A G E N D A
CIBMTR WORKING COMMITTEE FOR MORBIDITY, RECOVERY, AND SURVIVORSHIP
San Antonio, Texas
Friday, February 23, 2024, 1:00 pm – 3:00 pm CST

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Co-Chair:	**Mohamed Sorror, MD, MSc; Fred Hutchinson Cancer Research Center, Seattle, WA; Phone: 206-667-6298; Email: msorror@fredhutch.org**
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1. **Introduction**
   a. Minutes and Overview Plan from February 2023 meeting (Attachment 1)

2. **Accrual Summary** (Attachment 2)

3. **Presentations, published or submitted papers**

   a. **RT18-01a:** Broglie L, Friend BD, Chhabra S, Logan BR, Bupp C, Schiller G, Savani BN, Stadtmauer E, Abraham AA, Aljurf M, Badawy SM, Perez MAD, Guinan EC, Hashem H, Krem MM, Lazarus HM, Rotz SJ, Wirk B, Yared JA, Pasquini M, Thakar MS, Sorror ML. Expanded HCT-CI definitions capture comorbidity better for younger patients of allogeneic HCT for nonmalignant diseases. ***Transplantation and Cellular Therapy. 2023 Feb 1; 29(2):125.e1-125.e9. doi:10.1016/j.jtct.2022.11.020. Epub 2022 Nov 25. PMC9911359.***

   b. **RT18-01b:** Friend BD, Broglie L, Logan BR, Chhabra S, Bupp C, Schiller G, Beitinjaneh A, Perez MAD, Guilcher G, Hashem H, Hildebrandt GC, Krem MM, Lazarus HM, Nishihori T, Nusrat R, Rotz SJ, Wirk B, Wieduwilt M, Pasquini M, Savani BN, Stadtmauer EA, Sorror ML, Thakar MS. Adapting the HCT-CI definitions for children, adolescents, and young adults with hematologic malignancies undergoing allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2023 Feb 1; 29(2):123.e1-123.e10. doi:10.1016/j.jtct.2022.11.019. Epub 2022 Nov 26. PMC9911376.***

c. **LE19-01a:** Zinter M, Brazauskas R, Strom J, Chen S, Bo-Subait S, Sharma A, Beitinjaneh A, Dimitrova D, Guilcher G, Preussler J, Myers K, Bhatt N, Ringden O, Hematti P, Hayashi R, Patel S, De Oliveira S, Rotz S, Badawy S, Nishihori T, Buchbinder D, Hamilton B, Savani B, Schoemans H, Sorror M, Winestone L, Duncan C, Phelan R, Dvorak C. Intensive care risk and long-term outcomes in pediatric allogeneic hematopoietic cell transplant recipients. ***Blood Advances. doi:10.1182/bloodadvances.2023011002. Epub 2023 Dec 21.***

d. **LE20-02:** Taylor MR, Cole SW, Strom J, Brazauskas R, Baker KS, Phelan R, Buchbinder D, Hamilton B, Schoemans H, Shaw BE, Sharma A, Bhatt NS, Badawy SM, Winestone LE, Preussler JM, Mayo S, Jamani K, Nishihori T, Lee MA, Knight JM. Unfavorable transcriptome profiles and social disadvantage in hematopoietic cell transplantation: A CIBMTR analysis. ***Blood Advances. 2023 Nov 28; 7(22):6830-6838. doi:10.1182/bloodadvances.2023010746. Epub 2023 Sep 29.***

e. **LE16-02b** Late effects after AlloHCT for pediatric patients with non-malignant diseases. (J Kahn/ P Satwani) ***Submitted.***

4. Studies in progress (Attachment 3)

a. **LE12-03a:** Outcomes for patients undergoing hematopoietic cell transplantation followed by solid organ transplants (M Gupta/ PL Abt/ M Levine) **Manuscript Preparation.**
b. **LE12-03b:** Outcomes for patients undergoing solid organ transplants followed by hematopoietic cell transplantation (M Gupta/ PL Abt/ M Levine) **Manuscript Preparation.**
c. **LE17-01a:** Late effects after hematopoietic stem cell transplantation for sickle cell disease. (E Stenger/ R Phelan/ S Shenoy/ L Krishnamurti) **Manuscript Preparation.**
d. **LE17-01b:** Comparison of survival between transplanted and non-transplanted SCD patients. (E Stenger/ R Phelan/ S Shenoy/ L Krishnamurti) **Data File Preparation.**
e. **LE18-01:** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies. (L Broglie/ P Satwani) **Manuscript Preparation.**
f. **LE19-01b:** POP TA-DAH! - Predictors of Pediatric Transplant Associated Diffuse Alveolar Hemorrhage (M Zinter/ C Dvorak/ C Duncan) **Data File preparation.**
g. **LE19-02:** Incidence and predictors of long-term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. (M Veeraputhiran/ S Pingali/ A Mukherjee/ L Muffly) **Analysis.**
h. **LE20-01:** Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/ E Chow) **Protocol Development.**
i. **LE21-01:** Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/ I Muhsen/ L Yanez San Segundo/ S K. Hashmi/ M- Angel Perales/ A Kansagra) **Data File Preparation.**
j. **RT19-01:** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/ A Nagler) **Data File Preparation.**
k. **RT19-02:** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima) **Protocol Development.**
l. **RT20-01:** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients (R Jayani/ H Murff) **Data File Preparation.**

m. **MRS22-01:** Racial/ethnic disparities and role of poverty in long-term health outcomes among survivors of allogeneic hematopoietic cell transplant performed in childhood (N Bhatt/ A Sharma/ C Duncan/ L Jimenez-Kurlander) **Protocol Development.**
n. **MRS22-02:** Post-transplant cyclophosphamide related cardiomyopathy; incidence, risk factors and outcome: A retrospective review from CIBMTR database (K Poonsombudlert/ C Strouse) **Protocol Development.**
o. **MRS23-01:** Updated Analysis of Long-Term Survival and Late Deaths after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies and Severe Aplastic Anemia (U Rao/ M Battiwalla) **Protocol Pending.**

