 (6)	14 (7)
MDS Disease status at transplant			
Early	163 (31)	41 (27)	52 (44)
Advanced	315 (60)	95 (63)	48 (40)
Missing	45 (9)	15 (10)	19 (16)
Recipient age at transplant			
0-9 years	115 (15)	36 (16)	45 (23)
10-19 years	75 (9)	17 (7)	22 (11)
20-29 years	55 (7)	9 (4)	14 (7)
30-39 years	75 (9)	22 (10)	19 (10)
40-49 years	111 (14)	28 (12)	25 (13)
50-59 years	163 (21)	50 (22)	40 (20)
60-69 years	161 (20)	56 (24)	31 (16)
70+ years	35 (4)	11 (5)	2 (1)
Median (Range)	47 (0-80)	50 (1-76)	39 (0-73)
Recipient race/ethnicity			
Caucasian, non-Hispanic	473 (60)	157 (69)	120 (61)
African-American, non-Hispanic	131 (17)	27 (12)	25 (13)
Asian, non-Hispanic	50 (6)	17 (7)	17 (9)
Pacific islander, non-Hispanic	7 (1)	0	2 (1)
Native American, non-Hispanic	3 (<1)	1 (<1)	2 (1)
Hispanic	98 (12)	24 (10)	12 (6)
Missing	28 (4)	3 (1)	20 (10)
Recipient sex			
Male	467 (59)	135 (59)	109 (55)
Female	323 (41)	94 (41)	89 (45)
Karnofsky score			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
10-80	202 (26)	70 (31)	56 (28)
90-100	571 (72)	146 (64)	126 (64)
Missing	17 (2)	13 (6)	16 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	13 (2)	5 (3)	1 (1)
4/6	343 (45)	100 (51)	100 (55)
5/6	329 (43)	78 (40)	74 (41)
6/6	78 (10)	12 (6)	7 (4)
Unknown	27 (N/A)	34 (N/A)	16 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	410 (62)	87 (63)	101 (68)
6/8	153 (23)	31 (22)	34 (23)
7/8	71 (11)	18 (13)	11 (7)
8/8	29 (4)	3 (2)	3 (2)
Unknown	127 (N/A)	90 (N/A)	49 (N/A)
HLA-DPB1 Match			
Double allele mismatch	125 (46)	12 (44)	10 (32)
Single allele mismatch	126 (46)	11 (41)	18 (58)
Full allele matched	20 (7)	4 (15)	3 (10)
Unknown	519 (N/A)	202 (N/A)	167 (N/A)
High resolution release score			
No	599 (76)	223 (97)	196 (99)
Yes	191 (24)	6 (3)	2 (1)
KIR typing available			
No	632 (80)	229 (100)	197 (99)
Yes	158 (20)	0	1 (1)
Graft type			
UCB	730 (92)	193 (84)	186 (94)
PBSC+UCB	59 (7)	36 (16)	12 (6)
Others	1 (<1)	0	0
Number of cord units			
1	636 (81)	0	163 (82)
2	152 (19)	0	35 (18)
Unknown	2 (N/A)	229 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	438 (55)	119 (52)	112 (57)
RIC/Nonmyeloablative	352 (45)	109 (48)	86 (43)
TBD	0	1 (<1)	0
Donor age at donation			
To Be Determined/NA	29 (4)	11 (5)	15 (8)
0-9 years	688 (87)	176 (77)	172 (87)
10-19 years	43 (5)	18 (8)	4 (2)
20-29 years	11 (1)	8 (3)	1 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
30-39 years	9 (1)	6 (3)	2 (1)
40-49 years	6 (1)	4 (2)	0
50+ years	4 (1)	6 (3)	4 (2)
Median (Range)	3 (0-64)	4 (0-72)	3 (0-69)
Donor/Recipient CMV serostatus			
+/+	170 (22)	38 (17)	46 (23)
+/-	96 (12)	13 (6)	17 (9)
-/+	157 (20)	56 (24)	29 (15)
-/-	101 (13)	29 (13)	23 (12)
CB - recipient +	144 (18)	50 (22)	42 (21)
CB - recipient -	116 (15)	35 (15)	32 (16)
CB - recipient CMV unknown	6 (1)	8 (3)	9 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	2 (<1)	0	1 (1)
TDEPLETION +- other	1 (<1)	1 (<1)	0
CD34 select +- other	53 (7)	31 (14)	11 (6)
Cyclophosphamide alone	0	0	1 (1)
Cyclophosphamide +- others	2 (<1)	3 (1)	10 (5)
FK506 + MMF +- others	238 (30)	68 (30)	32 (16)
FK506 + MTX +- others(not MMF)	27 (3)	4 (2)	9 (5)
FK506 +- others(not MMF,MTX)	32 (4)	11 (5)	10 (5)
FK506 alone	24 (3)	9 (4)	4 (2)
CSA + MMF +- others(not FK506)	335 (42)	79 (34)	84 (42)
CSA + MTX +- others(not MMF,FK506)	8 (1)	3 (1)	4 (2)
CSA +- others(not FK506,MMF,MTX)	26 (3)	12 (5)	23 (12)
CSA alone	9 (1)	1 (<1)	5 (3)
Other GVHD Prophylaxis	33 (4)	7 (3)	4 (2)
Donor/Recipient sex match			
CB - recipient M	467 (59)	135 (59)	109 (55)
CB - recipient F	323 (41)	94 (41)	89 (45)
Year of transplant			
1996-2000	0	0	1 (1)
2001-2005	18 (2)	11 (5)	2 (1)
2006-2010	242 (31)	67 (29)	69 (35)
2011-2015	353 (45)	72 (31)	80 (40)
2016-2020	169 (21)	78 (34)	43 (22)
2021	8 (1)	1 (<1)	3 (2)
Follow-up among survivors, Months			
N Eval	304	109	96
Median (Range)	68 (3-170)	49 (3-202)	60 (1-188)

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	2173	319	153
Source of data			
CRF	1043 (48)	131 (41)	80 (52)
TED	1130 (52)	188 (59)	73 (48)
Number of centers	73	44	34
Disease at transplant			
Other leukemia	189 (9)	35 (11)	14 (9)
CML	314 (14)	36 (11)	20 (13)
MDS	1277 (59)	191 (60)	92 (60)
MPN	393 (18)	57 (18)	27 (18)
MDS Disease status at transplant			
Early	209 (16)	26 (14)	18 (20)
Advanced	1026 (80)	154 (81)	69 (75)
Missing	42 (3)	11 (6)	5 (5)
Recipient age at transplant			
0-9 years	47 (2)	10 (3)	2 (1)
10-19 years	81 (4)	4 (1)	2 (1)
20-29 years	64 (3)	14 (4)	3 (2)
30-39 years	101 (5)	17 (5)	8 (5)
40-49 years	249 (11)	23 (7)	15 (10)
50-59 years	617 (28)	91 (29)	37 (24)
60-69 years	839 (39)	140 (44)	75 (49)
70+ years	175 (8)	20 (6)	11 (7)
Median (Range)	59 (1-78)	60 (1-76)	62 (2-74)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1588 (73)	205 (64)	121 (79)
African-American, non-Hispanic	188 (9)	34 (11)	9 (6)
Asian, non-Hispanic	89 (4)	17 (5)	4 (3)
Pacific islander, non-Hispanic	9 (<1)	1 (<1)	0
Native American, non-Hispanic	6 (<1)	2 (1)	1 (1)
Hispanic	221 (10)	47 (15)	16 (10)
Missing	72 (3)	13 (4)	2 (1)
Recipient sex			
Male	1310 (60)	202 (63)	102 (67)
Female	863 (40)	117 (37)	51 (33)
Karnofsky score			
10-80	914 (42)	154 (48)	87 (57)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
90-100	1216 (56)	155 (49)	59 (39)
Missing	43 (2)	10 (3)	7 (5)
Graft type			
Marrow	346 (16)	38 (12)	28 (18)
PBSC	1811 (83)	278 (87)	124 (81)
UCB (related)	0	1 (<1)	0
BM+PBSC	5 (<1)	0	0
BM+UCB	0	1 (<1)	0
PBSC+UCB	0	0	1 (1)
Others	11 (1)	1 (<1)	0
Conditioning regimen			
Myeloablative	1029 (47)	146 (46)	58 (38)
RIC/Nonmyeloablative	1142 (53)	172 (54)	94 (61)
TBD	2 (<1)	1 (<1)	1 (1)
Donor age at donation			
To Be Determined/NA	3 (<1)	2 (1)	0
0-9 years	30 (1)	6 (2)	2 (1)
10-19 years	87 (4)	13 (4)	5 (3)
20-29 years	199 (9)	26 (8)	21 (14)
30-39 years	271 (12)	45 (14)	26 (17)
40-49 years	394 (18)	47 (15)	23 (15)
50+ years	1189 (55)	180 (56)	76 (50)
Median (Range)	52 (0-82)	52 (0-76)	50 (8-73)
Donor/Recipient CMV serostatus			
+/+	855 (39)	138 (43)	47 (31)
+/-	273 (13)	20 (6)	15 (10)
-/+	504 (23)	82 (26)	42 (27)
-/-	517 (24)	73 (23)	47 (31)
CB - recipient +	0	1 (<1)	0
Missing	24 (1)	5 (2)	2 (1)
GvHD Prophylaxis			
No GvHD Prophylaxis	8 (<1)	0	0
TDEPLETION alone	4 (<1)	3 (1)	2 (1)
TDEPLETION +- other	6 (<1)	1 (<1)	1 (1)
CD34 select alone	6 (<1)	7 (2)	0
CD34 select +- other	86 (4)	17 (5)	16 (10)
Cyclophosphamide alone	62 (3)	11 (3)	6 (4)
Cyclophosphamide +- others	599 (28)	71 (22)	44 (29)
FK506 + MMF +- others	164 (8)	14 (4)	1 (1)
FK506 + MTX +- others(not MMF)	849 (39)	127 (40)	67 (44)
FK506 +- others(not MMF,MTX)	185 (9)	40 (13)	12 (8)
FK506 alone	14 (1)	3 (1)	0
CSA + MMF +- others(not FK506)	36 (2)	6 (2)	1 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CSA + MTX +- others(not MMF,FK506)	103 (5)	12 (4)	1 (1)
CSA +- others(not FK506,MMF,MTX)	1 (<1)	1 (<1)	0
CSA alone	9 (<1)	0	1 (1)
Other GVHD Prophylaxis	25 (1)	0	1 (1)
Missing	16 (1)	6 (2)	0
Donor/Recipient sex match			
Male-Male	743 (34)	116 (36)	59 (39)
Male-Female	451 (21)	56 (18)	29 (19)
Female-Male	564 (26)	83 (26)	42 (27)
Female-Female	411 (19)	60 (19)	22 (14)
CB - recipient M	0	1 (<1)	1 (1)
CB - recipient F	0	1 (<1)	0
Missing	4 (<1)	2 (1)	0
Year of transplant			
2006-2010	147 (7)	21 (7)	9 (6)
2011-2015	804 (37)	92 (29)	39 (25)
2016-2020	1108 (51)	181 (57)	87 (57)
2021	114 (5)	25 (8)	18 (12)
Follow-up among survivors, Months			
N Eval	1143	156	78
Median (Range)	37 (1-150)	25 (0-124)	25 (2-120)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Chronic Leukemia Working Committee Members

FROM: Wael Saber, MD, MS; Scientific Director for the Chronic Leukemia Working Committee

RE: 2020-2021 Studies in Progress Summary

CK16-01 Identification of germline predisposition mutations in young myelodysplastic syndrome patients. (L Godley) The primary aims of the study are: 1) to determine the frequency of germline variants in candidate genes in a cohort of paired samples derived from patients with myelodysplastic syndromes and their HLA-matched related donors; 2) to compare clinical/mobilization characteristics in related donors with a germline mutation versus related donors without germline mutations; 3) to compare engraftment parameters in MDS patients with germline deleterious mutations who underwent HCT from HLA-matched related donors who shared the germline variant versus those who do not share the variant. The manuscript has been submitted and is under review. The goal of this study is to have the manuscript submitted by June 2022.

CK17-01 Development of a prognostic scoring system predictive of outcomes in patients with myelofibrosis after allogeneic hematopoietic cell transplantation. (T Roni/SA Giralt/J Palmer) The primary objective of the study is to identify patient-, disease-, and transplant-specific factors that positively associate with overall survival after allo-HCT for patients with myelofibrosis; the secondary objective is to develop a scoring system prognostic of OS post allo-HCT; the third objective is to validate the scoring system in an independent dataset. This study is in collaboration with the EBMT. The PI is currently working on the manuscript preparation. The goal of this study is to have the manuscript submitted by June 2022.

CK18-02 The impact of somatic mutations on allogeneic transplant in chronic myelomonocytic leukemia. (M Mei/ R Nakamura/ R Pillai) The primary aims of this study are: 1) determine the impact of somatic mutations and copy numbers variants on outcomes after allo-HCT in patients with CMML; 2) determine if the CPSS-Mol score correlates with outcomes after allo-HCT in patients with CMML to improve the scoring system for allo-HCT recipients with broader mutation analyses. The manuscript has been accepted in Haematologica. The goal of this study was to publish by June 2022.

CK19-01A Outcomes after HCT for rare chronic leukemias: Evaluating outcomes of Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemias (H Murthy/B Dholaria/M Kharfan/ S Bal/C Sauter/ L Gowda/F Foss/M Kalaycio/H Alkhateeb) The primary objectives of this study are to describe clinical outcomes of patients with T-cell prolymphocytic leukemia undergoing allo-HCT which includes 1) calculate the overall survival 2) estimate Progression Free Survival 3) estimate the cumulative incidence of non-relapse mortality 4) calculate the cumulative incidence of acute graft versus host disease (aGVHD) 5) calculate the cumulative incidence of chronic graft versus host disease (aGVHD)

and estimate the cumulative incidence of relapse. Also identify the impact of patient-, disease-, and transplant-related factors on the outcomes. The manuscript has been published in TCT. The goal of this study was to publish by June 2022.

CK19-01B Outcomes after HCT for rare chronic leukemias: Outcomes of chronic neutrophilic leukemia patients who underwent allogeneic hematopoietic cell transplantation. (B Dholaria/B Savani/M Kharfan) The primary objectives of this study are to describe clinical outcomes of patients with chronic neutrophilic leukemia undergoing first allo-HCT reported to the CIBMTR and EBMT. For this purpose of this study, we will calculate: the overall survival, leukemia free survival and relapse of the patients. This will may provide the largest experience of using allo-HCT in CNL and potentially define the curative role of allo-HCT for this disease. This study is in collaboration with the EBMT. The manuscript has been submitted and is currently under review. The goal of this study is to have the manuscript submitted by June 2022.

CK20-01 Outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis based on the conditioning regimen. (G Murthy/ W Saber) The primary objectives of this study are to determine clinical outcomes based on the choice of conditioning regimen used in MAC and RIC setting, for patients with MF undergoing allo-HCT for: overall survival (OS), disease free survival (DFS), non-relapse mortality (NRM), relapse, incidence of graft failure, incidence of acute graft versus host disease (GVHD), incidence of Chronic GVHD and GRFS. The manuscript has been submitted and is currently under review. The goal of this study is to have the manuscript submitted by June 2022.

CK21-01 Outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis based on the conditioning regimen. (Tania Jain/ M Queralt Sala/V Gupta/ T Nishihori) The objectives of this study are to explore the impact of donor type on overall survival of patient undergoing BMT for myelofibrosis. Also, we will compare clinical outcomes i.e. non-relapse mortality, cumulative incidence of relapse, acute GVHD, chronic GVHD, time to engraftment and primary graft failure between haploidentical donor, matched sibling donor (MSD), matched unrelated donor (MUD) and mismatched unrelated donors (MMUD). This study is currently on data file preparation stage. The goal of this study is to have the manuscript submitted by June 2022.

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Allogeneic Hematopoietic Cell Transplantation (HCT) for the Treatment of Myelodysplastic Syndromes (MDS) in Younger Adults

Q2. Key Words

MDS AYA HCT

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Antonio M. Jimenez Jimenez
Email address:	amjimenez@med.miami.edu
Institution name:	University of Miami
Academic rank:	Assistant Professor

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

- No

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Trent P Wang
Email address:	trentwang@med.miami.edu
Institution name:	University of Miami
Academic rank:	Assistant Professor

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

- Yes

Q8. Do you identify as an underrepresented/minority?

- No

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

Antonio M. Jimenez Jimenez

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Chronic Leukemia

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

- No

Q15. RESEARCH QUESTION:

What are the clinical outcomes of young patients with MDS who receive allogeneic HCT consolidation, and which prognostic factors can affect HCT outcomes in this cohort?

Q16. RESEARCH HYPOTHESIS:

Consolidation with allogeneic Hematopoietic Cell Transplant (HCT) is an effective strategy for the treatment of Myelodysplastic Syndromes (MDS) in young patients

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

Suggested word limit of 200 words:

Specific Aims:
We propose to evaluate the clinical outcomes following allogeneic HCT in younger MDS patients (i.e., <60 years at the time of HCT). To achieve this objective, we will:
AIM 1. Describe clinical features and outcomes (overall survival, relapse-free survival, GVHF-free, relapse-free survival, non-relapse mortality, and cumulative incidence of relapse) in younger patients with MDS receiving allogeneic HCT consolidation
AIM 2. Evaluate differences in transplant outcomes (overall survival, relapse-free survival, cumulative incidence of relapse, cumulative incidence of non-relapse mortality and cumulative incidence of acute and chronic GVHD) between sub-cohorts stratified on the basis of IPSS-R categories, age (AYA: 16-39, 40-49, 50-59) conditioning regimen, graft/donor source and HCT-CI.
Study Outcomes:
Primary Outcome:
• 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.
Secondary Outcomes:
• Relapse-free survival (RFS): will be defined as time to relapse or death from any cause. Patients are censored at last follow-up
• GVHD-free, relapse-free survival (GRFS): will be defined as time to development of grade 3-4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death from any cause. Patients are censored at last follow-up
• Non-relapse mortality (NRM): Cumulative incidence of NRM. NRM is defined as death without preceding disease relapse/progression. Relapse is competing event.
• Relapse/Progression: Cumulative incidence of disease relapse/progression, with NRM as 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.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

Allogeneic hematopoietic cell transplantation remains the only curative treatment strategy for patients with MDS. Given disease epidemiology, available data demonstrating the effectiveness of allogeneic HCT in the treatment of MDS in young patients is very limited. Thus, we aim to investigate the clinical outcomes of young patients with MDS who received allogeneic HCT consolidation and estimate prognostic factors for HCT outcomes in this cohort.
Completion of these aims and data obtained from this analysis will inform clinicians (and patients) on the impact of HCT consolidation in this group.

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

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders, characterized by ineffective hematopoiesis, resulting in peripheral cytopenias and a variable risk of progression to acute myeloid leukemia (AML) or overt marrow failure. MDS is the most common myeloid malignancy in the United States, and remains primarily a disease of the elderly with a median age at diagnosis of 71 years and a marked increase in incidence after the sixth decade of life: the incidence rate is 0.22/100 000 in those younger than 49 years, 4.8/100 000 between the ages of 50 and 70 years, and 22.8/100 000 in those older than 70 years

MDS can sporadically affect younger adults and occurs rarely in the pediatric population. Available data suggests that MDS in pediatric and AYA patients may be associated with distinct pathophysiologic and molecular features. Other studies suggest despite age-related differences in molecular features, younger patients with MDS likely belong to a disease continuum with distinct early ancestral events. This study did not include therapy-related MDS diagnoses. Allogeneic hematopoietic cell transplantation (HCT) remains the only curative treatment option for patients with MDS - including pediatric and younger adults. However, there is limited data describing the clinical outcomes of younger MDS patients who proceeded to HCT consolidation. A retrospective study from the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) reported clinical outcomes in 628 AYA patients with MDS receiving their first HCT. Median age was 30 years, most patients had high-risk IPSS and received MAC. Five-year OS post-HCT was 70% (65.6-73.2%) with acceptable rates of NRM. Single-institution studies and prior registry analyses (not restricted to MDS or younger patients) also demonstrate encouraging survival outcomes and low-NRM in younger MDS patients receiving transplant, but contemporary multi-center data addressing this important question is lacking. We propose a retrospective cohort study to evaluate the clinical outcomes following allogeneic HCT in younger MDS patients (i.e., <60 years at the time of HCT).

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

N/A

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

Inclusion Criteria

- Patients with a diagnosis of MDS transplanted between 2010-2020
- Ages 59 and younger
- First allogeneic transplantation

Q21. Does this study include pediatric patients?

- Yes

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

Variables to be described:
Patient-related:
• Age at transplant (16-39, 40-49, 50-59)
• Patient gender
• Race/Ethnicity
• Karnofsky performance status at transplant: ≥ 90 vs. < 90
• HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3
• Detail (if available) of history of prior malignancies based on HCT-CI
Disease-related:
• Clinical onset of MDS: De novo vs. therapy related
• Blast percentage at HCT (<5, 5-10, >10)
• Disease status prior to HCT
o CR
o HI
o NR/SD
o Progression/relapse
o Not assessed/missing
• WHO classification at diagnosis:
o MDS-SLD
o MDS-MLD
o MDS RS
o MDS 5q
o MDS EB
o MDS Unclassified
• IPSS-R at diagnosis
• Cytogenetic Classification per IPSS-R
• Pre-HCT therapy:
o Supportive care: transfusional support, growth factors
o Hypomethylating agent (HMA) Therapy
o Lenalidomide
o Induction-like chemotherapy
o Others
• MRD prior to transplant: yes/no
Transplant-related:
• Conditioning intensity: MAC vs. RIC/NMA
• Graft source: bone marrow vs. peripheral blood vs. cord blood
• Donor type: HLA-identical sibling vs. haploidentical vs. matched-unrelated vs. mismatched unrelated vs. cord blood
• Donor-recipient sex match
• Donor-recipient CMV status
• Donor age
• GVHD prophylaxis regimen
• Time from diagnosis to HCT
• Year of transplant

Q23. **PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.**

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

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

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

N/A

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

N/A

Q26. REFERENCES:

1. Ma X. Epidemiology of myelodysplastic syndromes. Am J Med. 2012;125(7 Suppl):S2-S5. doi:10.1016/j.amjmed.2012.04.014
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Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

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

- No, I do not have any conflicts of interest pertinent to this proposal

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

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of MDS patients reported to CIBMTR between the period 2008 to 2019.

Characteristic	N (%)
No. of patients	1683
No. of centers	173
Patient age - median (min-max)	52 (18-59)
Age - no. (%)	
10-19	40 (2)
20-29	135 (8)
30-39	174 (10)
40-49	395 (23)
50-59	939 (56)
Sex - no. (%)	
Male	986 (59)
Female	697 (41)
Region - no. (%)	
US	1480 (88)
Canada	8 (0)
Europe	52 (3)
Asia	72 (4)
Australia/New Zealand	26 (2)
Mideast/Africa	9 (1)
Central/South America	36 (2)
Race - no. (%)	
Caucasian	1341 (80)
African-American	126 (7)
Asian	125 (7)
Pacific islander	11 (1)
Native American	11 (1)
More than one race	10 (1)
Missing	59 (4)
Karnofsky score - no. (%)	
90-100	1039 (62)
< 90	614 (36)
Missing	30 (2)
HCT-CI - no. (%)	
0	445 (26)
1	241 (14)
2	204 (12)

Characteristic	N (%)
3+	758 (45)
TBD, review needed for history of malignancies	2 (0)
TBD, inconsistencies between parent and sub-questions	5 (0)
Missing	28 (2)
Time from diagnosis to HCT - median (min-max)	7 (-99-497)
Graft source - no. (%)	
Bone marrow	259 (15)
Peripheral blood	1253 (74)
Cord blood	171 (10)
Conditioning regimen intensity - no. (%)	
MAC	1071 (64)
RIC	432 (26)
NMA	120 (7)
TBD	44 (3)
Missing	16 (1)
GVHD prophylaxis - no. (%)	
No GVHD prophylaxis	18 (1)
Ex-vivo T-cell depletion	11 (1)
CD34 selection	54 (3)
Post-CY + other(s)	191 (11)
Post-CY alone	2 (0)
TAC + MMF +- other(s) (except post-CY)	255 (15)
TAC + MTX +- other(s) (except MMF, post-CY)	717 (43)
TAC + other(s) (except MMF, MTX, post-CY)	92 (5)
TAC alone	33 (2)
CSA + MMF +- other(s) (except post-CY)	125 (7)
CSA + MTX +- other(s) (except MMF, post-CY)	131 (8)
CSA + other(s) (except MMF, MTX, post-CY)	9 (1)
CSA alone	9 (1)
Other(s)	21 (1)
Missing	15 (1)
Donor type - no. (%)	
HLA-identical sibling	474 (28)
Twin	10 (1)
Other related	219 (13)
Well-matched unrelated (8/8)	629 (37)
Partially-matched unrelated (7/8)	145 (9)
Mis-matched unrelated (<= 6/8)	13 (1)

Characteristic	N (%)
Multi-donor	4 (0)
Unrelated (matching TBD)	18 (1)
Cord blood	171 (10)
Donor/recipient sex match - no. (%)	
M-M	562 (33)
M-F	364 (22)
F-M	328 (19)
F-F	249 (15)
CB - recipient M	92 (5)
CB - recipient F	79 (5)
Missing	9 (1)
Donor/recipient CMV serostatus - no. (%)	
+/+	519 (31)
+/-	163 (10)
-/+	374 (22)
-/-	448 (27)
CB - recipient +	112 (7)
CB - recipient -	57 (3)
CB - recipient CMV unknown	2 (0)
Missing	8 (0)
Disease risk status at HCT - no. (%)	
MDS advanced	520 (31)
MDS early	996 (59)
Other	167 (10)
Blast in marrow at diagnosis - no. (%)	
< 5%	1271 (76)
5-10%	227 (13)
11-20%	134 (8)
Missing	51 (3)
Blast in marrow prior to HCT - no. (%)	
< 5%	1296 (77)
5-10%	187 (11)
11-20%	47 (3)
Missing	153 (9)
Cytogenetic score - no. (%)	
Favorable	649 (39)
Intermediate	220 (13)
Poor	643 (38)

Characteristic	N (%)
TBD (needs rev.)	118 (7)
Not tested	21 (1)
Missing	32 (2)
IPSS prior to HCT - no. (%)	
Low	237 (14)
Intermediate-1	676 (40)
Intermediate-2	423 (25)
High	28 (2)
Missing	319 (19)
IPSS-R prior to HCT - no. (%)	
Very low	179 (11)
Low	400 (24)
Intermediate	382 (23)
High	224 (13)
Very high	149 (9)
Missing	349 (21)
Year of HCT - no. (%)	
2008	173 (10)
2009	200 (12)
2010	150 (9)
2011	94 (6)
2012	96 (6)
2013	162 (10)
2014	177 (11)
2015	179 (11)
2016	139 (8)
2017	119 (7)
2018	107 (6)
2019	87 (5)
Follow-up - median (range)	61 (3-148)

Response Summary:

This form is intended to be completed by a physician/researcher for the purpose of proposing a study. Content should not include Personal Identifiable Information (PII) or Protected Health Information (PHI). If you are a patient, do not complete this form. Patients: Contact your healthcare provider immediately for reports of problems with your treatment or problems with products received for your treatment. The CIBMTR uses de-identified data and is unable to associate reported treatment problems, adverse events, or corrections of information with a center, clinical trial, or healthcare provider.

Q1. Study Title

Impact of Somatic Mutations on Outcomes after Allogeneic Hematopoietic Cell Transplantation in Patients with Myelodysplastic Syndrome with Ring Sideroblasts (MDS-RS) and MDS/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T)

Q2. Key Words

Myelodysplastic Syndrome with Ring Sideroblasts, MDS-RS, MDS/myeloproliferative neoplasm with RS and thrombocytosis, MDS/MPN-RS-T, Allogeneic Hematopoietic Cell Transplantation. HCT, Somatic Mutations

Q3. PRINCIPAL INVESTIGATOR

Provide the following information for each investigator:

Principal Investigator #1:

First and last name, degree(s):	Shukaib Arslan, MD
Email address:	sarslan@coh.org
Institution name:	City of Hope National Medical Center
Academic rank:	Assistant Professor, Hematology-HCT

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

- Yes

Q5. Do you identify as an underrepresented/minority?

- Yes

Q6. Principal Investigator #2 (If applicable):

First and last name, degree(s):	Ryotaro Nakamura
Email address:	rnakamura@coh.org
Institution name:	City of Hope National Medical Center
Academic rank:	Professor, Hematology-HCT

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

- No

Q8. Do you identify as an underrepresented/minority?

- No

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

N/A

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

N/A

LETTER OF COMMITMENT:

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

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

N/A

Q13. PROPOSED WORKING COMMITTEE:

- Chronic Leukemia

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

- No

Q15. RESEARCH QUESTION:

Do somatic mutations impact HCT outcomes of MDS-RS and MDS/MPN-RS-T

Q16. RESEARCH HYPOTHESIS:

We hypothesize that 1) Allogeneic HCT is highly effective and associated with long-term survival in MDS-RS and MDS/MPD-RS-T and 2) Somatic mutations have prognostic relevance in MDS-RS and MDS/MPD-RS-T.

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

Suggested word limit of 200 words:

1. To evaluate the outcome of patients with MDS-RS or MDS/MPD-RS-T who underwent allogeneic HCT and were registered in the Center for International Blood and Marrow Transplant Research (CIBMTR).
2. To characterize the mutation profile in the MDS-RS or MDS and MPD-RS-T in patients who underwent HCT and determine the incidence of high-risk mutations in this population, and examine potential impact of somatic mutations on HCT outcomes adjusted for other clinical risk factors.

Q18. SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.

While the benefit of HCT in patients with high-risk MDS has been widely accepted (1-5) the precise indication of HCT and optimal timing of the procedure for “lower-risk” MDS have not been well studied or agreed by the community. This is in part due to the heterogeneity in clinical and prognostic conditions among patients with “lower-risk” MDS and relative lack of transplant data focused on this population.

Our proposed study would be the first to focus on specific subtypes of lower-risk MDS, namely, MDS-RS and MDS/MPD-RS-T with regards to the patient demographics, somatic mutations, transplant characteristics, and outcomes after HCT. The descriptive outcome data from our analyses will inform physicians and patients who have debilitating anemia and wish to proceed with the curative therapy, even though they may not be immediately life-threatened by their MDS-RS/MDS-RS-T. This study is especially timely and relevant in the era of effective non-HCT therapy such as luspatercept.

Our proposed study will be the first to describe the landscape of somatic mutations in this specific patient population. The molecular and clinical risk factor analyses will also inform the researchers in the filed towards development of novel approaches for patients with identified risk factors.

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

MDS: MDS is a heterogenous stem cell disorder driven by genetic alterations leading to ineffective hematopoiesis and cytopenia (6). Clinical presentation ranges from mild asymptomatic cytopenia to severe symptomatic transfusion dependent cytopenia, recurrent infections and rapid progression to acute leukemia. A Revised International Prognostic Scoring System (IPSS-R) (7) has been developed by the International Working Group for the Prognosis of MDS (IWG-PM) that utilizes clinical/hematologic prognostic features to risk stratify MDS. This risk stratification has been used in determining therapeutic interventions to the patients with MDS ranging from supportive care, hypomethylating agents (HMA), and allogeneic hematopoietic cell transplantation (alloHCT).

HCT for MDS: Allogeneic HCT is the only curative therapy available for the patients with MDS. However, it is associated with significant risks of transplant-related mortality/morbidities due to graft-versus-host disease (GVHD), infections, and regimen-related toxicities. As a result, HCT has been generally offered to fit/young patients with higher-risk disease, and such practice is supported by decision analysis studies in recipients of both myeloablative conditioning (MAC) and reduced intensity conditioning (RIC) HCT (1, 2).

While IPSS/IPSS-R are highly informative and predictive of prognosis of MDS, the models do not consider somatic mutations as a prognostic variable. Several prognostic mutations have been identified in MDS and their role has been studied on survival after allogeneic HCT. A CIBMTR analysis of 1514 samples from the MDS patients who underwent HCT between 2005 and 2014 (8) included 746 patients who had lower-risk MDS (very low 119, low 287, intermediate 340). This analysis showed that TP53 mutations were present in 19% of the patients (13% of lower risk) and were associated with poor survival and increased risk of relapse with both reduced intensity and myeloablative conditioning for HCT. Presence of RAS pathway mutations predicted poor survival and increased risk of relapse with RIC HCT and this poor risk feature was overcome by myeloablative conditioning (MAC) HCT. JAK2 mutations predicted poor survival without an increased risk of relapse and this poor risk feature was not overcome by MAC HCT.

HCT for lower risk MDS: However, no specific analyses were performed for a subgroup of patients with “lower-risk” MDS in this study. A recent EBMT retrospective analysis on “lower-risk” (defined as low/intermediate-1 by IPSS) MDS patients showed that most of these patients (76%) were reclassified as intermediate or higher risk according to IPSS-R. The 3-year overall survival (OS) and PFS were 58% and 54%, respectively, in this cohort (9). Although this report analyzed various factors that affected transplant outcome including IPSS-R, disease status at transplant, prior treatment, stem cell source, CMV serostatus, T-cell depletion, conditioning therapy, the role of somatic mutations was not evaluated.

Given the increasing knowledge and evidence of prognostic effect of somatic mutations, it is important to better understand the outcome of HCT in lower-risk MDS.

MDS-RS and MDS/MPN-RS-T: Ring sideroblasts (RS) are erythroid precursors with abnormal perinuclear mitochondrial iron accumulation. Two myeloid neoplasms defined by the presence of RS, include MDS-RS and MDS/MPN-RS-T. Mutations in SF3B1 are seen in ≥80% of patients with MDS-RS-SLD and MDS/MPN-RS-T, and strongly correlate with the presence of BM RS; MDS/MPN-RS-T patients also demonstrate JAK2V617F, ASXL1, DNMT3A, SETBP1, and TET2 mutations. Cytogenetic abnormalities are uncommon in both. For MDS-RS, luspatercept has been approved. It is a soluble fusion protein that inhibits molecules in the TGF-β (transforming growth factor) superfamily, increasing hemoglobin levels by targeting a pathway fundamentally distinct from EPO (10-12). The MEDALIST trial, a phase III, randomized, double blind, placebo-controlled study, demonstrated the efficacy of luspatercept versus placebo in lower risk patients who were refractory/intolerant or ineligible for ESA (EPO level >200 U/L) and were RBC-TD (≥2 units of RBC in 8 weeks) (12). The primary end point of RBC-TI≥8 weeks was achieved in 58 (31.9%) patients in the luspatercept arm versus 10 (13.2%) in the placebo arm ($p<0.0001$).

However, luspatercept is not a curative therapy and the response rate (transfusion independence rate) is not very high. Thus, we propose a study to assess the outcome of allogeneic HCT in patients with specific subtypes – namely MDS-RS or MDS/MPD-RS-T with the specific goal of determining the prognostic impact of somatic mutations in this understudied population.

Mutation Landscape and Its Prognostic Impact on MDS-RS and MDS/MPN-RS-T

Approximately half of MDS patients carry somatic mutations in spliceosome genes, of which SF3B1 is the most common. The SF3B1 gene encodes the splicing factor 3b subunit 1 and is typically mutated in MDS-RS (13, 14). A recent comprehensive analysis by the International Working Group for the Prognosis of MDS (IWG-PM) analyzed the available evidence supporting the recognition of SF3B1-mutant MDS as a distinct entity(15), and confirmed that SF3B1-mutant MDS is associated with a better prognosis compared with SF3B1-wild type MDS, and that co-mutations with RUNX1 or EZH2 were associated with poorer overall survival. However, there have been no data available to date regarding the prognostic impact of SF3B1 or additional mutations in MDS-RS/RS-T patients who proceed with HCT.

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

N/A

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

Patients with very low, low, and intermediate risk MDS by IPSS-R, both at the time of diagnosis and at the time of HCT, aged 18 and above who underwent alloHCT from 2001 through 2019 will be included in the study to allow at least two-year follow-up period. All patients who progressed to higher risk subtype (i.e. MDS-EB) or AML after initial diagnosis and before HCT would be excluded. Only patients who have available biologic samples in the NMDP repository will be included. To reduce the heterogeneity of the cohort we plan to exclude those who received ex-vivo T cell depletion, haploidentical donor HCT, and umbilical cord blood as a stem cell source.

Q21. Does this study include pediatric patients?