5. Future/Proposed Studies

a. **PROP 2305-05/2310-55:** Defibrotide prophylaxis for hepatic sinusoidal obstructive syndrome in hematopoietic cellular therapy recipients: real-world outcomes and health care utilization implications (M Pamukcuoglu/ M Schoettler/ K Williams) (Attachment 4)
b. **PROP 2310-28:** Toxicity profile and survival of patients with BMI >30 undergoing allogeneic stem cell transplantation (N Tijaro Ovalle/ A Jakubowski) (Attachment 5)
c. **PROP 2310-35/2310-210:** Incidence, risk factors, and characteristics of subsequent neoplasms in CAR-T recipients and its impact on survival (M Shah/ V Irizarry Gatell/ R Faramand) (Attachment 6)
d. **PROP 2310-45:** The impact of obesity and body weight on immune mediated toxicities and outcomes of patients with relapsed/refractory large B cell lymphoma treated with CD19 CAR T cells (K Wudhikarn) (Attachment 7)
e. **PROP 2310-53/2310-232:** Impact of renal injury before CAR-T therapy (H Murthy/ M Iqbal/ A Mirza /L Gowda) (Attachment 8)
f. **PROP 2310-128/2310-136/2310-212/2310-245**: Immune effector cell associated HLH-like Syndrome (IEC-HS) in patients undergoing CAR T cell therapy (T Jain/ K McNerney/ J Roman Diaz/ C Freeman/ L Gowda/ A Mirza/ S Gupta/ V Bachanova) (Attachment 9)
g. **PROP 2310-160:** Determinants of Immune Effector Cell-Associated Hematotoxicity (ICAHT) following CAR-T therapy across Disease Entities (K Rejeski/ R Shouval) (Attachment 10)
h. **PROP 2310-173:** Return to work among adolescent and young adult survivors of autologous stem cell transplantation in the US (N Khan) (Attachment 11)

Proposed studies; not accepted for consideration at this time

a. **PROP 2305-04:** Comparing Icteric Veno-occlusive disease with Anicteric Veno-occlusive disease (VOD) according to Overall Survival (OS), VOD resolution time (RT) under the Defibrotide treatment. *Unavailability of bilirubin data.*

b. **PROP 2309-07**: Cardiac Toxicity in Haploidentical transplant with PTCy vs Matched transplant with PTCy vs Matched Transplant with CNI. **O***verlaps with MRS 22-02.*

c. **PROP 2309-10:** Use of Anakinra for the Treatment of ICANS after Anti-CD19 Autologous CART in B-cell Lymphoma. *Lower impact.*

d. **PROP 2310-48:** Psychiatric and Cognitive Health Among Survivors of Chimeric Antigen Receptor Therapy in the United States. *Not enough PRO data.*

e. **PROP 2310-65:** Machine Learning based Mortality Risk Assessment in Stem cell Transplant for Non-Malignant Bone Marrow Disorders. *Low power with rare disease and low mortality.*

f. **PROP 2310-69:** Trends in Primary Graft Failure in allogeneic hematopoietic stem Cell Transplant Recipients. *Lower impact.*

g. **PROP 2310-95:** Merging CIBMTR and SEER data to provide a resource for studying rare prior and subsequent neoplasms. *May consider as a separate effort.*

h. **PROP 2310-148:** Incidence and risk factors of engraftment syndrome in autologous hematopoietic cell transplant recipients and its impact on outcomes. *Lower impact.*

i. **PROP 2310-159:** Early Platelet count recovery before white cell count recovery after allogeneic hematopoietic cell transplantation and effect on transplant outcomes. *Lower impact.*

j. **PROP 2310-163:** Risk factors for long-term osteoporosis and fragility fractures after pediatric HCT. *Not enough data for pediatric osteoporosis/fracture.*

k. **PROP 2310-189:** Updated Analysis of the Prevalence of Cellular Therapy Survivors in the United States. *May consider as a separate effort.*

l. **PROP 2310-195:** A comparison of Melphalan (Mel) dosing in the setting of post-transplant cyclophosphamide (PTCy) GVHD prophylaxis*. Limitations on Mel dosing data.*

m. **PROP 2310-211:** Sexual Health Among Survivors of Chimeric Antigen Receptor T-cell Therapy in the United States. *Not enough PRO data.*

n. **PROP 2310-216:** Long-term survival and late mortality among patients treated with allogeneic hematopoietic cell transplant for inborn errors of metabolism. *Two MRSWC studies looking at late mortality.*

o. **PROP 2310-217:** Comprehensive Assessment of Health-Related Quality of Life (HRQoL), Toxicity and Clinical Outcomes Following Chimeric Antigen Receptor T-Cell Therapy for Hematological Malignancies. *Not enough PRO data.*

p. **PROP 2310-218:** Efficacy of Three Prophylactic Measures to Mitigate the Toxicities in Chimeric Antigen Receptor (CAR) T-cell Therapy in Lymphoma. *Low numbers of patients receiving prophylactic therapies.*

q. **PROP 2310-250:** Incidence of hypogammaglobulinemia following CD19-directed CAR-T therapy and its impact on CAR-T persistence and outcomes*. Not enough data on this topic.*

r. **PROP 2310-269:** Late mortality and standardized mortality ratio (SMR) in patients surviving after allogeneic hematopoietic cell transplantation (HCT). *Overlaps with MRS 23-01.*

6. Closing Remarks

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR MORBIDITY, RECOVERY, AND SURVIVORSHIP
Orlando, Florida
Thursday, February 16, 2023, 12:15 pm – 2:15 pm (EST)

Co-Chair:	**Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven; Leuven, Belgium;** **Phone: 321-634-6880; E-mail: helene.schoemans@uzleuven.be**
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Co-Chair:	**Bipin Savani, MD; Vanderbilt University Medical Center** **Phone: 615-936-8422; Email: bipin.savani@vumc.org**
Co-Chair:	**Mohamed Sorror, MD, MSc; Fred Hutchinson Cancer Research Center** **Phone: 206-667-6298; Email: msorror@fredhutch.org**
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Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center, Milwaukee, WI;** **Telephone: 414-456-8687; E-mail: ruta@mcw.edu**
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1. Introduction

The CIBMTR Morbidity Recovery and Survivorship Working Committee (MRSWC) meeting was called to order at 12:15 EST on Thursday, February 16, 2023 by Dr. Rachel Phelan. She introduced the working committee chairs and other leadership and announced the end of Dr. David Buchbinder's and Dr. Edward Stadtmauer's terms. There will not be any incoming chairs this year. She also provided a reminder about the merging of the Late Effects & Quality of Life Working Committee (LEWC) and the Regimen-Related Toxicity Working Committee (RTWC) to form the Morbidity, Recovery, and Survivorship Working Committee (MRSWC). This merge was announced via email in the fall of 2022 and was done to better align the goals of both working committees in the study of both early and late complications of transplants. Proposals that were submitted to either LEWC or RTWC were considered for presentation at this session, the inaugural MRSWC Tandem session.