- No

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

N/A

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

Patient characteristics (age, gender, KPS, HCT-CI), disease-specific characteristics (prior treatment, blood and marrow blasts, HCT-specific IPSS), HCT-related variables (conditioning regimen, GVHD prophylaxis, donor type, graft source, donor-recipient sex match, donor-recipient CMV status).
Outcome measures will include GVHD (acute GVHD grade 2-4, chronic GVHD at 1, 3, and 5 years post-HCT), NRM, relapse, DFS, and OS (assessed at 100 days, six months, 1 year and 3-year time), and cause of death.
The study will be a retrospective analysis of patients who underwent alloHCT for very low, low and intermediate risk MDS from 2001 through 2020. Descriptive analyses of patient-, disease- and donor-variables will be performed. Kaplan-Meier curves will be used for OS and DFS. Cumulative incidence curves will be used for NRM, relapse, and GVHD. Probabilities of OS, DFS, NRM, relapse, and GVHD at specified time points and 95%CIs will be estimated from these curves. Multivariate analyses for survival (OS, DFS), NRM, relapse, and GVHD will be performed using the Cox proportional hazards model and the proportional sub-distribution hazards model for competing risks adjusting for the effects of covariates whenever appropriate. The covariates to be evaluated will include patient-specific variables (age, gender, KPS, HCT-CI), disease-related variables (disease classification at the time of diagnosis, time from diagnosis to HCT, IPSS, and IPSS-R at diagnosis and pre-HCT, treatment before transplantation, diseases status at HCT, transfusion dependence, transfusion burden, percentage of marrow blasts at transplant), and transplant-related variables (graft source, donor type, GVHD prophylaxis, conditioning regimen (RIC, MAC), donor-recipient sex match, donor-recipient CMV serostatus, donor-recipient ABO typing, year of transplantation). Both univariate and multivariate analyses will be conducted to examine the associations between single somatic mutations, composite mutations, and the IPSS-Mol (once published), and alloHCT outcomes.
SF3B1 mutations can be seen in ~80% of patients with MDS-RS-SLD, ~40% of patients with MDS-RS-MLD, with the percentage of BM RS often correlating directly with the SF3B1 mutant allele burden (13, 14, 16, 17). Gene mutations encountered in patients with MDS/MPN-RS-T include; SF3B1 (~85%), JAK2V617F (~50%), TET2 (~25%), ASXL1 (~20%), DNMT3A (~15%) and SETBP1 (~10%) (18-21). The prognostic impact of SF3B1 and JAK2 mutations will be analyzed. While the frequency of comutation with RUNX1 or EZH2 is expectedly low (4-5%), we plan to explore its impact on the outcome as well.
The sample size of ~300 would be sufficient to narrowly define overall survival (OS), the primary endpoint. The secondary endpoints include disease-free survival (DFS), nonrelapse mortality, relapse incicence, acute and chronic GVHD. The sample size would also be sufficient to generate preliminary data on associations between somatic mutations and OS/other clinical endpoints.

Q23. PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A description of the hypothesis specific to PROS.

For additional information on what PRO measures have been collected and timepoints of collection, please reach out to the Late Effects and Quality of Life or Health Services Working Committee leadership: https://www.cibmtr.org/About/WhoWeAre/Com

N/A

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

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

We propose to assay for recurrent somatic mutations using biologic samples from the NMDP repository, and HopeSeq mutation assay. The feasibility of detecting genetic mutations using the archived CIBMTR sample repository has been previously demonstrated in a large successful MDS study by Lindsey et al (8). We propose to include the data for "lower-risk" MDS patients from that study and include additional patients in the repository between 2001-2004 and 2015-2016. At City of Hope, Dr. Pillai and we collaborated on a few successful projects in molecularly characterizing patients with MDS, myelofibrosis, and chronic myelomonocytic leukemia (CK18-02, PI: Mei) who underwent HCT, and the exact gene panels and methods have been described in detail. Depending on the final number of samples to be tested for somatic mutations, City of Hope's institutional fund would be available.

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

N/A

Q26. REFERENCES:

1. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Perez WS, Anasetti C, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104(2):579-85.
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Q27. **CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning:**

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

- No, I do not have any conflicts of interest pertinent to this proposal

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

N/A

BEFORE FINAL SUBMISSION, please review the PI checklist to ensure that you have completed all necessary steps. This will increase the likelihood of submitting a feasible and successful proposal.

Embedded Data:

N/A

Table 1. Characteristics of Refractory anemia (RA), Refractory anemia with ringed sideroblasts (RARS), and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN–RS–T)patients, with very low, low, and intermediate risk (IPSS-r) at diagnosis and HCT (both timepoints) reported to CIBMTR between the period 2008 to 2019.

Characteristic	TED	CRF	Total
No. of patients	73	148	221
No. of centers	46	68	90
Samples available - no. (%)			
Recipient and Donor	27 (37)	68 (46)	95 (43)
Recipient Only	9 (12)	30 (20)	39 (18)
Donor Only	5 (7)	5 (3)	10 (5)
Missing	32 (44)	45 (30)	77 (35)
Subdisease - no. (%)			
Refractory cytopenia with unilineage dysplasia (RCUD) (includes refractory anemia (RA)	31 (42)	74 (50)	105 (48)
Refractory anemia with ringed sideroblasts (RARS)	35 (48)	71 (48)	106 (48)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN–RS–T)	7 (10)	3 (2)	10 (5)
Age - median (min-max)	60 (18-72)	63 (19-77)	61 (18-77)
Age - no. (%)			
18-29	3 (4)	6 (4)	9 (4)
30-39	4 (5)	2 (1)	6 (3)
40-49	5 (7)	19 (13)	24 (11)
50-59	21 (29)	34 (23)	55 (25)
60-69	38 (52)	62 (42)	100 (45)
>= 70	2 (3)	25 (17)	27 (12)
Sex - no. (%)			
Male	38 (52)	85 (57)	123 (56)
Female	35 (48)	63 (43)	98 (44)
Region - no. (%)			
US	51 (70)	142 (96)	193 (87)
Canada	3 (4)	0 (0)	3 (1)
Europe	12 (16)	1 (1)	13 (6)
Asia	1 (1)	0 (0)	1 (0)
Australia/New Zealand	4 (5)	1 (1)	5 (2)
Mideast/Africa	0 (0)	1 (1)	1 (0)
Central/South America	2 (3)	3 (2)	5 (2)
Race - no. (%)			

Characteristic	TED	CRF	Total
White	62 (85)	133 (90)	195 (88)
Black or African American	1 (1)	6 (4)	7 (3)
Asian	1 (1)	4 (3)	5 (2)
Native Hawaiian or other Pacific Islander	1 (1)	0 (0)	1 (0)
More than one race	0 (0)	2 (1)	2 (1)
Missing	8 (11)	3 (2)	11 (5)
Karnofsky score - no. (%)			
90-100	39 (53)	78 (53)	117 (53)
< 90	34 (47)	67 (45)	101 (46)
Missing	0 (0)	3 (2)	3 (1)
Time from diagnosis to HCT - median (min-max)	15 (1-153)	20 (1-135)	18 (1-153)
Graft source - no. (%)			
Bone marrow	11 (15)	17 (11)	28 (13)
Peripheral blood	62 (85)	123 (83)	185 (84)
Cord blood	0 (0)	8 (5)	8 (4)
IPSS-R at diagnosis - no. (%)			
Very low	1 (1)	6 (4)	7 (3)
Low	28 (38)	71 (48)	99 (45)
Intermediate	44 (60)	71 (48)	115 (52)
IPSS-R prior to HCT - no. (%)			
Very low	2 (3)	6 (4)	8 (4)
Low	29 (40)	69 (47)	98 (44)
Intermediate	42 (58)	73 (49)	115 (52)
Year of HCT - no. (%)			
2008	1 (1)	11 (7)	12 (5)
2009	0 (0)	9 (6)	9 (4)
2010	0 (0)	8 (5)	8 (4)
2011	0 (0)	14 (9)	14 (6)
2012	0 (0)	3 (2)	3 (1)
2013	1 (1)	19 (13)	20 (9)
2014	16 (22)	9 (6)	25 (11)
2015	9 (12)	9 (6)	18 (8)
2016	5 (7)	14 (9)	19 (9)
2017	8 (11)	22 (15)	30 (14)
2018	10 (14)	16 (11)	26 (12)
2019	23 (32)	14 (9)	37 (17)

Characteristic	TED	CRF	Total
Follow-up - median (range)	36 (12-73)	60 (12-148)	49 (12-148)

Table 2. Characteristics of Refractory anemia (RA), Refractory anemia with ringed sideroblasts (RARS), and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN–RS–T)patients, with very low, low, and intermediate risk (IPSS-r) prior to HCT reported to CIBMTR between the period 2008 to 2019.

Characteristic	TED	CRF	Total
No. of patients	113	216	329
No. of centers	67	79	102
Samples available - no. (%)			
No Sample	51 (45)	64 (30)	115 (35)
Recipient and Donor	37 (33)	101 (47)	138 (42)
Recipient Only	19 (17)	45 (21)	64 (19)
Donor Only	6 (5)	6 (3)	12 (4)
Subdisease - no. (%)			
Refractory cytopenia with unilineage dysplasia (RCUD) (includes refractory anemia (RA)	44 (39)	97 (45)	141 (43)
Refractory anemia with ringed sideroblasts (RARS)	55 (49)	116 (54)	171 (52)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN–RS–T)	14 (12)	3 (1)	17 (5)
Age - median (min-max)	60 (18-74)	63 (19-78)	61 (18-78)
Age - no. (%)			
18-29	5 (4)	8 (4)	13 (4)
30-39	10 (9)	2 (1)	12 (4)
40-49	6 (5)	23 (11)	29 (9)
50-59	35 (31)	54 (25)	89 (27)
60-69	53 (47)	96 (44)	149 (45)
>= 70	4 (4)	33 (15)	37 (11)
Sex - no. (%)			
Male	61 (54)	126 (58)	187 (57)
Female	52 (46)	90 (42)	142 (43)
Region - no. (%)			
US	85 (75)	210 (97)	295 (90)
Canada	4 (4)	0 (0)	4 (1)
Europe	13 (12)	1 (0)	14 (4)
Asia	1 (1)	0 (0)	1 (0)
Australia/New Zealand	6 (5)	1 (0)	7 (2)
Mideast/Africa	0 (0)	1 (0)	1 (0)
Central/South America	4 (4)	3 (1)	7 (2)
Race - no. (%)			
White	97 (86)	197 (91)	294 (89)

Characteristic	TED	CRF	Total
Black or African American	3 (3)	7 (3)	10 (3)
Asian	1 (1)	5 (2)	6 (2)
Native Hawaiian or other Pacific Islander	1 (1)	0 (0)	1 (0)
American Indian or Alaska Native	1 (1)	0 (0)	1 (0)
More than one race	0 (0)	2 (1)	2 (1)
Missing	10 (9)	5 (2)	15 (5)
Karnofsky score - no. (%)			
90-100	64 (57)	113 (52)	177 (54)
< 90	49 (43)	100 (46)	149 (45)
Missing	0 (0)	3 (1)	3 (1)
Time from diagnosis to HCT - median (min-max)	19 (1-226)	22 (1-220)	21 (1-226)
Graft source - no. (%)			
Bone marrow	19 (17)	23 (11)	42 (13)
Peripheral blood	93 (82)	183 (85)	276 (84)
Cord blood	1 (1)	10 (5)	11 (3)
IPSS-R at diagnosis - no. (%)			
Very low	1 (1)	6 (3)	7 (2)
Low	28 (25)	71 (33)	99 (30)
Intermediate	44 (39)	71 (33)	115 (35)
High	6 (5)	8 (4)	14 (4)
Missing	34 (30)	60 (28)	94 (29)
IPSS-R prior to HCT - no. (%)			
Very low	3 (3)	9 (4)	12 (4)
Low	44 (39)	105 (49)	149 (45)
Intermediate	66 (58)	102 (47)	168 (51)
Year of HCT - no. (%)			
2008	2 (2)	19 (9)	21 (6)
2009	0 (0)	11 (5)	11 (3)
2010	0 (0)	11 (5)	11 (3)
2011	0 (0)	17 (8)	17 (5)
2012	0 (0)	9 (4)	9 (3)
2013	1 (1)	28 (13)	29 (9)
2014	20 (18)	19 (9)	39 (12)
2015	13 (12)	12 (6)	25 (8)
2016	9 (8)	23 (11)	32 (10)
2017	13 (12)	28 (13)	41 (12)
2018	17 (15)	19 (9)	36 (11)

Characteristic	TED	CRF	Total
2019	38 (34)	20 (9)	58 (18)
Follow-up - median (range)	31 (5-139)	61 (11-148)	49 (5-148)

CIBMTR Study Proposal

Study Title:

Impact of Pre-Allogeneic Hematopoietic Stem Cell Transplantation Treatment on Outcomes of Patients with Higher-Risk MDS and CMML: A Propensity Score Analysis

Key words:

Myelodysplastic syndrome, Chronic myelomonocytic leukemia, Hypomethylating agent, Allogeneic hematopoietic stem cell transplantation, Propensity score

1st PI Information:

PI Name: Rory M. Shallis
Degree(s): MD
Email Address: rory.shallis@yale.edu
Institution Name: Yale School of Medicine
Academic rank: Assistant Professor
Junior investigator status: Yes
Do you identify as an underrepresented/minority?: No

2nd PI Information:

PI Name: Piyanuch Kongtim
Degree(s): MD, PhD
Email Address: pkongtim@uci.edu
Institution Name: University of California Irvine, Orange, CA
Academic rank: Associate Professor
Junior investigator status: Yes
Do you identify as an underrepresented/minority?: Yes

3rd PI Information:

PI name: Amer M. Zeidan
Degree(s): MBBS, MHS
Email Address: amer.zeidan@yale.edu
Institution Name: Yale School of Medicine
Academic rank: Professor
Junior investigator status: No
Do you identify as an underrepresented/minority?: No

4th PI Information:

PI Name: Stefan O Ciurea
Degree(s): MD
Email Address: sciurea@uci.edu
Institution Name: University of California Irvine, Orange, CA
Academic rank: Professor
Junior investigator status: No
Do you identify as an underrepresented/minority?: No

1st and 2nd PIs and 3rd and 4th PIs have equal contribution.

Corresponding PIs:
Stefan O. Ciurea and Amer M. Zeidan

Current ongoing work with CIBMTR:
Shallis: LK20-01 co-PI, LK21-01 co-PI

Proposed working committee:
Chronic Leukemia Working Committee

Research question:
Does treatment prior to allogeneic hematopoietic cell transplant (AHCT) improve the outcome of patients with higher-risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML)?

Hypothesis:
Pre-AHCT treatment with an HMA can reduce disease burden with acceptable toxicity and results in improved outcomes after AHCT for patients with higher-risk MDS and CMML when compared with patients either treated with pre-AHCT intensive chemotherapy or, among those without excess blasts, receiving no pre-AHCT therapy.

Specific Objectives:
Primary objective:
To compare the post-AHCT relapse-free survival (RFS) of patients with higher-risk MDS and CMML who received pre-AHCT treatment with HMA vs. intensive chemotherapy vs. no therapy among those patients without excess blasts receiving AHCT.

Secondary objectives:

1. To compare post-AHCT overall survival (OS), GvHD-free relapse-free survival (GRFS), cumulative incidence of non-relapse mortality (NRM), relapse, acute GvHD and chronic GvHD in patients with higher-risk MDS and CMML who received pre-AHCT treatment with HMA vs. intensive chemotherapy vs. no therapy
2. To identify factors that are associated with favorable outcomes of patients with higher-risk MDS and CMML based on each type of pre-AHCT strategy.

Scientific Impact
It is currently unknown if patients with higher-risk MDS/CMML should receive pre-AHCT therapy or not and, if so, which strategy is optimal. Using the CIBMTR database, we aim to answer the question whether treatment with HMA, intensive chemotherapy or no therapy provides better post-AHCT outcomes. The results from this proposed study will help address an unmet need and guide transplant physicians in determining the optimal pre-AHCT strategy for subgroups of patients with higher-risk MDS/CMML receiving AHCT.

Scientific Justification:
MDS and CMML are clonal hematopoietic stem cell disorders with variable clinical symptom burden and risk of progression to acute myeloid leukemia (AML). The median survival for patients with MDS and CMML ranges from several months to several years and depends mainly on the percentage of marrow blasts, karyotype, cytogenetics, molecular lesions, and the number and depth of cytopenias. As the clinical manifestations and prognosis of both MDS and CMML are variable, several risk stratification tools, such as International Prognostic Scoring System (IPSS) and revised-IPSS for MDS or CMML-specific prognostic

scoring system (CPSS), have been developed to tailor management decisions to the individual patient. Supportive care with blood transfusion, antimicrobial prophylaxis, growth factors and immunosuppressive drugs are often employed to relieve cytopenia-related symptoms and complications in patients with lower-risk disease. Conversely, patients with higher-risk MDS and CMML have a higher risk of AML transformation and a reduced life-expectancy warranting a more aggressive, disease-modifying approach.

The DNA-methyltransferase inhibitors or hypomethylating agents (HMAs) 5-azacitidine (AZA) and decitabine (DEC) were approved for treatment of advanced MDS and CMML. AZA has been shown in a randomized study of patients with higher-risk MDS to prolong the median time to AML progression or death and improve OS when compared with best available therapy including intensive therapy and best supportive care.(1) Although similar benefits were reported in clinical trials using DEC, this has not consistently translated to an OS benefit when compared with best supportive care.(2, 3) Additionally, no more than 20% of patients achieve a complete remission using HMA alone and among these patients responses are not long-lasting with most patients eventually experiencing disease relapse/progression.(1, 4-9). This might be related to the questionable disease-modifying activity imparted by HMA therapy. In a pivotal study, serial whole exome sequencing of HMA-treated CMML patients demonstrated that these agents do not alter the mutational allele burdens, even in responding patients.(10)

For these reasons, AHCT, the only potentially curative therapeutic modality for higher-risk MDS and CMML, should be considered for all eligible patients. Indeed, a recent prospective multicenter open-label phase II study (VIDAZALLO) confirms a survival benefit of early AHCT with RIC over continuous HMA therapy for relatively older patients with MDS.(11) A study from the EBMT registry reported 43% and 35% rates of 5-year and 10-year OS, respectively, for patients with MDS treated with AHCT.(12) A similar CIBMTR-led study of 209 adult patients with CMML receiving AHCT between 2001-2012 demonstrated a 30% and 23% rate of 3-year OS for patients with CPSS low/intermediate-1 and intermediate-2/high-risk disease, respectively; however, relapse remained a major cause of treatment failure as approximately 50% of the patients in this study relapsed after AHCT.(13) Given the significant proportion of MDS/CMML patients who are diagnosed at an advanced age, which is associated with higher rates of transplant-related mortality (TRM), the wider use of reduced-intensity conditioning (RIC) regimens has increased the number of eligible patients and the safety of AHCT in patients older than 70 years.(14)

However, due to their acceptable toxicity profile when compared with conventional, intensive AML-type induction chemotherapy, the HMAs have been preferably used for pre-AHCT disease “debulking” with the ultimate goal of reducing relapse risk and prolonging post-AHCT survival. Furthermore, pre-AHCT HMA treatment might offer benefit in enhancing the graft-versus-leukemia or -myelodysplasia effect as preclinical studies have shown that it associates with increases expression of KIR,(15) minor histocompatibility antigen,(16) and various tumor antigens.(17) The benefits of this strategy, however, are unclear. Pre-AHCT “debulking” therapy has been preferentially offered for patients with excess blasts at diagnosis, but the role for pre-AHCT “debulking” for the subgroup of patients with higher-risk MDS/CMML is essentially unknown.