Dr. Betty Hamilton continued by reviewing the CIBMTR conflict of interest policy and displaying the conflict of interest declarations for MRSWC leadership. She then provided information about CIBMTR's publicly available data sets and encouraged investigators to use them for research studies. She explained

how to become a member of MRSWC and the goals of this committee.

Dr. Hélène Schoemans continued by explaining the scoring process for proposals and ensuring that attendees were able to access the online scoring sheet. She also reviewed authorship guidelines for publications of CIBMTR studies and provided an overview of different data types within CIBMTR, including the data sources most relevant to this committee's studies.

Dr. Bipin Savani then provided some tips to investigators for writing a strong proposal. He announced the CIBMTR Early Clinical Investigator training program and encouraged applications to said program. He explained the process that CIBMTR studies follow.

a. **Minutes and Overview Plan from April 2022 meeting**
   - Late Effects and Supportive Care (Attachment 1a)
   - Regimen-Related Toxicity and Supportive Care (Attachment 1b)

2. Accrual Summary (Attachment 2) and PRO data accrual (Attachment 3)

3. Presentations, published or submitted papers

Dr. Bipin Savani gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **R718-S1:** Broglie L, Friend BD, Chhabra S, Bupp C, Schiller GJ, Logan B, Pasquini MC, Savani B, Stadtmauer EA, Thakar MS, Sorror M. Differential use of the hematopoietic cell transplantation-comorbidity index among adult and pediatric transplant physicians. ***Leukemia & Lymphoma. 2022 Oct 1; 63(10):2507-2510. doi:10.1080/10428194.2022.2076848. Epub 2022 May 18.***
b. **RT18-02:** Abou-Ismail MY, Fraser R, Allbee-Johnson M, Metheny L 3rd, Ravi G, Ahn KW, Bhatt NS, Lazarus HM, de Lima M, El Jurdy N, Hematti P, Beitinjaneh AM, Nishihori T, Badawy SM, Sharma A, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation? ***British Journal of Haematology. 2022 May 1; 197(3):326-338. doi:10.1111/bjh.18108. Epub 2022 Mar 14. PMC9675037.***
c. **RT18-03:** Patel SS, Ahn KW, Khanal M, Bupp C, Allbee-Johnson M, Majhail NS, Hamilton BK, Rotz SJ, Hashem H, Beitinjaneh A, Lazarus HM, Krem MM, Prestidge T, Bhatt NS, Sharma A, Gadalla SM, Murthy HS, Broglie L, Nishihori T, Freytes CO, Hildebrandt GC, Gergis U, Seo S, Wirk B, Pasquini MC, Savani BN, Sorror ML, Stadtmauer EA, Chhabra S. Noninfectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. ***Transplantation and Cellular Therapy. 2022 Jun 1; 28(6):310-320. doi:10.1016/j.jtct.2022.03.015. Epub 2022 Mar 18. PMC9197865.***
d. **LE20-02:** Association between patient-reported social determinant of health outcomes and a social genomics profile in allogeneic hematopoietic cell transplantation: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) ***Oral presentation, ASH 2022. Poster presentation, Tandem 2023.***
e. **RT18-01a:** Expanded Definitions in the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) Better Classifies Comorbidity in Children and Young Adults with Non-Malignant Diseases. (L Broglie/B Friend/G Schiller/M Thakar /M Sorror) ***Accepted.***
f. **RT18-01b:** Adapting the HCT-CI Applicability for Children, Adolescents, and Young Adults with Hematologic Malignancies Undergoing Allogeneic Stem Cell Transplantation. (B Friend/L Broglie/G Schiller/M Thakar/M Sorror) ***Accepted.***

4. Studies in progress (Attachment 3)
Dr. Ed Stadtmauer presented the studies in progress.

a. **LE16-02b** Late effects after AlloHCT for pediatric patients with non-malignant diseases (J Kahn/ P Satwani) **Manuscript Preparation.**
b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Manuscript Preparation.**
c. **LE17-01a** Late effects after hematopoietic stem cell transplantation for sickle cell disease. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) **Manuscript Preparation.**
d. **LE17-01b** Comparison of survival between transplanted and non-transplanted SCD patients. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) **Data File Preparation.**
e. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Manuscript Preparation.**
f. **LE18-03** Incorporating patient reported outcomes into individualized prognostication tools for survival and quality of life in transplant patients. (B Shaw) **Manuscript Preparation.**
g. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) **Analysis.**
h. **LE19-02** Incidence and predictors of long-term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) **Analysis.**
i. **LE20-01** Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) **Protocol Development.**
j. **LE20-02** Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) **Manuscript Preparation.**
k. **LE21-01** Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M- Angel Perales/A Kansagra) **Data File Preparation.**
l. **RT19-01** Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/B Savani/A Nagler) **Data File Preparation.**
m. **RT19-02** Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants (K Adekola/N Ali/O Frankfurt/L Metheny/J Moreira/M de Lima) **Protocol Development.**
n. **RT20-01** Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients (R Jayani/H Murff) **Data File Preparation.**
o. **MRS22-01** Racial/ethnic disparities and role of poverty in long-term health outcomes among survivors of allogeneic hematopoietic cell transplant performed in childhood (N Bhatt/A Sharma/C Duncan/L Jimenez-Kurlander) **Protocol Development.**
p. **MRS22-02** Post-transplant cyclophosphamide related cardiomyopathy; incidence, risk factors and outcome: A retrospective review from CIBMTR database (K Poonsombudlert/C Strouse) **Protocol Development.**

5. Future/Proposed Studies

a. **PROP 2210-30** Impact of melphalan dose reduction on regimen-related toxicity in multiple myeloma patients undergoing autologous transplant. (M Krem/C Wagner) (Attachment 5)

Dr. Ed Stadtmauer introduced Dr. Maxwell Krem. The aim of this proposal is to compare pre- and post-auto-HCT complication measures for multiple myeloma patients who received reduced melphalan dose MEL140 or standard melphalan dose MEL200. The CIBMTR identified n=981 adults with dose MEL140 and n=5562 adults with dose MEL200 undergoing

autologous transplant for multiple myeloma between 2012-2018.