Prior attempts to answer these questions have been limited in number and methodology. Our group has previously reported on the outcomes of 83 patients with CMML treated with AHCT and demonstrated that patients who were treated with pre-AHCT HMA had a significantly lower risk of relapse and better progression-free survival (PFS) when compared with those receiving other pre-AHCT treatments. The benefit of pre-AHCT HMA was seen only in patients who achieved a complete remission before AHCT, but was abrogated when evaluating patients who were not in remission pre-AHCT as they were shown to have

similar relapse rates and survival. This analysis was limited by a low number of patients included in the study and thus low statistical power.(18) In evaluating patients with MDS, a meta-analysis of seven studies showed no survival differences between patients with MDS treated with pre-AHCT HMA and those receiving pre-AHCT best supportive care (HR = 0.86, 95% CI: 0.64–1.15, p = 0.32).(19) However, the fact that all studies included in this meta-analysis were retrospective and with relatively small numbers of patients invokes significant biases that limit the strength of the conclusions. To date there has been no prospective study comparing the outcomes of patients with MDS/CMML based on the receipt of pre-AHCT HMA vs. intensive chemotherapy vs. no pre-AHCT therapy, particularly among patients without excess blasts at diagnosis, nor a study identifying subgroups of patients who are likely to benefit from pre-AHCT HMA treatment.

We therefore propose this study using data from a large cohort of patients with higher-risk MDS and CMML reported to the CIBMTR to explore their outcomes based on pre-AHCT treatment type and intensity. Additionally, we propose a propensity score analysis to reduce the risk of selection bias between treatment groups that could exist based on the possibility that patients who received pre-AHCT HMA or intensive chemotherapy may either have other high-risk features prompting it to be offered by a provider or may require such therapy due to delays in securing an appropriate donor.

Patient Eligibility Population:

Inclusion criteria:

- Patients with de novo or therapy related MDS or CMML
- Patients who had the following disease risk **at diagnosis** (regardless of disease status at AHCT)
    - Int-2/high IPSS
    - Int-1 IPSS with high-risk cytogenetics
    - Int/high/very high IPSS-R
    - Had >/=5 bone marrow blasts regardless of risk category.
- Patients underwent 1st AHCT from January 2005 to December 2020 (since the first HMA, 5-azacytidine was approved for MDS treatment in 2004, we will include patients registered to the CIBMTR from 2005 to 2020 to ensure that HMAs were one of the treatment options available for these patients.)
- Age 18 years or older
- Patients who received AHCT using stem cell from HLA-matched related, HLA-matched unrelated, HLA-mismatched related, HLA-mismatched unrelated and haploidentical donor
- Received myeloablative, reduced intensity and non-myeloablative conditioning

Exclusion criteria:

- Patients receiving AHCT from a syngeneic donor
- Second AHCT
- Umbilical cord blood AHCT
- Ex vivo T cell depleted haploidentical AHCT
- Patients with missing data of disease risk at diagnosis or pre-AHCT treatment
- Patients who received post-AHCT maintenance therapy

Data Requirements:

The study will use data collected from the CIBMTR. No additional data are required.

Sample Requirements:

No clinical samples are required.

Study Design:

This is a retrospective cohort analysis to evaluate the impact of induction therapy on outcomes of AHCT. Eligible patients will be categorized into 4 groups based on their history of induction treatment.

1. MDS/CMML patients who completed at least 1 cycle of either IV or oral HMA (HMAs)
2. MDS/CMML patients who completed at least 1 cycle of AML-type intensive induction therapy such as 7+3, FLAG or intermediate/high dose cytarabine regimen (high intensity chemotherapy group)
3. MDS/CMML patients who completed at least 1 cycle of low intensity chemotherapy such as low dose cytarabine (low intensity chemotherapy group)
4. MDS/CMML patients who received no pre-AHCT therapy (control group).

Patients who received both HMA and intensive chemotherapy will be excluded from the analysis or will be analyzed separately.

AHCT outcomes of patients in these groups will be compared using propensity score analysis (matching/adjustment/stratification).

Primary outcome: RFS at 3 years after AHCT

Secondary outcome measures include the following:

1. OS at 3 years after AHCT
2. GRFS at 3 years after AHCT
3. 100-day-cumulative incidence of acute grades II-IV and III-IV GvHD
4. 3-year-cumulative incidence of overall and extensive chronic GvHD
5. Cumulative incidence of NRM at 1 and 3 years after AHCT
6. Cumulative incidence of relapse at 3 years after AHCT

Variables to be analyzed are

Patient related characteristics:

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

Disease related characteristics:

- WBC, hemoglobin, platelet, absolute monocyte at diagnosis
- Percentage of blast count in peripheral blood and bone marrow at diagnosis
- WHO CMML and MDS subtype(20)
- CMML-specific cytogenetic risk levels at diagnosis(21)
- IPSS and revised-IPSS
- Molecular genetic abnormality (if available)
- Transfusion dependency
- Iron overload
- Time from diagnosis to AHCT
- Induction treatments (HMAs vs. chemotherapy vs. no treatment)
- Number of cycles of induction treatment

- Disease response before AHCT according to the CIBMTR response criteria(22)

Transplant related characteristics:

- Year of AHCT
- Transplant center
- Type of donor
- Conditioning regimen (RIC/NMA/MA)
- Graft source (peripheral blood, bone marrow)
- GvHD prophylaxis regimen
- Donor/recipient CMV status
- Donor-recipient gender match

Endpoint definitions and statistical analysis

The propensity score will be used to adjust for any potential bias derived from imbalanced baseline characteristics at diagnosis between the HMA, intensive chemotherapy and control group that would impact the decision of pre-AHCT therapy type. Initially, the appropriate regression model (depends on data and model assumptions) will be used for propensity score calculation from baseline patient characteristics associated with decision on choosing types of induction treatment (HMAs vs. low intensity vs. high intensity chemotherapy vs. no treatment). The following independent factors determined at diagnosis will be included in the regression model for calculation of propensity score: age, sex, KPS, HCT-CI, WBC, hemoglobin, platelet, absolute monocyte, percentage of blast count in peripheral blood and bone marrow, WHO CMML subtype (MPN-CMML vs. MDS-CMML), cytogenetic abnormalities, molecular genetic abnormalities, transplant center and year of diagnosis. Propensity score then will be used for either matching, stratification, or adjustment of impact of the pre-AHCT treatments on RFS after AHCT.

Patient- and AHCT-related characteristics will be summarized using descriptive statistics. Categorical variables will be reported as numbers and percentages while medians and ranges will be used for continuous variable. The Fisher's exact test will be used for categorical variables and the Kruskal–Wallis test by ranks for continuous variables to compare patient-, disease-, and AHCT-related characteristics between the treatment groups.

RFS is computed from date of AHCT to date of disease relapse, death, or the last evaluation date. Patients who were alive and did not experience progression of disease at the last follow-up date will be censored. OS and NRM will be computed from date of AHCT to last known vital sign. Patients alive at the last follow-up date will be censored. GRFS is defined as the first event among acute GvHD grades 3-4, extensive chronic GvHD , relapse, and death.(23) Those patients who did not experience the events will be censored. The Kaplan-Meier method will be used to estimate all survival measures. Differences in survival between subgroups of interest will be assessed using the log-rank test. Associations between survival outcomes (RFS, OS and GRFS) and HMA induction treatment as well as other potential prognostic factors will be determined using univariable and multivariable Cox proportional hazards regression models. All variables of interest will be tested for the proportional hazard assumption and interaction terms.

The cumulative incidence function with the competing risks method will be used to estimate the endpoints of relapse, NRM, acute GvHD , and chronic GvHD . The competing risk will be included for NRM is relapse, and the competing risk included for relapse is death in CR. For GvHD , the competing risks is death without GvHD. Differences in cumulative incidence between subgroups will be assessed using Fine and Gray's test.(24) The univariable and multivariable Fine and Gray's subdistribution hazard regression will be used to assess the impact of HMA induction treatment as well as other potential prognostic factors on cumulative incidence outcomes.

Disease status before AHCT will be used as a stratified factor in the time to event regression models. A P value of less than 0.05 is considered for statistical significance. In line with the essentially exploratory nature of the study, no adjustment for multiple testing will be applied. Multiple imputation will be used to impute missing data of variables with >5% missing rate.

We would be happy to do the analysis to save statistician time for CIBMTR.

Non-CIBMTR Data Source: If not enough patients will be in the CIBMTR database, a combined proposal with EBMT data will be considered.

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Table 1. Characteristics of MDS patients reported to CIBMTR between the period 2008 to 2019.

Characteristic	No therapy	Chemo +/- HMA	HMA alone
No. of patients	622	334	1882
No. of centers	134	100	131
Patient age - median (min-max)	59 (18-81)	61 (18-78)	65 (18-79)
Age - no. (%)			
10-19	18 (3)	3 (1)	2 (0)
20-29	36 (6)	14 (4)	21 (1)
30-39	46 (7)	24 (7)	30 (2)
40-49	77 (12)	34 (10)	124 (7)
50-59	188 (30)	94 (28)	463 (25)
60-69	229 (37)	137 (41)	1029 (55)
70-80	28 (5)	28 (8)	213 (11)
Sex - no. (%)			
Male	383 (62)	217 (65)	1174 (62)
Female	239 (38)	117 (35)	708 (38)
Region - no. (%)			
US	562 (90)	311 (93)	1843 (98)
Canada	2 (0)	1 (0)	2 (0)
Europe	22 (4)	11 (3)	4 (0)
Asia	19 (3)	3 (1)	24 (1)
Australia/New Zealand	4 (1)	5 (1)	8 (0)
Mideast/Africa	3 (0)	1 (0)	0 (0)
Central/South America	10 (2)	2 (1)	1 (0)
Race - no. (%)			
White	543 (87)	296 (89)	1680 (89)
Black or African American	28 (5)	19 (6)	77 (4)
Asian	27 (4)	9 (3)	75 (4)
Native Hawaiian or other Pacific Islander	1 (0)	1 (0)	4 (0)
American Indian or Alaska Native	2 (0)	1 (0)	6 (0)
More than one race	2 (0)	0 (0)	7 (0)
Missing	19 (3)	8 (2)	33 (2)
Karnofsky score - no. (%)			
90-100	360 (58)	174 (52)	1004 (53)
< 90	248 (40)	153 (46)	851 (45)
Missing	14 (2)	7 (2)	27 (1)
HCT-CI - no. (%)			
0	121 (19)	69 (21)	315 (17)

Characteristic	No therapy	Chemo +/- HMA	HMA alone
1	62 (10)	42 (13)	205 (11)
2	74 (12)	43 (13)	230 (12)
3+	290 (47)	165 (49)	1092 (58)
Missing	75 (12)	15 (4)	40 (2)
Graft source - no. (%)			
Bone marrow	92 (15)	55 (16)	235 (12)
Peripheral blood	530 (85)	279 (84)	1647 (88)
Blast in marrow at diagnosis - no. (%)			
< 5%	471 (76)	186 (56)	1288 (68)
5-10%	116 (19)	66 (20)	368 (20)
11-20%	33 (5)	82 (25)	226 (12)
Missing	2 (0)	0 (0)	0 (0)
Blast in marrow prior to HCT - no. (%)			
< 5%	441 (71)	289 (87)	1486 (79)
5-10%	79 (13)	27 (8)	253 (13)
11-20%	23 (4)	6 (2)	66 (4)
Missing	79 (13)	12 (4)	77 (4)
Cytogenetic score - no. (%)			
Favorable	98 (16)	86 (26)	361 (19)
Intermediate	93 (15)	68 (20)	312 (17)
Poor	421 (68)	170 (51)	1186 (63)
TBD (needs rev.)	3 (0)	2 (1)	4 (0)
Not tested	3 (0)	6 (2)	9 (0)
Missing	4 (1)	2 (1)	10 (1)
IPSS-R at diagnosis - no. (%)			
Very low	0 (0)	1 (0)	15 (1)
Low	51 (8)	12 (4)	84 (4)
Intermediate	269 (43)	111 (33)	718 (38)
High	164 (26)	102 (31)	542 (29)
Very high	70 (11)	68 (20)	288 (15)
Missing	68 (11)	40 (12)	235 (12)
IPSS prior to HCT - no. (%)			
Low	16 (3)	42 (13)	92 (5)
Intermediate-1	204 (33)	167 (50)	956 (51)
Intermediate-2	296 (48)	98 (29)	686 (36)
High	16 (3)	4 (1)	35 (2)
Missing	90 (14)	23 (7)	113 (6)
IPSS-R prior to HCT - no. (%)			

Characteristic	No therapy	Chemo +/- HMA	HMA alone
Very low	17 (3)	34 (10)	97 (5)
Low	68 (11)	89 (27)	338 (18)
Intermediate	194 (31)	89 (27)	663 (35)
High	160 (26)	59 (18)	437 (23)
Very high	90 (14)	27 (8)	210 (11)
Missing	93 (15)	36 (11)	137 (7)
Conditioning regimen intensity - no. (%)			
MAC	302 (49)	151 (45)	670 (36)
RIC	242 (39)	127 (38)	961 (51)
NMA	61 (10)	40 (12)	208 (11)
TBD	12 (2)	11 (3)	36 (2)
Missing	5 (1)	5 (1)	7 (0)
GVHD prophylaxis - no. (%)			
CD34 selection	9 (1)	4 (1)	22 (1)
Post-CY + other(s)	67 (11)	60 (18)	214 (11)
Post-CY alone	0 (0)	0 (0)	3 (0)
TAC + MMF +- other(s) (except post-CY)	107 (17)	48 (14)	352 (19)
TAC + MTX +- other(s) (except MMF, post-CY)	266 (43)	129 (39)	912 (48)
TAC + other(s) (except MMF, MTX, post-CY)	42 (7)	24 (7)	146 (8)
TAC alone	11 (2)	7 (2)	28 (1)
CSA + MMF +- other(s) (except post-CY)	38 (6)	22 (7)	118 (6)
CSA + MTX +- other(s) (except MMF, post-CY)	54 (9)	28 (8)	53 (3)
CSA + other(s) (except MMF, MTX, post-CY)	2 (0)	2 (1)	5 (0)
CSA alone	4 (1)	1 (0)	4 (0)
Other(s)	11 (2)	3 (1)	14 (1)
Missing	11 (2)	6 (2)	11 (1)
Donor type - no. (%)			
HLA-identical sibling	194 (31)	95 (28)	488 (26)
Other related	70 (11)	50 (15)	195 (10)
Well-matched unrelated (8/8)	303 (49)	157 (47)	1037 (55)
Partially-matched unrelated (7/8)	55 (9)	32 (10)	161 (9)
Missing	0 (0)	0 (0)	1 (0)
Donor/recipient sex match - no. (%)			
M-M	252 (41)	144 (43)	818 (43)
M-F	140 (23)	65 (19)	448 (24)
F-M	131 (21)	72 (22)	356 (19)
F-F	99 (16)	52 (16)	256 (14)
Missing	0 (0)	1 (0)	4 (0)

Characteristic	No therapy	Chemo +/- HMA	HMA alone
Donor/recipient CMV serostatus - no. (%)			
+/+	191 (31)	105 (31)	578 (31)
+/-	66 (11)	33 (10)	210 (11)
-/+	173 (28)	117 (35)	561 (30)
-/-	187 (30)	76 (23)	526 (28)
Missing	5 (1)	3 (1)	7 (0)
Disease risk status at HCT - no. (%)			
MDS advanced	251 (40)	20 (6)	454 (24)
MDS early	262 (42)	296 (89)	1284 (68)
Other	109 (18)	18 (5)	144 (8)
Duration of therapy - median (min-max)	NE	3 (0-69)	4 (0-153)
Time from diagnosis to HCT - median (min-max)	5 (0-690)	7 (0-264)	7 (1-370)
Year of HCT - no. (%)			
2007	71 (11)	12 (4)	17 (1)
2008	52 (8)	22 (7)	70 (4)
2009	61 (10)	22 (7)	100 (5)
2010	43 (7)	17 (5)	70 (4)
2011	32 (5)	27 (8)	144 (8)
2012	35 (6)	24 (7)	197 (10)
2013	54 (9)	43 (13)	254 (13)
2014	48 (8)	28 (8)	170 (9)
2015	62 (10)	30 (9)	210 (11)
2016	55 (9)	37 (11)	183 (10)
2017	46 (7)	24 (7)	192 (10)
2018	37 (6)	26 (8)	169 (9)
2019	26 (4)	22 (7)	106 (6)
Follow-up - median (range)	72 (3-148)	72 (4-156)	65 (3-149)

Chemo-drugs: Bendamustine, Cytarabine(Ara-C), Idarubicin(Idamycin), Clofarabine, 7+3, CPX, Vincristine, Venclexta(Venetoclax), Fludarabine, Arsenic, Carboplatin(ABT888|ABT-888), Mylotarg, Adriamycin, Cyclophosphomide(Cytoxan), Daunorubicin(Vyxeos), Midostaurin(Rydapt)
HMA: Azacytidine(Vidaza), Decitabine(Dacogen)

Table 2. Characteristics of MDS patients with <5% marrow blasts at diagnosis AND IPSS-R intermediate/high/very high risk disease at diagnosis reported to CIBMTR between the period 2008 to 2019.