Dr. Krem was asked why non-relapse mortality (NRM) was chosen as the primary endpoint for analysis in this proposal, rather than event-free survival (EFS). He answered that he considers both to be equally important endpoints to study, but NRM was ultimately chosen as the primary endpoint due to its association with frailty. EFS will be a secondary endpoint in analysis.

It was confirmed that pre-transplant disease response will be included as a potential predictor in multivariate analysis.

One attendee wished to know whether there is data available about why a given melphalan dose was selected (i.e. whether a reduced dose was selected due to patient frailty). This data is not collected within CIBMTR, but it may be possible to infer such reasoning from the co-morbidities collected as part of the HCT-CI index.

There was some question as to whether ISS should be used as a predictor in multivariate analysis. The reasoning for this variable is that it was the primary measure used during the time span that the study encompasses.

It was confirmed that tandem transplants were excluded from the prospective study population.

This proposal received a mean scientific impact score of 4.2 and a median score of 4 from n=77 participants. Ultimately, this proposal was not chosen to proceed as a CIBMTR study due to lower scientific impact.

b. **PROP 2210-63/2210-117/2210-219** Modifying the risk and mortality of veno-occlusive disease via development of a contemporary risk assessment model. *(M Schoettler/K Williams/W Stock/G Roloff/C Strouse*) (Attachment 6)
Dr. Hélène Schoemans introduced Dr. Gregory Roloff. The aim of this proposal is to identify patient-, disease-, and treatment-related variables associated with the incidence of veno-occlusive disease in adult and pediatric patients undergoing allogeneic transplant. This includes the investigation of defibrotide prophylaxis and inotuzumab ozogamycin or gemtuzumab ozogamycin therapy prior to transplant as potential risk factors. The CIBMTR identified n=22605 cases of allogeneic transplant for all ages and all diseases between 2013-2019.

There was a comment about the limitation of the proposed analysis method, propensity score matching, for this study. It was stated that a limitation of propensity score matching is that some of the variables needed for the matching often end up not existing within the data set. They also brought up a concern that this method biases the analysis toward patients who have all the available data for matching.

One attendee wished to know why autologous transplants were excluded from the prospective study population, as pediatric autologous transplants are also at risk of developing veno-occlusive disease. This was not a risk well known to the study team during proposal development, but could be taken into consideration if the study proceeds.

There was a question about the time span of the presented prospective study population, as it ends in 2019 but would benefit from the addition of more recent data. It was explained that population data was only available from CIBMTR through 2019 due to a database transition within the organization. If the study proceeds, more recent data will be added for analysis.

Related to the previous point, attendees asked about the frequency of inotuzumab ozogamycin

and gemtuzumab ozogamycin administration in the more recent years that were not included in the population description. Within the data available, frequency of these therapies are fairly low, and it would be helpful to have a clear idea of how many more cases with these therapies would be available in later years. This data is unfortunately not available at this time, but we can assume based on the fact that these therapies were approved in 2019 for clinical use that their frequency was increased in more recent years.

There was a question about whether dosing of induction therapies of this population were consistent throughout the years. This is not information that was available at the time of this session, but could potentially be explored if this study proceeds.

There was a question about whether the timing of inotuzumab ozogamycin and gemtuzumab ozogamycin administration. Are we able to look at the timing of these therapies compared to the timing of subsequent transplants and outcomes? We may able to analyze the timing of these therapies but we can also censor patients at subsequent transplants to reduce the confounding effects of the factors associated with transplants such as conditioning regimens and prophylactic treatment.

The final question concerned patients receiving post-transplant cyclophosphamide. A total of n=598 patients received PT-Cy within the population summary provided for this proposal, and more are expected to accrue in the later years that would be added to the study population. The presenter acknowledges that PT-Cy would be an interesting factor to study in the context of this proposal.

This proposal received a mean scientific impact score of 4.2 and a median score of 4 from n=78 participants. Ultimately, this proposal was not chosen to proceed as a CIBMTR study due to lower scientific impact.

c. **PROP 2210-91** Updated analysis of long-term survival and late deaths after allogeneic hematopoietic cell transplantation for hematologic malignancies and severe aplastic anemia. *(U Rao/M Battiwalla)* (Attachment 7)
Dr. Betty Hamilton introduced Dr. Uttam Rao. The aim of this proposal is to determine the probability of being alive at 10 years post-HCT, including an evaluation of risk factors for late mortality after transplant, an evaluation of any change in late mortality over time, a description of causes of late deaths, and a comparison of relative mortality after transplant with that of the general population. The CIBMTR identified n=28589 cases of first allogeneic transplant for hematological malignancies or severe aplastic anemia for adults between 2000-2015.

The proposal discussion began with a comment about the importance of this study. Survival estimates are used in policy decisions, patient consulting, and other settings. Therefore it is necessary to continue updating long-term survival estimates as practices change to ensure that decisions are being made with accurate information. Additionally, it was suggested that this study, if chosen, be merged with a study team that proposed a similar question a couple years ago.

A suggestion was made to start the time frame of the study at 2008 (rather than the proposed 2015) to allow for the use of HCT-CI data in analysis (this data was only collected beginning in 2008). This person also suggested that the study team report the overall survival estimates of all patients, not just 2-year survivors. They concluded with a comment about how the CIBMTR data set is in fact the best way to accomplish this study, an important factor in the decision process for selecting studies to proceed.

There was a suggestion to limit the study to the more common diseases, which would have a larger population for analysis. This would improve the precision of estimated survival rates.

Another attendee suggested comparing survival rates to other groups to provide context to the survival estimates. Some suggestions were to compare survival estimates to other patients with the same or similar diseases but different treatment, or to compare to the general population.

One commenter asked why the pediatric population was excluded. This decision was made because there is an ongoing study (LE18-01) which is investigating the same question within the pediatric population.

The final question was regarding the lack of race, ethnicity, and other socio-economic and demographic factors from the proposed analysis. The presenter clarified that these variables are planned for inclusion in analysis even though they were not summarized on the presented slides.