Characteristic	No therapy	Chemo +/- HMA	HMA alone	Missing IPSS-R
No. of patients	389	164	1112	141
No. of centers	121	78	120	55
Patient age - median (min-max)	59 (18-77)	62 (21-78)	66 (18-79)	65 (18-81)
Age - no. (%)				
10-19	12 (3)	1 (1)	2 (0)	1 (1)
20-29	30 (8)	5 (3)	4 (0)	3 (2)
30-39	32 (8)	9 (5)	10 (1)	4 (3)
40-49	37 (10)	11 (7)	69 (6)	7 (5)
50-59	111 (29)	43 (26)	253 (23)	36 (26)
60-69	146 (38)	74 (45)	624 (56)	70 (50)
70-80	21 (5)	21 (13)	150 (13)	20 (14)
Sex - no. (%)				
Male	246 (63)	103 (63)	680 (61)	95 (67)
Female	143 (37)	61 (37)	432 (39)	46 (33)
Region - no. (%)				
US	341 (88)	153 (93)	1093 (98)	136 (96)
Canada	1 (0)	1 (1)	2 (0)	0 (0)
Europe	15 (4)	5 (3)	2 (0)	1 (1)
Asia	19 (5)	3 (2)	8 (1)	3 (2)
Australia/New Zealand	3 (1)	2 (1)	6 (1)	0 (0)
Mideast/Africa	2 (1)	0 (0)	0 (0)	0 (0)
Central/South America	8 (2)	0 (0)	1 (0)	1 (1)
Race - no. (%)				
White	325 (84)	138 (84)	989 (89)	126 (89)
Black or African American	21 (5)	12 (7)	55 (5)	5 (4)
Asian	24 (6)	8 (5)	38 (3)	5 (4)
Native Hawaiian or other Pacific Islander	1 (0)	0 (0)	2 (0)	0 (0)
American Indian or Alaska Native	1 (0)	1 (1)	5 (0)	1 (1)
More than one race	1 (0)	0 (0)	4 (0)	0 (0)
Missing	16 (4)	5 (3)	19 (2)	4 (3)
Karnofsky score - no. (%)				
90-100	218 (56)	71 (43)	517 (46)	93 (66)
< 90	162 (42)	91 (55)	577 (52)	47 (33)
Missing	9 (2)	2 (1)	18 (2)	1 (1)

Characteristic	No therapy	Chemo +/- HMA	HMA alone	Missing IPSS-R
HCT-CI - no. (%)				
0	75 (19)	29 (18)	164 (15)	29 (21)
1	43 (11)	24 (15)	119 (11)	17 (12)
2	47 (12)	22 (13)	134 (12)	20 (14)
3+	198 (51)	87 (53)	678 (61)	70 (50)
Missing	26 (7)	2 (1)	17 (2)	5 (4)
Graft source - no. (%)				
Bone marrow	62 (16)	20 (12)	140 (13)	17 (12)
Peripheral blood	327 (84)	144 (88)	972 (87)	124 (88)
Blast in marrow at diagnosis - no. (%)				
< 5%	389 (100)	164 (100)	1112 (100)	141 (100)
Blast in marrow prior to HCT - no. (%)				
< 5%	311 (80)	155 (95)	1013 (91)	124 (88)
5-10%	17 (4)	3 (2)	40 (4)	10 (7)
11-20%	7 (2)	0 (0)	7 (1)	2 (1)
Missing	54 (14)	6 (4)	52 (5)	5 (4)
Cytogenetic score - no. (%)				
Favorable	52 (13)	20 (12)	129 (12)	0 (0)
Intermediate	69 (18)	34 (21)	202 (18)	0 (0)
Poor	268 (69)	110 (67)	780 (70)	141 (100)
TBD (needs rev.)	0 (0)	0 (0)	1 (0)	0 (0)
IPSS prior to HCT - no. (%)				
Low	8 (2)	6 (4)	32 (3)	0 (0)
Intermediate-1	135 (35)	87 (53)	597 (54)	47 (33)
Intermediate-2	183 (47)	63 (38)	420 (38)	81 (57)
High	7 (2)	0 (0)	5 (0)	2 (1)
Missing	56 (14)	8 (5)	58 (5)	11 (8)
IPSS-R at diagnosis - no. (%)				
Intermediate	246 (63)	78 (48)	593 (53)	0 (0)
High	118 (30)	63 (38)	385 (35)	0 (0)
Very high	25 (6)	23 (14)	134 (12)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	141 (100)
IPSS-R prior to HCT - no. (%)				
Very low	9 (2)	5 (3)	34 (3)	6 (4)
Low	31 (8)	32 (20)	159 (14)	13 (9)
Intermediate	138 (35)	54 (33)	465 (42)	44 (31)
High	104 (27)	47 (29)	267 (24)	47 (33)
Very high	50 (13)	13 (8)	118 (11)	12 (9)

Characteristic	No therapy	Chemo +/- HMA	HMA alone	Missing IPSS-R
Missing	57 (15)	13 (8)	69 (6)	19 (13)
Conditioning regimen intensity - no. (%)				
MAC	168 (43)	61 (37)	356 (32)	52 (37)
RIC	170 (44)	69 (42)	598 (54)	65 (46)
NMA	43 (11)	24 (15)	130 (12)	17 (12)
TBD	6 (2)	6 (4)	22 (2)	6 (4)
Missing	2 (1)	4 (2)	6 (1)	1 (1)
GVHD prophylaxis - no. (%)				
CD34 selection	6 (2)	3 (2)	11 (1)	0 (0)
Post-CY + other(s)	55 (14)	43 (26)	176 (16)	20 (14)
Post-CY alone	0 (0)	0 (0)	2 (0)	1 (1)
TAC + MMF +- other(s) (except post-CY)	57 (15)	21 (13)	211 (19)	22 (16)
TAC + MTX +- other(s) (except MMF, post-CY)	167 (43)	52 (32)	546 (49)	59 (42)
TAC + other(s) (except MMF, MTX, post-CY)	25 (6)	10 (6)	61 (5)	16 (11)
TAC alone	6 (2)	5 (3)	13 (1)	6 (4)
CSA + MMF +- other(s) (except post-CY)	20 (5)	14 (9)	55 (5)	7 (5)
CSA + MTX +- other(s) (except MMF, post-CY)	35 (9)	9 (5)	22 (2)	6 (4)
CSA + other(s) (except MMF, MTX, post-CY)	2 (1)	1 (1)	3 (0)	0 (0)
CSA alone	3 (1)	0 (0)	2 (0)	0 (0)
Other(s)	7 (2)	1 (1)	4 (0)	2 (1)
Missing	6 (2)	5 (3)	6 (1)	2 (1)
Donor type - no. (%)				
HLA-identical sibling	126 (32)	42 (26)	283 (25)	37 (26)
Other related	58 (15)	37 (23)	149 (13)	16 (11)
Well-matched unrelated (8/8)	173 (44)	70 (43)	579 (52)	76 (54)
Partially-matched unrelated (7/8)	32 (8)	15 (9)	101 (9)	12 (9)
Donor/recipient sex match - no. (%)				
M-M	155 (40)	69 (42)	468 (42)	72 (51)
M-F	77 (20)	32 (20)	272 (24)	31 (22)
F-M	91 (23)	33 (20)	212 (19)	23 (16)
F-F	66 (17)	29 (18)	158 (14)	15 (11)
Missing	0 (0)	1 (1)	2 (0)	0 (0)
Donor/recipient CMV serostatus - no. (%)				
+/+	130 (33)	55 (34)	337 (30)	45 (32)
+/-	40 (10)	15 (9)	112 (10)	14 (10)
-/+	111 (29)	54 (33)	348 (31)	38 (27)
-/-	105 (27)	38 (23)	311 (28)	44 (31)
Missing	3 (1)	2 (1)	4 (0)	0 (0)

Characteristic	No therapy	Chemo +/- HMA	HMA alone	Missing IPSS-R
Disease risk status at HCT - no. (%)				
MDS advanced	183 (47)	8 (5)	324 (29)	53 (38)
MDS early	114 (29)	144 (88)	666 (60)	74 (52)
Other	92 (24)	12 (7)	122 (11)	14 (10)
Therapy - no. (%)				
No therapy	389 (100)	0 (0)	0 (0)	36 (26)
Chemo +/- HMA	0 (0)	164 (100)	0 (0)	12 (9)
HMA alone	0 (0)	0 (0)	1112 (100)	93 (66)
Duration of therapy - median (min-max)	NE	3 (0-26)	4 (0-134)	3 (0-73)
Time from diagnosis to HCT - median (min-max)	5 (0-205)	6 (0-264)	7 (2-370)	7 (3-137)
Year of HCT - no. (%)				
2007	20 (5)	1 (1)	3 (0)	1 (1)
2008	23 (6)	5 (3)	16 (1)	4 (3)
2009	28 (7)	3 (2)	29 (3)	5 (4)
2010	22 (6)	4 (2)	19 (2)	3 (2)
2011	17 (4)	3 (2)	35 (3)	5 (4)
2012	22 (6)	0 (0)	53 (5)	11 (8)
2013	27 (7)	7 (4)	78 (7)	17 (12)
2014	41 (11)	20 (12)	134 (12)	18 (13)
2015	49 (13)	24 (15)	177 (16)	15 (11)
2016	47 (12)	34 (21)	157 (14)	24 (17)
2017	41 (11)	22 (13)	170 (15)	12 (9)
2018	31 (8)	22 (13)	146 (13)	17 (12)
2019	21 (5)	19 (12)	95 (9)	9 (6)
Follow-up - median (range)	60 (3-148)	48 (4-144)	49 (3-146)	61 (7-144)

Chemo-drugs: Bendamustine, Cytarabine(Ara-C), Idarubicin(Idamycin), Clofarabine, 7+3, CPX, Vincristine, Venclexta(Venetoclax), Fludarabine, Arsenic, Carboplatin(ABT888|ABT-888), Mylotarg, Adriamycin, Cyclophosphomide(Cytoxan), Daunorubicin(Vyxeos), Midostaurin(Rydapt)
HMA: Azacytidine(Vidaza), Decitabine(Dacogen)

Characteristics Associated with Improved Survival Following Allogeneic Hematopoietic Cell Transplant (HCT) for Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Syndromes

1st PI Information:
PI Name (First, Middle, Last): Hany Elmariah
Degree(s): MD, MS
Academic Rank: Assistant Member
Email Address: hany.elmariah@moffitt.org
Institution Name: H. Lee Moffitt Cancer Center

2nd PI Information *if applicable*:
PI Name (First, Middle, Last): Rory Shallis
Degree(s): MD
Academic Rank: Assistant Professor
Email Address: rory.shallis@yale.edu
Institution Name: Yale Cancer Center

3rd PI Information *if applicable*:
PI Name (First, Middle, Last): Taiga Nishihori
Degree(s): MD
Academic Rank: Associate Member
Email Address: taiga.nishihori@moffitt.org
Institution Name: H. Lee Moffitt Cancer Center

4th PI Information *if applicable*:
PI Name (First, Middle, Last): Lohith Gowda
Degree(s): MD
Academic Rank: Assistant Professor
Email Address: lohith.gowda@yale.edu
Institution Name: Yale Cancer Center

Research Hypothesis:

We hypothesize that [A] outcomes of allogeneic (allo) hematopoietic cell transplant (HCT) for patients with myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes (MDS/MPN) will be improved with the use of myeloablative conditioning (MAC) over reduced intensity conditioning (RIC), and that [B] haploidentical donor HCT with post-transplant cyclophosphamide (PTCy) yields similar outcomes to matched sibling and matched unrelated donor transplants.

Specific Aims:

1. In patients with MDS/MPN having undergone allo HCT, compare DFS by histologic category: chronic myelomonocytic leukemia (CMML) versus atypical chronic myelogenous leukemia (aCML) versus MDS/MPN-unclassified (MDS/MPN-u) versus refractory anemia with ringed sideroblasts with thrombocytosis (RARS-T)

2. In patients with MDS/MPN having undergone allo HCT, compare overall survival (OS) by histologic category: chronic myelomonocytic leukemia (CMML) versus atypical chronic myelogenous leukemia (aCML) versus MDS/MPN-unclassified (MDS/MPN-u) versus refractory anemia with ringed sideroblasts with thrombocytosis (RARS-T)
3. In patients with MDS/MPN having undergone allo HCT, compare DFS by donor platform: haplo with PTCy versus matched related donor versus matched unrelated donor.
4. In patients with MDS/MPN having undergone allo HCT, compare OS by donor platform: haplo with PTCy versus matched related donor versus matched unrelated donor.
5. In patients with MDS/MPN having undergone allo HCT, compare DFS by conditioning intensity: RIC versus MAC.
6. In patients with MDS/MPN having undergone allo HCT, compare OS by conditioning intensity: RIC versus MAC
7. Develop a predictive model for survival post-allo HCT for MDS/MPNs.

Scientific Impact:

Based on the rarity of MDS/MPN, a prospective multi-site study addressing the true potential of haploidentical allo HCT is unlikely to be conducted. Hence, the observations from our proposed CIBMTR study would help address the unmet need of guiding the future practice MDS/MPN. Haploidentical allo HCT with post-transplant cyclophosphamide (PTCy) is an increasingly utilized platform to expand the donor pool for patients requiring transplant. This platform has demonstrated favorable rates of graft-versus-host disease (GVHD), NRM, and survival in a number of hematologic malignancies. However, no studies have evaluated haplo transplant with PTCy for MDS/MPNs. Additionally, while myeloablative conditioning (MAC) has shown superior survival in some myeloid malignancies, this benefit has not been demonstrated in MDS/MPNs. Studies are warranted to confirm identify optimal approaches to allo HCT for MDS/MPNs and to identify factors that may improve outcomes.

Scientific Justification:

The MDS/MPN overlap syndromes (including CMML, aCML, and MDS/MPN-u) include features of both MDS and MPNs.[1] Although the behavior of these diseases is diverse, they are all characterized by the potential to cause severe morbidity, including progression to acute myeloid leukemia (AML), or death. Although both non-disease-modifying medications and chemotherapy may control the disease, allo HCT is the only curative therapy for many patients.[2-5] Indeed, long term DFS may be achieved in 30-50% of patients with MDS/MPNs after allo HCT.[3,6,7] Thus, current guidelines recommend allo HCT for patients with intermediate or high risk MDS/MPNs by risk current prognostic scoring systems.[7-9]

While allo HCT is recommended for higher risk MDS/MPN patients, the optimal approach to this strategy is unclear. In other myeloid malignancies including AML and MDS, myeloablative conditioning provides a DFS and OS advantage over reduced intensity conditioning.[10-13] However, large scale data is not available comparing the outcomes of patients with MDS/MPNs by conditioning intensity.

The feasibility of allo HCT, historically, was limited in part by lack of a suitable HLA matched donor.[14] In recent years, the potential donor pool for hematologic malignancies has been expanded with the increased use of HLA haploidentical donor HCT. Specifically, the administration of high doses of PTCy has proven to be a potent intervention to prevent GVHD and allow for safe allo HCT with HLA haploidentical donors.[15] Multiple studies have shown that haploidentical allo HCT with PTCy results in relatively low

rates of GVHD and NRM as well as ultimately comparable survival when compared with that expected with more traditional allo HCT platforms across a number of hematologic malignancies.[15-19]

While allo HCT is recommended for patients with higher risk MDS/MPNs, the uncommon nature of these diseases limits the feasibility of other approaches to evaluate the optimal approaches to allo HCT and identify covariates predictive of outcomes beyond that provided by the large, high-fidelity CIBMTR database. Thus, we propose to evaluate outcomes of patients with MDS/MPN proceeding to allo HCT with a focus on identifying the utility of MAC versus RIC conditioning, the utility of haploidentical allo HCT with PTCy compared to matched donor platforms, and otherwise identify disease-related factors that may influence outcomes.

Patient Eligibility Population:

Inclusion:

1. Adult patients (age ≥ 18) who received allo HCT between 2010 and 2020 and reported to CIBMTR
2. MDS/MPN as the indication for allo HCT including:
    a. Chronic myelomonocytic leukemia (CMML)
    b. Atypical chronic myelogenous leukemia (aCML)
    c. MDS/MPN-unspecified (MDS/MPN-u)
    d. refractory anemia with ringed sideroblasts with thrombocytosis (RARS-T)
3. Donors may be HLA matched related, matched unrelated, haploidentical relative
    a. Haploidentical donors must have received T-cell replete graft with PTCy-based GVHD prophylaxis
4. Marrow or peripheral blood graft source

Exclusion:

1. Umbilical cord blood grafts
2. Mismatched unrelated donor transplant

Data Requirements:

If supplemental data is required, please review data collection forms at:
http://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx

Patient Related Variables:

1. Age: continuous, divided by decade
2. Gender: male vs. female
3. Ethnicity/Race: Caucasian vs. African American vs. Asian/Pacific Islander vs. Hispanic vs. Others vs. missing
4. Functional status (ECOG or KPS): KPS < 90 vs. 90-100
5. Hematopoietic cell transplant comorbidity index (HCT-CI)[20]: 0-2, 3+

Disease Related Variables:

1. BMT Disease Risk Index (DRI)[21]

2. Chronic myelomonocytic prognostic score (CPSS)[7]
3. Cytogenetics
4. Somatic mutation profile
5. CMML subgroup: CMML-0, CMML-1, CMML-2
6. Marrow blasts at time of transplant: <5%, 5-10%, >10%
6. Treatments prior to HCT
    a. Chemotherapy: yes vs. no
    b. Hypomethylating therapy: yes vs. no
    c. Other therapies
7. Number of lines of therapy: continuous

BMT Related Variables:

1. Conditioning regimen
    a. Myeloablative versus reduced intensity
    b. Use of radiation-based vs. chemotherapy-based conditioning
2. Donor age: continuous divided by decade
3. Donor gender: male vs. female
4. Donor relationship: sibling, parent, children, unrelated, other
5. Donor Type (matched unrelated donor, haploidentical related donor, mismatched unrelated donor)
6. Donor/Recipient cytomegalovirus
7. Donor/recipient ABO compatibility: major, minor, bidirectional, matched
8. Graft source (peripheral blood vs. marrow)
9. GVHD prophylactic regimen
    a. PTCy based versus tacrolimus/methotrexate versus tacrolimus/sirolimus versus other
10. Post-BMT maintenance therapy (if any)

Outcomes

1. Overall survival (OS): Time from allogeneic HCT to death from any cause. Patients will be censored at the time of last follow up.
2. Non-relapse mortality (NRM): Death due to any cause in the first 28 days or death due to conditions other than disease relapse or progression beyond 28 days. Events will be summarized by the cumulative incidence estimate with relapse as a competing risk.
3. Progression-free survival (PFS): Time from allogeneic HCT to death or relapse. Patients will be censored at the time of last follow up.
4. Relapse/progression: Development of relapse/progression as defined by the CIBMTR. The event will be summarized by the cumulative incidence estimate. NRM will be a competing risk for this outcome.
5. Acute GVHD: Time to development of grade II-IV acute GVHD using the Glucksberg grading system. The event will be summarized by the cumulative incidence estimate, where death and relapse without grade II-IV acute GVHD will be treated as a competing risk.

6. Chronic GVHD: Time to the development of limited or extensive chronic GVHD. The event will be summarized by the cumulative incidence estimate, where death without chronic GVHD will be treated as the competing risk. Patients will be censored at second transplant or date of last follow-up. This will have both univariate and multivariate analyses.
7. Acute and chronic GVHD, relapse-free survival (GRFS): Survival without acute grade III-IV GVHD plus chronic GVHD plus disease relapse or progression or death
8. Graft failure: Primary and secondary graft failure are considered as one outcome. Primary graft failure is defined as failure to achieve absolute neutrophil count (ANC) of 0.5 x 10^9/L or donor chimerism <5% in any compartment (T-cell chimerism ≤5%, unsorted blood or marrow chimerism). Secondary graft failure is defined as initial engraftment followed by graft loss evidenced by sustained drop in neutrophil recovery to less than 0.5 x 10^9/L or loss of donor chimerism to <5% in any compartment (T-cell chimerism ≤5%, unsorted blood or marrow chimerism) or a second infusion within the first year after transplant in patients with documented clinical remission. When there is recurrent disease it is assumed that graft failure is related to disease recurrence and not considered an event for this study. Time to graft failure is the interval between date of chimerism/date of ANC decline/date of second infusion and date of transplant; patients who are engrafted (full donor or mixed) are censored at 12 months.
9. Cause of death: causes of death will be presented in a table

Sample Requirements:
N/A

Study Design:
This is a retrospective data review of all adult patients who have undergone allo HCT for MDS/MPN. The primary objective will be to identify patients who experience superior survival outcomes with a focus on 1.) outcomes by histologic category 2.) outcomes by conditioning intensity and 3.) outcomes by donor type within the CIBMTR database. The primary endpoint is disease free survival (DFS). Other endpoints of interest will include OS, relapse rates, NRM, GVHD, engraftment, and GRFS, all calculated from the time of HCT. Survival endpoints will be calculated using the Kaplan-Meier method. Cumulative Incidences (CuI) of other endpoints including GVHD, relapse rates, and NRM will be determined. Univariate and multivariate analyses will be pursued to determine variables associated with outcomes. For comparisons, p-values $\leq$ 0.05 will be considered significant. We will create a cox proportional hazards model to predict survival in patients with MDS/MPNs. All variables associated with significant outcome in univariate modeling will be included in the cox model and expressed as hazard ratios with 95% confidence intervals. Based on the model, 3-5 risk stratification groups will be determined.

Non-CIBMTR Data Source:
None

Conflicts of Interest:

☐ Yes

X No

Proposal submission: E-mail your observational study proposal to: proposals.cibmtr@mcw.edu

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Table 1. Characteristics of MDS/MPN overlap syndromes patients reported to CIBMTR between the period 2010 to 2019.

Characteristic	CRF only	TED only
No. of patients	909	1156
No. of centers	131	189
Subdisease - no. (%)		
Ph- BCR/ABL-, Atypical CML NOS	11 (1)	41 (4)
Ph unk BCR/ABL-, Atypical CML NOS	1 (0)	3 (0)
Ph unk BCR/ABL unknown,Atypical CML NOS	1 (0)	2 (0)
CMMoL Chronic myelomonocytic leukemia	565 (62)	604 (52)
RARS Acquired idiopathic sideroblastic anemia	225 (25)	180 (16)
Myelodysplastic/myeloproliferative neoplasm,unclassifiable, MDS/MPN-U	97 (11)	274 (24)
Atypical chronic myeloid leukemia (aCML), BCR-ABL1	5 (1)	30 (3)
MDS/MPN with ring sideroblasts and thrombocytosis	4 (0)	22 (2)
Age - median (min-max)	65 (19-77)	60 (18-78)
Age at HCT - no. (%)		
18-29	6 (1)	27 (2)
30-39	14 (2)	54 (5)
40-49	53 (6)	116 (10)
50-59	180 (20)	378 (33)
60-69	503 (55)	515 (45)
>=70	153 (17)	65 (6)
Missing	0 (0)	1 (0)
Sex - no. (%)		
Male	626 (69)	720 (62)
Female	283 (31)	436 (38)
Region - no. (%)		
US	865 (95)	814 (70)
Canada	1 (0)	73 (6)
Europe	21 (2)	142 (12)
Asia	4 (0)	24 (2)
Australia/New Zealand	10 (1)	59 (5)
Mideast/Africa	2 (0)	13 (1)
Central/South America	6 (1)	31 (3)
Race - no. (%)		

Characteristic	CRF only	TED only
White	797 (88)	903 (78)
Black or African-American	50 (6)	40 (3)
Asian	32 (4)	34 (3)
Native Hawaiian or other Pacific Islander	2 (0)	2 (0)
American Indian or Alaska Native	2 (0)	3 (0)
More than one race	1 (0)	0 (0)
Missing	25 (3)	174 (15)
Karnofsky score - no. (%)		
>=90	484 (53)	675 (58)
<90	410 (45)	461 (40)
Missing	15 (2)	20 (2)
Graft type - no. (%)		
Bone marrow	117 (13)	121 (10)
Peripheral blood	746 (82)	1019 (88)
Cord blood	46 (5)	16 (1)
Reported planned conditioning intensity (MAC vs. RIC/NMA) - no. (%)		
RIC/NMA	616 (68)	642 (56)
MAC	291 (32)	495 (43)
Missing	2 (0)	19 (2)
Conditioning regimen - no. (%)		
TBI/Cy	17 (2)	27 (2)
TBI/Cy/Flu	107 (12)	100 (9)
TBI/Cy/Flu/TT	5 (1)	5 (0)
TBI/Cy/TT	1 (0)	1 (0)
TBI/Mel	26 (3)	17 (1)
TBI/Flu	60 (7)	110 (10)
TBI/other(s)	3 (0)	2 (0)
Bu/Cy	79 (9)	143 (12)
Bu/Mel	11 (1)	10 (1)
Flu/Bu/TT	8 (1)	6 (1)
Flu/Bu	351 (39)	432 (37)
Flu/Mel/TT	5 (1)	10 (1)
Flu/Mel	198 (22)	238 (21)
Cy/Flu	5 (1)	10 (1)
Cy alone	0 (0)	1 (0)
Mel alone	1 (0)	0 (0)

Characteristic	CRF only	TED only
Mel/other(s)	8 (1)	3 (0)
Treosulfan	8 (1)	26 (2)
Carb/other(s)	0 (0)	1 (0)
TLI	10 (1)	7 (1)
Other(s)	3 (0)	6 (1)
None	2 (0)	0 (0)
Missing	1 (0)	1 (0)
Donor type - no. (%)		
HLA-identical sibling	212 (23)	346 (30)
Haplo	112 (12)	83 (7)
URD 8/8	450 (50)	475 (41)
URD 7/8	62 (7)	84 (7)
URD <= 6/8	1 (0)	3 (0)
URD (Matching Unknown)	1 (0)	114 (10)
Multi-donor	2 (0)	6 (1)
Cord blood	46 (5)	16 (1)
Twin	2 (0)	1 (0)
Haplo wo PTcy	11 (1)	9 (1)
Other/missing	10 (1)	19 (2)
Donor/recipient sex match - no. (%)		
M-M	415 (46)	495 (43)
M-F	163 (18)	242 (21)
F-M	183 (20)	215 (19)
F-F	101 (11)	186 (16)
CB - recipient M	28 (3)	9 (1)
CB - recipient F	18 (2)	7 (1)
Missing	1 (0)	2 (0)
Donor/recipient CMV serostatus - no. (%)		
+/+	269 (30)	383 (33)
+/-	120 (13)	140 (12)
-/+	228 (25)	286 (25)
-/-	244 (27)	322 (28)
CB - recipient +	26 (3)	10 (1)
CB - recipient -	20 (2)	6 (1)
Missing	2 (0)	9 (1)
Molecular markers performed at dx? - no. (%)		

Characteristic	CRF only	TED only
No	236 (26)	2 (0)
Yes	363 (40)	4 (0)
Missing	310 (34)	1150 (99)
Molecular markers performed at hct? - no. (%)		
No	458 (50)	3 (0)
Yes	176 (19)	3 (0)
Missing	275 (30)	1150 (99)
Time from diagnosis to HCT - median (min-max)	10 (1-260)	9 (0-336)
Year of HCT - no. (%)		
2010	30 (3)	76 (7)
2011	51 (6)	70 (6)
2012	56 (6)	67 (6)
2013	90 (10)	58 (5)
2014	101 (11)	105 (9)
2015	106 (12)	87 (8)
2016	128 (14)	116 (10)
2017	124 (14)	164 (14)
2018	108 (12)	173 (15)
2019	115 (13)	240 (21)
Follow-up - median (range)	49 (3-123)	36 (3-124)

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Missing	2 (0)	9 (1)
Molecular markers performed at dx? - no. (%)		
No	236 (26)	2 (0)
Yes	363 (40)	4 (0)
Missing	310 (34)	1150 (99)
Molecular markers performed at hct? - no. (%)		
No	458 (50)	3 (0)
Yes	176 (19)	3 (0)
Missing	275 (30)	1150 (99)

Characteristic	CRF only	TED only
Time from diagnosis to HCT - median (min-max)	10 (1-260)	9 (0-336)
Year of HCT - no. (%)		
2010	30 (3)	76 (7)
2011	51 (6)	70 (6)
2012	56 (6)	67 (6)
2013	90 (10)	58 (5)
2014	101 (11)	105 (9)
2015	106 (12)	87 (8)
2016	128 (14)	116 (10)
2017	124 (14)	164 (14)
2018	108 (12)	173 (15)
2019	115 (13)	240 (21)
Follow-up - median (range)	49 (3-123)	36 (3-124)

I. Study Title

Impact of *TP53* Mutational Burden, Conditioning Regimen, and HLA Match on Cumulative Incidence of Relapse and Overall Survival after Allogeneic Stem Cell Transplant for *TP53*-Aberrant Myeloid Neoplasms

II. Key Words

TP53
myelodysplastic syndrome
myeloproliferative neoplasm
conditioning regimen
human leukocyte antigen

III. Principal Investigator Information (alphabetically)

Name:	Jan Cerny, MD, PhD, FACP
Academic rank:	Associate Professor
Institution:	UMass Chan Medical School and UMass Memorial Medical Center
E-mail:	jan.cerny@umassmemorial.org

Name:	Mark B. Juckett, MD
Academic rank:	Professor
Institution:	Univ. of Minnesota Medical School
E-mail:	juck0001@umn.edu

Name:	Joseph Maakaron, MD
Academic rank:	Assistant Professor
Institution:	Univ. of Minnesota Medical School
E-mail:	maaka001@umn.edu

Name:	Shyam A. Patel, MD, PhD
Academic rank:	Assistant Professor
Institution:	UMass Chan Medical School and UMass Memorial Medical Center
E-mail:	shyam.patel@umassmemorial.org

Name:	Wael Saber, MD, MS
Academic rank:	Professor
Institution:	Medical College of Wisconsin
E-mail:	wsaber@mcw.edu

IV. Proposed Working Committee

Chronic Leukemia

V. Research Question

For patients with *TP53*-aberrant myelodysplastic syndrome (MDS), or myeloproliferative neoplasms (MPNs), what is the impact of (1) *TP53* mutational burden, (2) conditioning regimen, (3) stem cell donor choice and degree of human leukocyte antigen (HLA) match, on the cumulative incidence of relapse and overall survival (OS) after allogeneic transplantation?

VI. Research Hypothesis

We hypothesize that higher intensity conditioning regimens are more effective at elimination of genomic MRD. We hypothesize that a graft-vs-leukemia (GvL) effect is the primary mediator of superior long-term outcomes. If so, HLA-mismatched transplant may improve the chance of a successful outcome through enhanced GvL effect. The enhanced GvL effect from a mismatched donor may be more apparent following a non-myeloablative preparative regimen.

VII. Specific Objectives/Outcomes to be Investigated

This study has 3 independent variables.

Independent variable 1: *TP53* mutational burden and Disease Risk Index (DRI)
We will perform subgroup analysis for *TP53* mutational burden as inferred from the co-occurring mutational profile and the presence or absence of complex karyotype (CK). **We have recently shown** that a low frequency of co-occurring mutations and high frequency of cytogenetic aberrations are directly correlated with high mutant *TP53* variant allele frequency (VAF), so we will use these as surrogates for mutant *TP53* VAF.[1] We will use the DRI to stratify patients based on disease risk.[2]

Independent variable 2: Conditioning regimen
We will perform subgroup analysis for myeloablative conditioning, reduced-intensity conditioning, and non-myeloablative conditioning, by CIBMTR definitions. We will distinguish whether any beneficial effect of regimen-intensity conditioning occurs with *TP53* mutation.

Independent variable 3: HLA haplotype of the stem cell donor
We will perform subgroup analysis for stem cell donor subtype, including matched related donor, matched unrelated donor, mismatched unrelated donor, cord blood, and haploidentical donor. We will distinguish whether any beneficial effect of HLA match occurs in patients with *TP53* mutation.

Primary endpoint: Cumulative incidence of relapse (CIR)
We will evaluate durability of remission (failure from relapse) at 30 days, 100 days, 6 months, 1 year, and 5 years. Failure from relapse is defined as absence of morphologic evidence of hematologic malignancy in a living patient. We will also assess durability of cytogenetic remission and molecular remission.

Secondary endpoints: OS, non-relapse mortality (NRM), and graft-vs-host disease (GvHD)

We will evaluate OS, NRM, and GvHD at 30 days, 100 days, 6 months, 1 year, and 5 years. OS refers to death from any cause. Patient who are alive will be censored at the time of last clinic follow up or the date of last contact, whichever is later. Multivariate Cox proportional hazard regression will be performed. Kaplan-Meier curves will be generated for subgroups of each of the 3 independent variables. Hazard ratio with 95% confidence interval (CI) will be obtained.

VIII. Scientific Impact

TP53-mutant myeloid neoplasms represent an area of unmet need. Several small and mostly single-center studies have shown positive impact of allogeneic transplant. We propose to investigate factors impacting CIR, OS, NRM, and GvHD in patients with *TP53*-mutant myeloid neoplasms undergoing allogenic transplant. The CIBMTR database offers the largest collection of transplant-related data about *TP53*-mutated patients and is the most valuable tool that would allow us to identify potential prognostic factors that would help in clinical practice. Specifically, the findings of this CIBMTR investigative effort will be impactful because they will:

- help clinicians decide on transplant candidacy for patients with *TP53* disruption, based on the *TP53* mutational burden (inferred from the co-occurring mutational profile and presence of CK)
- guide selection of the optimal conditioning regimen for transplant-eligible patients
- guide selection of the optimal donor and HLA haplotype for transplant-eligible patients
- inform translational investigations (including phase III clinical trials) of targeted therapy for this subset of patients in need of better outcomes
- inform decisions about post-transplant maintenance for this mutational subset

IX. Scientific Justification

It has been well-known that *TP53* aberrations have been associated with adverse outcomes for MDS, , and MPNs, and no targeted therapies are commercially available. The leading pharmacologic agent in late 2020 had been APR-246 (eprenatapopt), but this agent failed to meet the primary endpoint in phase III data, leaving us with no precision approaches for *TP53*-aberrant myeloid neoplasms. Since transplant outcomes data is a mandatory reporting requirement to the CIBMTR, many centers might choose to not offer transplant to this exceptionally high-risk subset of patients with myeloid neoplasms carrying *TP53* aberrations, since long-term outcomes have historically been poor. Instead, a management plan is often designed with palliative intent and frequently includes temporizing rather than definitive interventions.

Prior CIBMTR studies involving 1514 patients with *TP53*-mutant MDS showed that this mutational cohort has shorter survival (3-year OS of 20%) compared to wild-type *TP53*, and relapse rates were high.[3] **At UMass, we have recently shown** improvement in OS with transplant (compared to no transplant) for *TP53*-mutant myeloid neoplasm (14.7 vs. 5.1 months).[1] To understand the basis for the improved OS with transplant, we modeled clonal dynamics by annotating copy number variation analysis against *TP53* VAF to infer clonality.[1] We showed that *TP53*-mutant clone(s) persisted during morphologic remission and fueled relapse (with heterogenous descendant clones), but the *TP53*-mutant clones and descendant clones were eliminated only after allogeneic stem cell transplant.[1] This concept may justify

transplant, as transplant confers the highest chance of eliminating genomic MRD.[4] Our sample size was relatively small (n = 40 total and n = 11 who were transplanted). Our experience is similar to that of Yale Cancer Center, who also transplanted n = 11 patients and showed improvement in OS with transplant.[5] This CIBMTR proposal will impart a much higher power for analysis.

Much of the uncharted territory within *TP53*-mutant myeloid neoplasms includes the translational significance of allelic status (monoallelic vs. biallelic *TP53* hit) and the concurrent cytogenetics. The observation that isolated *TP53* mutation in the absence of CK is associated with improved outcome likely reflects monoallelic mutation rather than biallelic inactivation, which may occur due to various combinations of inactivating mutation on one allele with deletion, mutation, hypermethylation, or translocation on the other. For example, the largest study to date on allelic status of *TP53* mutations in MDS describes four groups: monoallelic mutation, biallelic mutations, monoallelic mutation and deletion, and monoallelic mutation and loss of heterozygosity representing 33%, 24%, 22%, and 21% of patients, respectively.[6] These groups can be consolidated into two groups according to whether one or both *TP53* genes are inactivated, and outcome was shown to be distinctly better for the monoallelic group (median OS 2.5 years) than for the multi-hit group (median OS 8.7 months). In considering the role of donor HLA-mismatch in the risk of relapse, we hypothesize that any actual effect on relapse risk will be most apparent in the population with the most chemotherapy-resistant disease, which is likely the biallelic *TP53* inactivation group. In our proposed analysis, the co-occurring mutation profile and presence/absence of CK will be used a surrogate for biallelic *TP53* inactivation.[1]

With regards to GvL effect, there is emerging data from CIBMTR about how HLA-DR and -DP mismatches in haploidentical transplant (with post-transplant cyclophosphamide) might improve outcomes.[7] This concept has not been systematically studied for *TP53*-mutant neoplasms. Thus, our proposal has great potential to expand on existing knowledge about the role of HLA factors in transplant for our mutational cohort of interest.

In summary, the scientific justification and novelty for this proposal is:

- CIBMTR registry data has thus far not been systematically analyzed for outcomes for patients with *TP53*-aberrant myeloid neoplasms, and this is the largest database that would allow us to determine prognostic factors.
- The analysis would allow us to determine which specific subgroups of *TP53*-aberrant neoplasms may derive benefit from specific conditioning regimens or HLA haplotypes. Aggregate outcomes data for this mutational subset may inform rational therapeutic design towards precision medicine or towards post-transplant maintenance.