This proposal received a mean scientific impact score of 3.1 and a median score of 3 from n=78 participants. This proposal was chosen by working committee and CIBMTR leadership to proceed as a study. This decision was made by considering the anticipated considerable contribution this study will provide to the transplant community, the reception from session attendees, and the high feasibility of completing the study in a reasonable timeline.

d. **PROP 2210-141** Evaluation of total and fractionated total body irradiation doses on late effects and outcomes in pediatric patients with acute leukemia undergoing allogeneic hematopoietic cell transplantation. (*L Appell/A Sharma*) (Attachment 8)
Dr. Bipin Savani introduced Dr. Lauren Appell. The aim of this proposal is to determine outcomes (overall survival, disease-free survival, non-relapse mortality, toxicities, and late effects) for pediatric patients with acute leukemia who received lower fractionated doses and lower total doses of TBI compared to those who received higher fractionated doses and total doses of TBI. The CIBMTR identified n=4109 patients under 21 years of age undergoing first allogeneic transplant for acute lymphoblastic leukemia (ALL) between 2000-2019.

The first comment on this proposal asked about trends in TBI usage in pediatric populations, as it is becoming less popular as a treatment for adult ALL patients. The presenter clarified that TBI is still widely used among pediatric patients with ALL due to its efficacy.

One attendee recommended further stratifying the TBI doses to be analyzed. TBI doses were summarized into two categories in the table provided for this proposal, but the study would break down those categories into more granular data for analysis. They also recommended, based on their clinical experience and other data, to focus particularly on cranial radiation and its impact on late effects in pediatric patients.

Another concern was about the large amount of variation in the manner of TBI administration, and how this could confound analysis. They recommended recruiting a radiation oncologist to consult on the study when determining how to categorize different TBI intensities and administration types.

There was a question about whether CIBMTR collects information about details such as organ

shielding. After consulting the forms, Dr. Phelan added that CIBMTR collects a variety of information about the details of TBI administration. Although this is true, further investigation after the meeting revealed that this information was only collected beginning in 2017, outside the scope of the proposed study cohort.

There was a suggestion to include fertility outcomes in the list of late effects in this study.

One attendee recommended a couple of papers that are either published or will be published soon as resources to inform analysis set-up.

This proposal received a median scientific impact score of 3.6 and a median score of 4 from n=75 participants. Although there was strong support for this study given its focus on pediatric patients, it was ultimately not prioritized to proceed as a CIBMTR study. The main reasoning for this decision is that working committee leadership did not expect the results to be impactful; the analysis would be based on older data, including older TBI practices, which do not reflect more modern clinical practice.

e. **PROP 2210-199/2210-202** Prediction of non-relapse mortality by EASIX and HCT-CI scores in patients undergoing allogeneic stem cell transplant (*H Alkhateeb/A Baranwal*) (Attachment 9)
Dr. Mohammed Sorror introduced Dr. Anmol Brarnwal. The aim of this proposal is to determine if the Endothelial Activation and Stress Index (EASIX) score can predict non-relapse mortality in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who undergo post-transplant cyclophosphamide treatment, or in patients with chronic myelomonocytic leukemia (CMML). The CIBMTR identified n=1141 adults with CMML and n=39438 adults with AML and other MDS undergoing first allogeneic transplant between 2011-2019.

The first question was about the availability of data used to calculate EASIX scores. This data is only available at the CRF level. They were also curious as to why the proposed analysis was to look out to 3 years post-transplant; they believe looking out to 18 months would be sufficient. Reducing the amount of follow-up time needed would allow for a cohort taken from later years and would encompass more of the time period when PT-Cy was widely used.

Another attendee wanted to know when the EASIX score is captured. The lab values contributing to the score are taken within 4 weeks of conditioning, but are not all captured on one specific day. Following the last question, they wanted to know whether EASIX scores could be calculated after administration of PT-Cy. It was clarified that the hypothesis is that EASIX predicts different outcomes after PT-Cy use, not that PT-Cy causes low EASIX scores.

There was a concern about whether this study would add to the existing literature, as it has been well-documented now that EASIX scores can predict outcomes. This study aims to add to literature by including the analysis of EASIX in the context of PT-Cy use, as the previous studies had low numbers of patients receiving that treatment.

One attendee commented that it would be helpful to have EASIX scores for the patients before and after PT-Cy treatment. This information is not collected within CIBMTR.

There was a concern that patients with prior history of co-morbidities and solid tumors would bias the data. This is expected to be a small number of patients, and will be controlled for using the HCT-CI score. Another commenter added that in other studies there are standard categories for stratifying HCT-CI risk among patients. A commenter later replied to this topic with a suggestion to look at HCT-CI at a more granular level to better determine how co-

morbidities affect incidence of organ toxicities.

There was a clarifying question about how a "high" EASIX score cut-off would be determined. In previous studies from this team, they found a statistically significant cut-off among EASIX scores compared to differences in outcomes. This cut-off will be applied as an a priori categorization to this study.

There was a suggestion to compare outcomes between patients receiving PT-Cy and patients receiving CNI-based prophylaxis.

The final question was about the labs that contribute to EASIX scores and whether they are all conducted on the same day. This is not necessarily the case, but CIBMTR does collect dates of each lab so the study population could potentially include only patients with labs that were collected on consecutive days, if not all on the same day.

This proposal received a mean scientific impact score of 4.8 and a median score of 5 from n=75 participants. Ultimately, this proposal was not selected to proceed as a CIBMTR study due to lower scientific impact.

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

f. **PROP 2204-02/2210-103/2210-173/2210-180/2210-227/2210-251/2210-269** Incidence, risk factors, and characteristics of secondary malignancies following CAR-T therapy and its impact on survival. *(V Irizarry-Gatell/M Shah/H Alkhateeb/R Faramand/D McQuinn/K Nadiminti/M Veeraputhiran/C Schinke/A Mirza/L Gowda/A Tun/P Johnston)*

This proposal was presented at the Collaborative Working Committee session. The discussion following the presentation of this study will therefore not be reflected in these minutes. However, this proposal was in consideration as MRSWC leadership determined their priorities for study acceptance. This study received a mean scientific impact score of 3.5 and a median score of 3 from n=90 participants. When considering the possibility of these results to impact CAR-T therapy practitioners and patients, as well as audience reception, this proposal was selected as one of this working committee's top priorities to proceed as a CIBMTR study. The main concern, which limits this proposal from being the top priority, is that the results will be limited by a lack of robust follow-up data as CAR-T therapy is still a newer practice. Due to this limitation, this study was ultimately not chosen to proceed as a CIBMTR study. It would, however, be a strong candidate for acceptance in a year or two.