X. Participant Selection Criteria

Inclusion criteria:

- Age ≥ 18 years at the time of diagnosis
- Diagnosis of MDS, , or MPN between 2005 and 2021, per WHO 2016 classification[8]
    - Presence of < 5% blasts prior to transplant for patients with MDS or MPN
    - Presence of complete remission prior to transplant for patients with AML
- History of allogeneic stem cell transplantation between 2005 and 2021

- Evidence of at least one of the following aberrations involving the *TP53* locus:
    - *TP53* missense mutation
    - Genomic deletion of the short arm of chromosome 17, i.e. del(17p)
    - Frameshift deletion
    - Frameshift insertion
    - Splice site deletion
    - In-frame deletion
    - Isochromosome 17

Exclusion criteria:

- Age < 18 years
- History of autologous stem cell transplantation
- Donor-derived clonal hematopoiesis involving *TP53* mutation
- Pregnant patients at the time of treatment
- Persons in prison at the time of treatment
- Persons in active military at the time of treatment
- No documented evidence of *TP53* disruption
- Advanced organ dysfunction (cardiac, renal, hepatic, pulmonary) at the time of treatment

XI. Data Requirements

Recipient data:
Age
Sex
Race
Ethnicity
Cytogenetics
Next generation sequencing with co-occurring mutation profile at diagnosis
Depth of remission prior to transplant
Hematopoietic cell transplant (HCT) comorbidity index
Time from diagnosis to HCT
Bone marrow blast percentage
Stem cell source (BM, PBSC, cord blood)
Conditioning regimen
GVHD prophylaxis regimen
Date of transplant
Time to neutrophil engraftment
Time to platelet engraftment
Immune recovery (T_{reg} frequency, CD4(+) cell frequency)
Mixed chimerism at 30 days, 100 days, 6 months, 1 year, and 5 years
Post-transplant infection (bacteria, fungal and/or viral)
Durability of remission
NGS results and MRD status at 30 days, 100 days, 6 months, 1 year, and 5 years
Relapse-free survival at 30 days, 100 days, 6 months, 1 year, and 5 years
Incidence of GvHD at 30 days, 100 days, 6 months, 1 year, and 5 years
OS at 30 days, 100 days, 6 months, 1 year, and 5 years

Not for publication or presentation

XII. Patient-Reported Outcome (PRO) Requirements

This is not applicable. The study does not require patient-reported outcomes.

XIII. Sample Requirements

This is not applicable. The study does not require biologic samples from the CIBMTR Repository.

XIV. Non-CIBMTR Data Source

This is not applicable. There is no external data source to which the CIBMTR data will be linked.

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XVI. Conflicts of Interest

The investigators declare no relevant conflicts of interest.

Table 1. Baseline characteristics of MDS and MPN patients undergoing 1st allo-HCT with TP53 mutation at any timepoint, between 2013 and 2019

Characteristic	MDS	MPN
No. of patients	293	38
No. of centers	76	22
Patient age - median (min-max)	66 (18-83)	62 (49-73)
Age - no. (%)		
Median (min-max)	6 (2-7)	6 (4-7)
18-29	4 (1)	0 (0)
30-39	2 (1)	0 (0)
40-49	11 (4)	2 (5)
50-59	47 (16)	14 (37)
60-69	160 (55)	17 (45)
70-80	69 (24)	5 (13)
Sex - no. (%)		
Male	179 (61)	26 (68)
Female	114 (39)	12 (32)
Race - no. (%)		
White	263 (90)	33 (87)
Black or African American	9 (3)	2 (5)
Asian	10 (3)	3 (8)
Native Hawaiian or other Pacific Islander	1 (0)	0 (0)
American Indian or Alaska Native	3 (1)	0 (0)
More than one race	1 (0)	0 (0)
Missing	6 (2)	0 (0)
Karnofsky score - no. (%)		
90-100	143 (49)	16 (42)
< 90	146 (50)	22 (58)
Missing	4 (1)	0 (0)
HCT-CI - no. (%)		
0	27 (9)	6 (16)
1	38 (13)	5 (13)
2	41 (14)	6 (16)
3+	185 (63)	20 (53)
TBD, review needed for history of malignancies	1 (0)	0 (0)
TBD, inconsistencies between parent and sub-questions	1 (0)	1 (3)
Therapy related (AML/MDS) - no. (%)		
No	185 (63)	35 (92)

Characteristic	MDS	MPN
Yes	100 (34)	1 (3)
Missing	8 (3)	2 (5)
Disease status prior to HCT - no. (%)		
MDS early	110 (38)	36 (95)
MDS advanced	181 (62)	0 (0)
Other	2 (1)	2 (5)
Cytogenetic score - no. (%)		
Favorable	33 (11)	11 (29)
Intermediate	18 (6)	4 (11)
Poor	242 (83)	21 (55)
TBD (needs rev.)	0 (0)	2 (5)
Blast in marrow prior to HCT - no. (%)		
< 5%	281 (96)	36 (95)
5-10%	1 (0)	0 (0)
Missing	11 (4)	2 (5)
Blast in blood prior to HCT - no. (%)		
<= 3%	232 (79)	26 (68)
> 3%	11 (4)	6 (16)
Missing	50 (17)	6 (16)
Hb count prior to HCT - no. (%)		
>= 100 g/L	144 (49)	12 (32)
< 100 g/L	149 (51)	26 (68)
ANC prior to HCT - no. (%)		
>= 1500 /uL	97 (33)	21 (55)
< 1500 /uL	185 (63)	14 (37)
Missing	11 (4)	3 (8)
Platelet count prior to HCT - no. (%)		
>= 100 x 10/L	157 (54)	22 (58)
< 100 x 10/L	135 (46)	16 (42)
Missing	1 (0)	0 (0)
Time from diagnosis to HCT - median (min-max)	6 (1-153)	16 (4-237)
Conditioning regimen intensity - no. (%)		
MAC	82 (28)	15 (39)
RIC	169 (58)	15 (39)
NMA	36 (12)	4 (11)
TBD	3 (1)	3 (8)
Missing	3 (1)	1 (3)
Conditioning regimen - no. (%)		

Characteristic	MDS	MPN
TBI/Cy	2 (1)	0 (0)
TBI/Cy/Flu	35 (12)	3 (8)
TBI/Cy/Flu/TT	1 (0)	0 (0)
TBI/Mel	12 (4)	2 (5)
TBI/Flu	24 (8)	4 (11)
TBI/other(s)	1 (0)	0 (0)
Bu/Cy	15 (5)	3 (8)
Bu/Mel	4 (1)	0 (0)
Flu/Bu/TT	5 (2)	0 (0)
Flu/Bu	104 (35)	13 (34)
Flu/Mel/TT	6 (2)	1 (3)
Flu/Mel	75 (26)	8 (21)
Cy/Flu	1 (0)	0 (0)
Mel/other(s)	1 (0)	1 (3)
Treosulfan	1 (0)	0 (0)
TLI	1 (0)	0 (0)
Other(s)	2 (1)	2 (5)
None	1 (0)	0 (0)
Missing	2 (1)	1 (3)
Donor type - no. (%)		
HLA-identical sibling	56 (19)	6 (16)
Other related	49 (17)	3 (8)
Well-matched unrelated (8/8)	159 (54)	27 (71)
Partially-matched unrelated (7/8)	16 (5)	2 (5)
Mis-matched unrelated (<= 6/8)	1 (0)	0 (0)
Cord blood	12 (4)	0 (0)
Donor/recipient sex match - no. (%)		
M-M	136 (46)	20 (53)
M-F	75 (26)	11 (29)
F-M	35 (12)	6 (16)
F-F	35 (12)	1 (3)
CB - recipient M	8 (3)	0 (0)
CB - recipient F	4 (1)	0 (0)
Donor/recipient CMV serostatus - no. (%)		
+/+	71 (24)	11 (29)
+/-	34 (12)	8 (21)
-/+	77 (26)	12 (32)
-/-	99 (34)	6 (16)

Characteristic	MDS	MPN
CB - recipient +	3 (1)	0 (0)
CB - recipient -	9 (3)	0 (0)
Missing	0 (0)	1 (3)
Graft source - no. (%)		
Bone marrow	31 (11)	0 (0)
Peripheral blood	250 (85)	38 (100)
Cord blood	12 (4)	0 (0)
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	1 (0)	0 (0)
CD34 selection	9 (3)	0 (0)
Post-CY + other(s)	70 (24)	8 (21)
TAC + MMF +- other(s) (except post-CY)	50 (17)	5 (13)
TAC + MTX +- other(s) (except MMF, post-CY)	122 (42)	17 (45)
TAC + other(s) (except MMF, MTX, post-CY)	22 (8)	2 (5)
TAC alone	3 (1)	0 (0)
CSA + MMF +- other(s) (except post-CY)	8 (3)	1 (3)
CSA + MTX +- other(s) (except MMF, post-CY)	2 (1)	2 (5)
Other(s)	2 (1)	3 (8)
Missing	4 (1)	0 (0)
ATG/Campath - no. (%)		
ATG alone	68 (23)	13 (34)
CAMPATH alone	5 (2)	0 (0)
No ATG or CAMPATH	213 (73)	24 (63)
Missing	7 (2)	1 (3)
Year of HCT - no. (%)		
2013	4 (1)	0 (0)
2014	9 (3)	0 (0)
2015	29 (10)	1 (3)
2016	39 (13)	4 (11)
2017	68 (23)	6 (16)
2018	82 (28)	11 (29)
2019	62 (21)	16 (42)
Follow-up - median (range)	36 (5-75)	24 (3-49)

CIBMTR Study Proposal

Study Title:

Long-term Outcomes of AML/MDS Patients Receiving Allogeneic Stem Cell Transplantation using Reduced-Intensity Conditioning: A propensity score analysis

Key Words:

Acute myeloid leukemia, Myelodysplastic syndrome, Allogeneic stem cell transplantation, Reduced intensity conditioning regimen, Fludarabine, Melphalan, Busulfan, Total body irradiation, Cyclophosphamide, Propensity score

1st PI Information:

PI Name: Piyanuch Kongtim
Degree(s): MD, PhD
Email Address: pkongtim@hs.uci.edu
Institution Name: The University of California Irvine, Orange, CA
Academic rank: Associate Professor
Junior investigator status: Yes
Do you identify as an underrepresented/minority?: Yes

2nd PI Information:

PI Name: Andrew J. Portuguese
Degree(s): MD
Email Address: aportugu@uw.edu
Institution Name: Fred Hutchinson Cancer Research Center, Seattle, WA
Academic rank: Fellow
Junior investigator status: Yes
Do you identify as an underrepresented/minority?: No

3rd PI Information:

PI Name: Stefan O. Ciurea
Degree(s): MD
Email Address: sciurea@hs.uci.edu
Institution Name: The University of California Irvine, Orange, CA
Academic rank: Professor
Junior investigator status: No
Do you identify as an underrepresented/minority?: No

4th PI Information:

PI Name: Bart Scott
Degree(s): MD
Email Address: bscott@fhcrc.org
Institution Name: Fred Hutchinson Cancer Research Center, Seattle, WA
Academic rank: Professor
Junior investigator status: No
Do you identify as an underrepresented/minority?: No

1st and 2nd PIs and 3rd and 4th PIs have equal contribution.

Corresponding PIs:

Stefan O. Ciurea and Bart Scott

Current ongoing work with CIBMTR:
None

Proposed working committee:
Chronic Leukemia Working Committee

Research Question:
Is there an optimal reduced intensity conditioning (RIC) regimen that can offer the best transplant outcomes with acceptable regimen-related toxicity for elderly AML/MDS patients?

Research Hypothesis:
Older patients were found to benefi from a RIC regimen using fludarabine and melphalan 100mg/m2 (FM100) when compared with more intense conditioning regimens including fludarabine and melphalan 140mg/m2 (FM140), myeloablative and RIC busulfan-based conditioning.[1] We hypothesize that FM100 regimen is associated with better long-term survival in elderly patients with AML and MDS compared with other RIC and non-myeloablative (NMA) conditioning regimens.

Specific Objectives:
Primary objective:
To compare 3-year and 5-year progression free survival (PFS) between the 5 commonly used RIC/NMA conditioning regimens

- Fludarabine and melphalan 100mg/m2 (FM100)
- Fludarabine and melphalan 140mg/m2 (FM140)
- Fludarabine and 2 days of busulfan (4 mg/kg/day PO or 3.2 mg/kg/day) (FB)
- Fludarabine, cyclophosphamide (14.5 mg/kg/d x 2 days) and 2Gy TBI (FCT)
- Fludarabine and 2GyTBI (FT)

for older patients with AML/MDS receiving allogeneic hematopoietic stem cell transplantation (AHCT).

Secondary objectives:
To compare:

1. Cumulative incidence of non-relapse mortality (NRM)
2. Cumulative incidence of relapse
3. Cumulative incidence of grades II-IV and III-IV acute GVHD
4. Cumulative incidence of extensive chronic GVHD
5. Overall survival (OS)
6. GVHD-free, relapse-free survival (GRFS)
7. Cumulative incidence of neutrophil engraftment

Scientific Impact:
Results from this analysis could have significant impact on choice of conditioning regimen for older AML/MDS patients receiving AHCT and better inform patients and transplant physicians on transplant outcomes.

Scientific Justification:
AHCT is a potentially curative treatment for patients with AML and MDS. However, this treatment modality has been traditionally limited to younger individuals and those without significant comorbidities because of higher regimen-related toxicity associated with myeloablative conditioning. Given that median age of patients with AML and MDS is >65 years, most these patients are not eligible for myeloablative AHCT.

In an attempt to extend this therapy to older and unfit patients, a major step forward was the introduction of RIC regimens [2,3], for which tumor eradication relies primarily on the graft-versus-tumor (GVT) effect [4,5] instead of myeloablation with high intensity conditioning, usually associated with prohibitive NRM. During the last several years, a variety of RIC regimens have been developed that usually include a combination of a purine analog (primarily fludarabine) with an alkylating agent (usually melphalan or busulfan) and/or low dose TBI. These regimens convey different degree of myelosuppression and have been successfully used in older or unfit patients with AML and MDS with reported long-term survival rates ranging between 30% and 60%.[6-15]

Results from a prospective multicenter phase II study evaluating the efficacy of fludarabine and busulfan (FB) RIC regimen for elderly patients with AML in first complete remission showed promising outcomes with 42% 2-year disease-free survival (DFS) and NRM of 15%.[16] Similarly, a group from Dana-Farber Cancer Institute reported encouraging AHCT outcomes in elderly AML patients using FB RIC regimen with busulfan total dose of either 3.2 or 6.4 mg/kg. In this study, PFS was comparable (40% vs. 39%, respectively) and NRM was less than 10% in both busulfan dose groups.[17] Adding rabbit ATG to the FB RIC regimen, the French group has shown a reduction of GVHD incidence without an increased risk of relapse.[18]

RIC regimens using-low dose TBI have also been commonly used.[19-21] Results with HLA-identical sibling grafts in elderly or medically infirm patients with hematological malignancies using low-dose TBI have been encouraging, and remissions, including molecular remissions, have been accomplished.[19,20] In a study by Niederwieser et al. evaluating outcomes of 52 elderly or medically unfit patients with hematological diseases who received AHCT using fludarabine in combination with 2 Gy TBI, the OS was 44% with only 11% regimen-related mortality at 100 days.[20]

The combination of melphalan with a purine nucleotide analog (fludarabine or cladribine) as conditioning regimens for AHCT in patients with hematological malignancies (including AML and MDS) has been developed at MDACC [22-25]. Several studies have reported favorable outcomes of fludarabine and melphalan (FM) 140-180 mg/m^2 conditioning regimen.[7,23,24,26,27] Results from a retrospective study in patients $\geq$ 55 years of age with AML and MDS from MDACC showed that the combination of fludarabine 100-150 mg/m^2 and melphalan 140-180 mg/m^2 RIC regimen provides better disease control than a truly non-myeloablative (NMA) regimen (120 mg/m^2 fludarabine, 4 g/m^2 cytarabine, and 36 mg/m^2 idarubicin [FAI]); however, an increased NRM and risk of GVHD were observed.[7] Investigators from the City of Hope showed that this regimen could be used safely in patients older than 70 years as rate of GVHD and NRM did not differ from those expected in younger patients treated with RIC regimens.[28]

Several studies also compared RIC FM and FB regimens for AHCT in patients with AML and MDS and reported significantly lower risk of relapse with use of FM regimen.[29-32] While overall survival was similar between the FM and FB regimens in most prior reported studies, mainly due to relapse benefit being offset by increased NRM[29-31], the CIBMTR registry study of 1258 AML and 951 MDS patients demonstrated significantly better OS and relapse-free survival benefit with FM as compared to RIC FB.[32] The total dose of melphalan used in FM conditioning in these reports was 140 mg/m^2, including in 82% of patients in the CIBMTR study. Another recent retrospective study from the CIBMTR comparing outcomes of MDS patients receiving FM vs. FB RIC regimens showed both long-term OS and DFS benefits in the FM arm due to lower relapse rates. In this study, the adjusted 3-year DFS was 46% vs. 39% in the FM and FB arm, respectively.[33]

To further reduce toxicity, melphalan 100 mg/m^2 in combination with fludarabine (FM100) has been proposed. Our group reported long-term outcomes of 36 patients with AML in complete remission who received AHCT from HLA-related and unrelated donor using fludarabine-melphalan RIC regimen, of which 21/36 patients received the FM100 regimen. With a median follow-up of 52 months, OS and PFS rates at 4 years were 71% and 68%, respectively. The cumulative incidence of NRM at 4 years was 20% and relapse-related mortality was only 8%.[24] Encouraging outcomes of fludarabine and melphalan 100 mg/m^2 or 140 mg/m^2 have also been reported in alternative donor AHCT in various hematologic malignancies.[34]

To determine whether using the FM100 regimen would provide better disease control without the risk of increased mortality in elderly patients with AML, we evaluated the effect of this RIC regimen on 404 patients with AML ≥60 years receiving AHCT between 01/2005-08/2018 at the MD Anderson Cancer Center. Conditioning regimens examined included: 1) fludarabine + melphalan 100mg/m^2 (FM100, N=78), 2) fludarabine + melphalan 140mg/m2 (FM140, N=89), 3) fludarabine + IV busulfan x 4 days with Bu AUC≥5,000/day (equivalent dose 130mg/m^2/day) (Bu≥5,000, N=131), 4) fludarabine + IV busulfan x 4 days with Bu AUC 4,000/day (equivalent dose 110mg/m^2/day) (Bu4,000, N=106). To adjust for potential selection bias in choices of conditioning regimen, a propensity score was calculated and used as a stratifying variable in a multivariable Cox regression model. Results from this analysis showed that older patients with AML benefitted from RIC with FM100, which was associated with significantly better survival compared with other more intense conditioning regimens evaluated (Figure 1), despite the fact that patients who could not receive more intense conditioning preferentially received FM100 regimen.[1]