Dropped Proposed Studies

a. **PROP 2210-49** Allogeneic hematopoietic stem cell transplant outcomes for patients with varying degrees of pre-transplant dysfunction and/or cirrhosis. ***Dropped due to unavailability of data.***
b. **PROP 2210-157** Factors at the onset of cytokine release syndrome may predict the development of severe immune effector cell-associated neurotoxicity syndrome post-CAR-T cell therapy for relapsed/refractory lymphoma. ***Dropped for overlap with an existing study.***
c. **PROP 2210-165** Impact of obesity on post-transplant cyclophosphamide. ***Dropped due to low scientific impact.***
d. **PROP 2210-181** Investigation of augmented hematopoietic cell transplant co-morbidity index as a predictor of outcomes following first allogeneic transplant in children. ***Dropped due to low scientific impact.***
e. **PROP 2210-233** Toxicity and outcome differences by conditioning regimen received in severely obese allogeneic stem cell transplant recipients. *Dropped due to low scientific impact.*

f. ***PROP 2210-298*** Hemophagocytic lympho-histiocytosis in the context of cellular therapies. ***Dropped due to low sample size.***

6. Closing Remarks

Dr. Mohammed Sorror reminded the audience that there was a proposal from MRSWC chosen to be presented at the Collaborative Working Committee Session and encouraged attendees to attend that session as well on February 18, 2023.

Dr. Rachel Phelan provided an open invitation for collaborations between MRSWC and other data registries.

Dr. Phelan then provided an update on the initiative to update international recommendations for screening and preventative practices for long-term survivors of transplantation and cellular therapies. This effort includes representative from many organizations worldwide, including CIBMTR (specifically MRSWC). The objective of this project is to comprehensively update guidelines of screening for TCT survivors and to provide user-friendly summaries of the revised information. A manuscript for this project is currently being written with an anticipated submission in 2023. Major recommendations are planned for presentation at 2023 EBMT Annual Meeting and 2024 Tandem Meetings.

The session was concluded at 2:10pm EST by Dr. Rachel Phelan.

Working Committee Overview Plan for 2023-2024		
Study number and title	**Current status**	**Chairs priority**
LE12-03: Solid organ transplantation and hematopoietic cell transplantation	Manuscript preparation	1
LE16-02b: Late effects after AlloHCT for pediatric patients with non-malignant diseases	Manuscript preparation	3
LE17-01a: Late effects after hematopoietic stem cell transplantation for sickle cell disease	Manuscript preparation	3
LE17-01b: Comparison of survival between transplanted and non-transplanted SCD patients	Data file preparation	3
LE18-01: Survival trends in two-year survivors of alloHCT	Manuscript preparation	2
LE19-01: Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Manuscript preparation	1
LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.	Analysis	1
RT19-01: Analysis of comorbidity-associated toxicity at a regimen-based level	Data file preparation	2
RT19-02: Hemorrhagic cystitis as a complication of hematopoietic stem cell transplantation in the post-transplant cyclophosphamide graft-versus-host disease prophylaxis era compared to other allogeneic stem cell transplants	Protocol development	2
LE20-01: Cardiometabolic Risk after Total Body Irradiation during Childhood	Protocol development	1
LE20-02: Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following	Submitted	1

hematopoietic cell transplant		
RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients	Data file preparation	2
LE21-01: Risk of subsequent neoplasms (SN) after the use of post-transplant cyclophosphamide (PTCy) for Graft-versus-host disease (GvHD) prophylaxis	Data file preparation	3
MRS22-01: The role of racial/ethnic disparities and poverty in long-term outcomes among survivors of allogeneic hematopoietic stem cell transplants	Protocol development	3
MRS22-02: Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis	Protocol development	3
MRS23-01: Updated analysis of long-term survival and late deaths after allogeneic hematopoietic cell transplantation for hematologic malignancies and severe aplastic anemia	Protocol pending	3

Table 1a. TED vs. CRF Follow-up of adult patients (age >= 18) after allogeneic transplant reported to CIBMTR, 1990-2023

Characteristic	TED	Research
All patients	216618	67693
3-year survivors	70524	22584
5-year survivors	49012	16216
10-year survivors	20216	6733
15-year survivors	6731	2215
Acute Myelogenous Leukemia	80562	21772
3-year survivors	24243	6973
5-year survivors	16263	5050
10-year survivors	6079	1990
Acute Lymphoblastic Leukemia	30247	8097
3-year survivors	9101	2498
5-year survivors	6003	1788
10-year survivors	2171	710
Chronic Myelogenous Leukemia	25612	9139
3-year survivors	10530	3193
5-year survivors	8153	2521
10-year survivors	4468	1502
Myelodysplastic/Myeloproliferative Diseases	35645	13814
3-year survivors	10329	4584
5-year survivors	6632	2982
10-year survivors	2235	924
Multiple Myeloma/Plasma Cell Disorders	3567	1151
3-year survivors	1216	368
5-year survivors	840	253
10-year survivors	359	91
Lymphoma	18895	5625
3-year survivors	6801	1978
5-year survivors	5177	1506
10-year survivors	2471	761

Characteristic	TED	Research
Other Malignant	10012	3212
3-year survivors	3435	1135
5-year survivors	2473	822
10-year survivors	1023	316
Severe Aplastic Anemia	8310	3582
3-year survivors	3511	1391
5-year survivors	2597	997
10-year survivors	1126	348
Immune deficiencies	503	131
3-year survivors	194	52
5-year survivors	120	36
10-year survivors	20	7
Other Non-malignant	3070	1169
3-year survivors	1126	412
5-year survivors	727	261
10-year survivors	248	84

Table 1b. CRF Follow-up of adult patients (age >= 18) after autologous transplant reported to CIBMTR, 1990-2023

Characteristic	TED	Research
All patients	282291	37348
3-year survivors	132902	18981
5-year survivors	89151	12531
10-year survivors	30904	3964
15-year survivors	8444	831
Acute Myelogenous Leukemia	7258	1342
3-year survivors	2578	440
5-year survivors	1899	300
10-year survivors	1021	127
Acute Lymphoblastic Leukemia	1180	210
3-year survivors	303	41
5-year survivors	204	26
10-year survivors	104	11
Chronic Myelogenous Leukemia	662	207
3-year survivors	283	94
5-year survivors	187	54
10-year survivors	84	20
Myelodysplastic/Myeloproliferative Diseases	255	44
3-year survivors	115	22
5-year survivors	75	11
10-year survivors	32	2
Multiple Myeloma/Plasma Cell Disorders	132701	15624
3-year survivors	67002	9989
5-year survivors	42999	6695
10-year survivors	11418	1899
Lymphoma	105109	12057
3-year survivors	49257	5911
5-year survivors	34897	4065
10-year survivors	14015	1510

Characteristic	TED	Research
Other Malignant	32920	7672
3-year survivors	12841	2404
5-year survivors	8563	1323
10-year survivors	4082	362
Severe Aplastic Anemia	15	3
3-year survivors	4	1
5-year survivors	3	1
10-year survivors	1	0
Immune deficiencies	18	3
3-year survivors	12	2
5-year survivors	9	1
10-year survivors	0	0
Other Non-malignant	2071	185
3-year survivors	455	76
5-year survivors	273	54
10-year survivors	118	32

Table 2a. CRF Follow-up of pediatric (age < 18) patients after allogeneic transplant reported to CIBMTR, 1990-2023

Characteristic	TED	Research
All patients	63396	24811
3-year survivors	27128	10881
5-year survivors	20138	8254
10-year survivors	9197	3980
15-year survivors	3072	1225
Acute Myelogenous Leukemia	11344	3927
3-year survivors	4243	1522
5-year survivors	3154	1191
10-year survivors	1521	595
Acute Lymphoblastic Leukemia	16155	5689
3-year survivors	6170	2201
5-year survivors	4629	1717
10-year survivors	2204	881
Chronic Myelogenous Leukemia	2288	858
3-year survivors	1060	407
5-year survivors	834	333
10-year survivors	428	187
Myelodysplastic/Myeloproliferative Diseases	3429	1327
3-year survivors	1456	585
5-year survivors	1104	473
10-year survivors	558	290
Multiple Myeloma/Plasma Cell Disorders	34	6
3-year survivors	14	3
5-year survivors	10	2
10-year survivors	4	0
Lymphoma	1330	454
3-year survivors	473	157
5-year survivors	359	121
10-year survivors	156	50

Characteristic	TED	Research
Other Malignant	1205	427
3-year survivors	464	184
5-year survivors	338	148
10-year survivors	159	76
Severe Aplastic Anemia	6153	2503
3-year survivors	3092	1215
5-year survivors	2326	905
10-year survivors	1040	381
Immune deficiencies	6235	2746
3-year survivors	2946	1452
5-year survivors	2188	1148
10-year survivors	997	557
Other Non-malignant	15193	6874
3-year survivors	7199	3155
5-year survivors	5190	2216
10-year survivors	2130	963

Table 2b. CRF Follow-up of pediatric (age < 18) patients after autologous transplant reported to CIBMTR, 1990-2023

Characteristic	TED	Research
All patients	18628	2920
3-year survivors	7673	1209
5-year survivors	5372	831
10-year survivors	2299	366
15-year survivors	734	92
Acute Myelogenous Leukemia	990	248
3-year survivors	394	50
5-year survivors	306	29
10-year survivors	163	14
Acute Lymphoblastic Leukemia	388	122
3-year survivors	126	18
5-year survivors	87	7
10-year survivors	47	0
Chronic Myelogenous Leukemia	23	3
3-year survivors	12	1
5-year survivors	7	0
10-year survivors	4	0
Myelodysplastic/Myeloproliferative Diseases	23	4
3-year survivors	7	0
5-year survivors	5	0
10-year survivors	3	0
Multiple Myeloma/Plasma Cell Disorders	102	3
3-year survivors	18	2
5-year survivors	11	1
10-year survivors	3	0
Lymphoma	3183	390
3-year survivors	1395	194
5-year survivors	983	138
10-year survivors	394	36

Characteristic	TED	Research
Other Malignant	13563	2042
3-year survivors	5589	899
5-year survivors	3888	625
10-year survivors	1660	312
Severe Aplastic Anemia	7	3
3-year survivors	4	2
5-year survivors	4	2
Not reported	18624	2918
10-year survivors	1	0
Immune deficiencies	86	64
3-year survivors	43	33
5-year survivors	24	20
10-year survivors	1	1
Other Non-malignant	236	41
3-year survivors	77	10
5-year survivors	51	9
10-year survivors	20	3