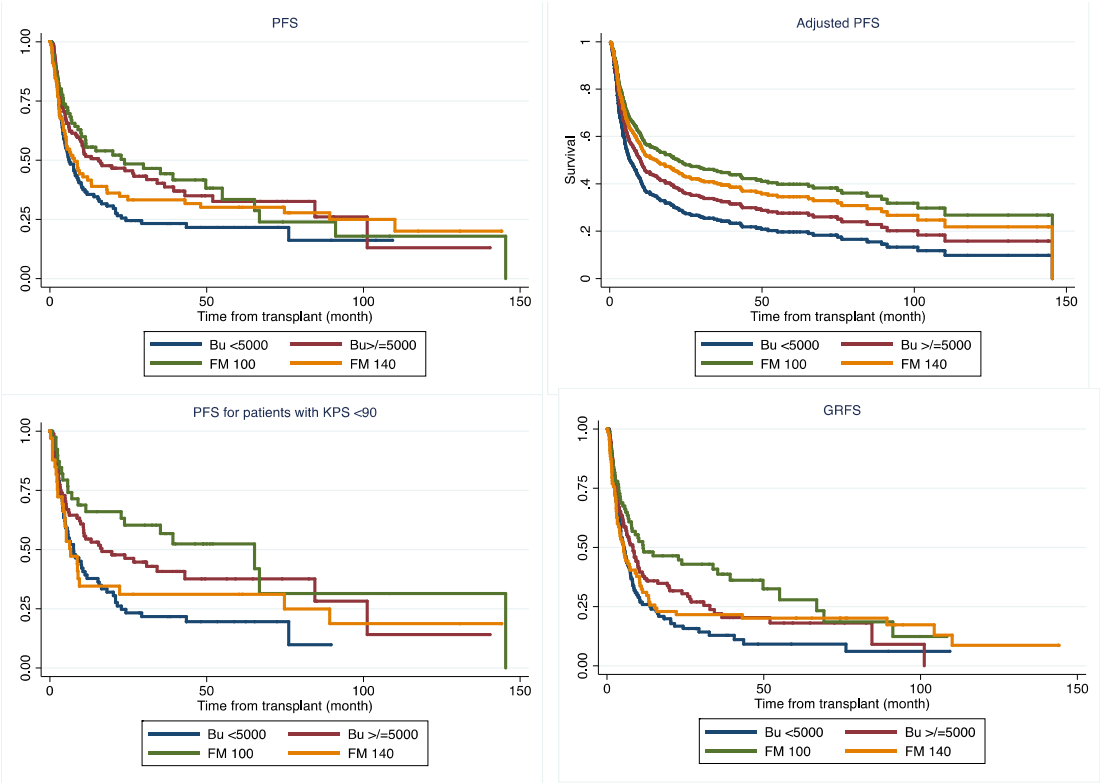

Figure 1. PFS, propensity score-adjusted PFS, PFS for patients with KPS<90% and GRFS

In a quest to find the best condition regimen for AHCT for older patients with AML/MDS, we purpose to compare outcomes between the most commonly used RIC regimens for these patients using the larger data set of patients reported to the CIBMTR.

Participant Selection Criteria:

Inclusion criteria:

- Patients with AML and MDS who underwent 1st AHCT from January 2008 to December 2020
- Age 60 years or older
- Patients in complete remission or with active disease at transplant
- Patients who received AHCT using stem cells from HLA-matched related, HLA-matched unrelated, HLA-mismatched related, HLA-mismatched unrelated and unmanipulated haploidentical donor
- Patients who received RIC/NMA conditioning regimens according to the previously defined guidelines.[2,35] This includes – fludarabine and melphalan 100mg/2 (FM100,) fludarabine and melphalan 140mg/m2

(FM140), RIC fludarabine and busulfan (FB), fludarabine, cyclophosphamide and 2Gy TBI (FCT) and fludarabine 2GyTBI (FT) regimens
- Patients who received stem cell products from bone marrow or peripheral blood

Exclusion criteria:
- Patients with a diagnosis of acute promyelocytic leukemia
- Patients who received ex vivo T cell depleted grafts
- Cord blood grafts
- Patients without complete data of conditioning regimen drug names and doses

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

Sample Requirements:
No clinical samples are required.

Study Design:
This is a retrospective cohort analysis to evaluate the impact of various RIC/NMA regimens on outcomes of elderly AML and MDS patients.
Eligible patients will be categorized into subgroups based on type of conditioning regimen as follows:
1. Patients who received reduced busulfan-based vs. FM100 vs. FM140 vs. FCT vs. FT
2. Transplant outcomes of patients in these subgroups will be compared.

Primary outcomes: PFS at 3 and 5 years after transplant

Secondary outcomes include the following:
1. Cumulative incidence of NRM at 3, 5 years
2. Cumulative incidence of relapse at 3 and 5 years
3. Cumulative incidence of grades II-IV and III-IV acute GVHD at 100 days
4. Cumulative incidence of extensive chronic GVHD at 3 and 5 years
5. OS at 3 and 5 years after transplant
6. GRFS at 3, 5 years after transplant
7. Cumulative incidence of neutrophil engraftment at 28 days.

Variables to be analyzed are

Patient related characteristics:
- Age of recipient at transplantation
- Gender (male or female)
- Karnofsky performance status (KPS)
- Hematopoietic comorbidity index (HCT-CI) with each specific category of organ dysfunction

Disease related variables at diagnosis and treatment prior to transplantation:
- Percentage of blast count in bone marrow at diagnosis
- IPSS and revised-IPSS for MDS
- Cytogenetic risk at diagnosis and at transplant for AML
- ELN 2017 genetic risk at diagnosis and at transplant for AML (if available)
- Disease risk index according to the previous described criteria[36]
- Disease status at time of transplant (active disease, 1st CR, > 1st CR)
- MRD status at transplant (if available)
- De novo or therapy-related MDS/AML
- Number of lines of therapy prior to transplantation
- Blood counts (Hgb, ANC, and platelets)

- Blast count in the peripheral blood
- Presence of pre-transplant fungal infection

Transplant related characteristics:

- Year of transplant
- Transplant center
- Type of donor
- Conditioning regimen (main effect)
- Graft source (peripheral blood, bone marrow)
- GVHD prophylaxis regimen
- Serotherapy (ATG/Alemtuzumab) use
- Donor/recipient CMV status
- Donor-recipient gender match
- Cell dose
- Donor age

Endpoint definitions and statistical analysis

The Chi-square or Fisher's exact test will be used for categorical variables and the Wilcoxon rank-sum or Kruskal–Wallis test for continuous variables to compare patient, disease, and transplant related characteristics between subgroups of interest. Primary outcome is PFS, while overall survival (OS), GVHD-free, relapse-free survival (GRFS), cumulative incidence of non-relapse mortality (NRM), relapse, acute GVHD and chronic GVHD will be assessed as secondary outcomes.

PFS is computed from date of AHCT to date of disease progression, death or the last evaluation date. Patients who were alive and did not experience progression of disease at the last follow-up date will be censored. OS and NRM will be computed from date of AHCT to last known vital sign. Patients alive at the last follow-up date will be censored. GRFS is defined as the first event among acute GVHD grades 3-4, extensive chronic GVHD, relapse, and death.[37] Those patients who did not experience an event will be censored. The Kaplan-Meier method will be used to estimate all survival measures. Differences in survival between different conditioning regimen groups will be assessed using the log-rank test. Associations between survival outcomes (PFS, OS and GRFS) and potential prognostic factors will be determined using univariable and multivariable Cox proportional hazards regression models. All variables of interest will be tested for the proportional hazard assumption and interaction terms.

The cumulative incidence function with the competing risks method will be used to estimate the endpoints of relapse, NRM, acute GVHD, and chronic GVHD. The competing risk will be included for NRM is relapse, and the competing risk included for relapse is death. For GVHD, the competing risks included is death without GVHD. Differences in cumulative incidence between subgroups will be assessed using Fine and Gray's test.[38] The univariable and multivariable Fine and Gray's subdistribution hazard regression will be used to assess the impact of variables of interest on cumulative incidence outcomes.

The propensity score adjusted analysis will be used to adjust for any potential bias derived from imbalanced pre-transplant factors between different conditioning regimen types. Initially, logistic regression model will be used for propensity score calculation from baseline patient characteristics associated with decision on choosing type of conditioning regimen. The following independent pre-transplant factors will be included in the binary logistic regression model for calculation of propensity score: age, diagnosis, disease risk index[36], KPS, HCT-CI, stem cell source, donor type, transplant center and year of transplant. The propensity score will be used as an adjusted variable in a univariable and multivariable regression model to calculate the impact of type of conditioning regimen on outcomes of interest. A P value of less than 0.05 is considered for statistical significance. Multiple imputation will be used to impute missing data of variables with >5% missing rate.

We would be happy to do the analysis to save statistician time for CIBMTR.

Non-CIBMTR Data Source: If not enough patients will be in the CIBMTR database, a combined proposal with EBMT data will be considered.

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Table 1. Baseline characteristics of AML and MDS patients undergoing 1st allo-HCT with Flu/Mel conditioning regimen, between 2008 and 2019

Characteristic	AML	MDS	Total
No. of patients	1774	2598	4372
No. of centers	137	126	152
Patient age - median (min-max)	66 (60-81)	68 (60-83)	67 (60-83)
Age - no. (%)			
60-69	1399 (79)	1868 (72)	3267 (75)
70-80	375 (21)	730 (28)	1105 (25)
Sex - no. (%)			
Male	1088 (61)	1734 (67)	2822 (65)
Female	686 (39)	864 (33)	1550 (35)
Race - no. (%)			
White	1527 (86)	2386 (92)	3913 (90)
Black or African American	104 (6)	81 (3)	185 (4)
Asian	87 (5)	77 (3)	164 (4)
Native Hawaiian or other Pacific Islander	9 (1)	4 (0)	13 (0)
American Indian or Alaska Native	9 (1)	5 (0)	14 (0)
More than one race	3 (0)	5 (0)	8 (0)
Missing	35 (2)	40 (2)	75 (2)
Karnofsky score - no. (%)			
90-100	870 (49)	1233 (47)	2103 (48)
< 90	884 (50)	1334 (51)	2218 (51)
Missing	20 (1)	31 (1)	51 (1)
HCT-CI - no. (%)			
0	338 (19)	374 (14)	712 (16)
1	233 (13)	280 (11)	513 (12)
2	233 (13)	329 (13)	562 (13)
3+	935 (53)	1579 (61)	2514 (58)
TBD, review needed for history of malignancies	0 (0)	3 (0)	3 (0)
TBD, inconsistencies between parent and sub-questions	15 (1)	25 (1)	40 (1)
NA, f2400 (pre-TED) not completed	8 (0)	4 (0)	12 (0)
Missing	12 (1)	4 (0)	16 (0)
Therapy related (AML/MDS) - no. (%)			
No	1555 (88)	2036 (78)	3591 (82)
Yes	171 (10)	490 (19)	661 (15)
Missing	48 (3)	72 (3)	120 (3)
Cytogenetic score - no. (%)			

Characteristic	AML	MDS	Total
Favorable	53 (3)	1055 (41)	1108 (25)
Intermediate	1050 (59)	356 (14)	1406 (32)
Poor	524 (30)	991 (38)	1515 (35)
TBD (needs rev.)	122 (7)	160 (6)	282 (6)
Not tested	10 (1)	12 (0)	22 (1)
Missing	15 (1)	24 (1)	39 (1)
Disease status at time of HCT - no. (%)			
PIF	237 (13)	0 (0)	237 (5)
CR1	1178 (66)	0 (0)	1178 (27)
CR2	211 (12)	0 (0)	211 (5)
>=CR3	11 (1)	0 (0)	11 (0)
Relapse	105 (6)	0 (0)	105 (2)
Missing	32 (2)	2598 (100)	2630 (60)
Disease risk of MDS - no. (%)			
MDS early	0 (0)	930 (36)	930 (21)
MDS advanced	0 (0)	1650 (64)	1650 (38)
Other	0 (0)	18 (1)	18 (0)
Missing	1774 (100)	0 (0)	1774 (41)
Blast in marrow prior to HCT - no. (%)			
< 5%	1467 (83)	2280 (88)	3747 (86)
5-10%	99 (6)	134 (5)	233 (5)
11-20%	33 (2)	38 (1)	71 (2)
> 20%	45 (3)	0 (0)	45 (1)
Missing	130 (7)	146 (6)	276 (6)
Blast in blood prior to HCT - no. (%)			
<= 3%	1349 (76)	2080 (80)	3429 (78)
> 3%	78 (4)	148 (6)	226 (5)
Missing	347 (20)	370 (14)	717 (16)
Hb count prior to HCT - no. (%)			
>= 100 g/L	1072 (60)	1160 (45)	2232 (51)
< 100 g/L	701 (40)	1438 (55)	2139 (49)
Missing	1 (0)	0 (0)	1 (0)
ANC prior to HCT - no. (%)			
>= 1500 /uL	1080 (61)	910 (35)	1990 (46)
< 1500 /uL	625 (35)	1578 (61)	2203 (50)
Missing	69 (4)	110 (4)	179 (4)
Platelet count prior to HCT - no. (%)			
>= 100 x 10/L	1083 (61)	1187 (46)	2270 (52)

Characteristic	AML	MDS	Total
< 100 x 10/L	679 (38)	1411 (54)	2090 (48)
Missing	12 (1)	0 (0)	12 (0)
Graft source - no. (%)			
Bone marrow	249 (14)	255 (10)	504 (12)
Peripheral blood	1525 (86)	2343 (90)	3868 (88)
IPSS prior to HCT - no. (%)			
Low	0 (0)	401 (15)	401 (9)
Intermediate-1	0 (0)	1248 (48)	1248 (29)
Intermediate-2	0 (0)	573 (22)	573 (13)
High	0 (0)	19 (1)	19 (0)
Missing	1774 (100)	357 (14)	2131 (49)
IPSS-R prior to HCT - no. (%)			
Very low	0 (0)	353 (14)	353 (8)
Low	0 (0)	677 (26)	677 (15)
Intermediate	0 (0)	683 (26)	683 (16)
High	0 (0)	354 (14)	354 (8)
Very high	0 (0)	138 (5)	138 (3)
Missing	1774 (100)	393 (15)	2167 (50)
Time from diagnosis to HCT - median (min-max)	6 (0-331)	9 (1-549)	7 (0-549)
Conditioning regimen intensity - no. (%)			
RIC	1297 (73)	2152 (83)	3449 (79)
NMA	477 (27)	446 (17)	923 (21)
Conditioning regimen (Main effect) - no. (%)			
FM100	125 (7)	195 (8)	320 (7)
FM140	410 (23)	697 (27)	1107 (25)
FB	669 (38)	1005 (39)	1674 (38)
FCT	381 (21)	361 (14)	742 (17)
FT	189 (11)	340 (13)	529 (12)
Donor type - no. (%)			
HLA-identical sibling	377 (21)	589 (23)	966 (22)
Other related	413 (23)	340 (13)	753 (17)
Well-matched unrelated (8/8)	819 (46)	1434 (55)	2253 (52)
Partially-matched unrelated (7/8)	134 (8)	209 (8)	343 (8)
Mis-matched unrelated (<= 6/8)	16 (1)	13 (1)	29 (1)
Multi-donor	6 (0)	8 (0)	14 (0)
Unrelated (matching TBD)	7 (0)	5 (0)	12 (0)
Missing	2 (0)	0 (0)	2 (0)
Donor/recipient sex match - no. (%)			

Characteristic	AML	MDS	Total
M-M	749 (42)	1231 (47)	1980 (45)
M-F	411 (23)	529 (20)	940 (22)
F-M	334 (19)	496 (19)	830 (19)
F-F	273 (15)	333 (13)	606 (14)
Missing	7 (0)	9 (0)	16 (0)
Donor/recipient CMV serostatus - no. (%)			
+/+	603 (34)	789 (30)	1392 (32)
+/-	164 (9)	292 (11)	456 (10)
-/+	627 (35)	782 (30)	1409 (32)
-/-	365 (21)	725 (28)	1090 (25)
Missing	15 (1)	10 (0)	25 (1)
GVHD prophylaxis - no. (%)			
CD34 selection	6 (0)	7 (0)	13 (0)
Post-CY + other(s)	438 (25)	410 (16)	848 (19)
Post-CY alone	1 (0)	3 (0)	4 (0)
TAC + MMF +- other(s) (except post-CY)	272 (15)	527 (20)	799 (18)
TAC + MTX +- other(s) (except MMF, post-CY)	678 (38)	1060 (41)	1738 (40)
TAC + other(s) (except MMF, MTX, post-CY)	90 (5)	239 (9)	329 (8)
TAC alone	49 (3)	54 (2)	103 (2)
CSA + MMF +- other(s) (except post-CY)	126 (7)	194 (7)	320 (7)
CSA + MTX +- other(s) (except MMF, post-CY)	67 (4)	56 (2)	123 (3)
CSA + other(s) (except MMF, MTX, post-CY)	11 (1)	10 (0)	21 (0)
CSA alone	14 (1)	6 (0)	20 (0)
Other(s)	22 (1)	32 (1)	54 (1)
ATG/Campath - no. (%)			
ATG alone	390 (22)	602 (23)	992 (23)
CAMPATH alone	67 (4)	78 (3)	145 (3)
No ATG or CAMPATH	1317 (74)	1918 (74)	3235 (74)
Year of HCT - no. (%)			
2008	156 (9)	43 (2)	199 (5)
2009	119 (7)	38 (1)	157 (4)
2010	34 (2)	15 (1)	49 (1)
2011	47 (3)	121 (5)	168 (4)
2012	56 (3)	176 (7)	232 (5)
2013	155 (9)	261 (10)	416 (10)
2014	233 (13)	267 (10)	500 (11)
2015	280 (16)	330 (13)	610 (14)
2016	221 (12)	362 (14)	583 (13)

Characteristic	AML	MDS	Total
2017	147 (8)	377 (15)	524 (12)
2018	170 (10)	348 (13)	518 (12)
2019	156 (9)	260 (10)	416 (10)
Follow-up - median (range)	60 (3-152)	49 (3-149)	58 (3-152)