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	48612	21726	12745
Source of data			
CRF	25221 (52)	8369 (39)	5985 (47)
TED	23391 (48)	13357 (61)	6760 (53)
Number of centers	264	244	382
Disease at transplant			
AML	16913 (35)	8236 (38)	4255 (33)
ALL	7024 (14)	2775 (13)	2038 (16)
Other leukemia	1487 (3)	456 (2)	317 (2)
CML	3553 (7)	1171 (5)	1049 (8)
MDS	7232 (15)	3914 (18)	1638 (13)
Other acute leukemia	535 (1)	263 (1)	146 (1)
NHL	4284 (9)	1493 (7)	940 (7)
Hodgkin Lymphoma	962 (2)	277 (1)	216 (2)
Plasma Cell Disorders, MM	945 (2)	298 (1)	209 (2)
Other malignancies	60 (<1)	14 (<1)	22 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1557 (3)	671 (3)	561 (4)
Inherited abnormalities erythrocyte diff fxn	718 (1)	255 (1)	241 (2)
Inherited bone marrow failure syndromes	36 (<1)	51 (<1)	30 (<1)
Hemoglobinopathies	31 (<1)	31 (<1)	20 (<1)
Paroxysmal nocturnal hemoglobinuria	4 (<1)	10 (<1)	3 (<1)
SCIDs	842 (2)	367 (2)	401 (3)
Inherited abnormalities of platelets	42 (<1)	16 (<1)	12 (<1)
Inherited disorders of metabolism	306 (1)	93 (<1)	153 (1)
Histiocytic disorders	391 (1)	135 (1)	133 (1)
Autoimmune disorders	28 (<1)	19 (<1)	13 (<1)
MPN	1603 (3)	1160 (5)	323 (3)
Others	52 (<1)	18 (<1)	24 (<1)
AML Disease status at transplant			
CR1	9303 (55)	5250 (64)	2139 (50)
CR2	3208 (19)	1365 (17)	838 (20)
CR3+	341 (2)	116 (1)	98 (2)
Advanced or active disease	3877 (23)	1467 (18)	1033 (24)
Missing	184 (1)	38 (<1)	147 (3)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
ALL Disease status at transplant			
CR1	3513 (50)	1625 (59)	870 (43)
CR2	1996 (28)	707 (25)	587 (29)
CR3+	581 (8)	180 (6)	191 (9)
Advanced or active disease	852 (12)	238 (9)	270 (13)
Missing	82 (1)	25 (1)	120 (6)
MDS Disease status at transplant			
Early	1535 (21)	712 (18)	370 (23)
Advanced	4722 (65)	2956 (76)	921 (56)
Missing	975 (13)	246 (6)	347 (21)
NHL Disease status at transplant			
CR1	613 (14)	290 (20)	133 (14)
CR2	800 (19)	296 (20)	153 (16)
CR3+	371 (9)	131 (9)	86 (9)
PR	449 (11)	111 (7)	94 (10)
Advanced	1959 (46)	637 (43)	440 (47)
Missing	72 (2)	20 (1)	31 (3)
Recipient age at transplant			
0-9 years	3999 (8)	1337 (6)	1694 (13)
10-17 years	3169 (7)	1049 (5)	1203 (9)
18-29 years	5825 (12)	2080 (10)	1687 (13)
30-39 years	5443 (11)	2021 (9)	1476 (12)
40-49 years	7259 (15)	2733 (13)	1823 (14)
50-59 years	9972 (21)	4217 (19)	2181 (17)
60-69 years	10440 (21)	6168 (28)	2185 (17)
70+ years	2505 (5)	2121 (10)	496 (4)
Median (Range)	48 (0-84)	55 (0-82)	42 (0-84)
Recipient race			
White	42622 (91)	19046 (91)	9527 (88)
Black or African American	2298 (5)	894 (4)	609 (6)
Asian	1235 (3)	664 (3)	553 (5)
Native Hawaiian or other Pacific Islander	70 (<1)	33 (<1)	40 (<1)
American Indian or Alaska Native	193 (<1)	96 (<1)	64 (1)
Other	49 (<1)	27 (<1)	28 (<1)
More than one race	285 (1)	129 (1)	62 (1)
Unknown	1860 (N/A)	837 (N/A)	1862 (N/A)
Recipient ethnicity			
Hispanic or Latino	4078 (10)	1642 (8)	1175 (11)
Non Hispanic or non-Latino	36772 (88)	17419 (90)	6776 (64)
Non-resident of the U.S.	882 (2)	297 (2)	2570 (24)

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Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	6880 (N/A)	2368 (N/A)	2224 (N/A)
Recipient sex			
Male	28201 (58)	12741 (59)	7579 (59)
Female	20411 (42)	8985 (41)	5166 (41)
Karnofsky score			
10-80	17009 (35)	8589 (40)	4027 (32)
90-100	29824 (61)	12491 (57)	8060 (63)
Missing	1779 (4)	646 (3)	658 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	29 (<1)	97 (<1)	7 (<1)
4/6	265 (1)	112 (1)	60 (1)
5/6	6582 (14)	2447 (12)	1794 (15)
6/6	40711 (86)	17245 (87)	10049 (84)
Unknown	1025 (N/A)	1825 (N/A)	835 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	901 (2)	156 (1)	83 (1)
6/8	1833 (4)	194 (1)	262 (3)
7/8	9074 (19)	2726 (16)	1995 (22)
8/8	35275 (75)	14215 (82)	6922 (75)
Unknown	1529 (N/A)	4435 (N/A)	3483 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11999 (29)	2830 (23)	1168 (25)
Single allele mismatch	22536 (54)	6397 (52)	2444 (52)
Full allele matched	7414 (18)	3115 (25)	1079 (23)
Unknown	6663 (N/A)	9384 (N/A)	8054 (N/A)
High resolution release score			
No	13343 (27)	21647 (>99)	12126 (95)
Yes	35269 (73)	79 (<1)	619 (5)
KIR typing available			
No	34811 (72)	21699 (>99)	12629 (99)
Yes	13801 (28)	27 (<1)	116 (1)
Graft type			
Marrow	16553 (34)	5318 (24)	4980 (39)
PBSC	31958 (66)	16179 (74)	7697 (60)
BM+PBSC	16 (<1)	20 (<1)	5 (<1)
PBSC+UCB	40 (<1)	186 (1)	10 (<1)
Others	45 (<1)	23 (<1)	53 (<1)
Conditioning regimen			
Myeloablative	29377 (60)	11114 (51)	7910 (62)
RIC/Nonmyeloablative	19007 (39)	10541 (49)	4668 (37)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
TBD	228 (<1)	71 (<1)	167 (1)
Donor age at donation			
To Be Determined/NA	788 (2)	1002 (5)	302 (2)
0-9 years	4 (<1)	33 (<1)	1 (<1)
10-17 years	1 (<1)	14 (<1)	1 (<1)
18-29 years	23838 (49)	11625 (54)	5477 (43)
30-39 years	13560 (28)	5555 (26)	3778 (30)
40-49 years	7985 (16)	2666 (12)	2414 (19)
50+ years	2436 (5)	831 (4)	772 (6)
Median (Range)	30 (0-69)	29 (0-89)	32 (4-77)
Donor/Recipient CMV serostatus			
+/+	12113 (25)	6051 (28)	3314 (26)
+/-	5690 (12)	2775 (13)	1552 (12)
-/+	15778 (32)	6481 (30)	3842 (30)
-/-	13788 (28)	5611 (26)	3360 (26)
CB - recipient +	36 (<1)	150 (1)	9 (<1)
CB - recipient -	4 (<1)	44 (<1)	2 (<1)
CB - recipient CMV unknown	0	1 (<1)	0
Missing	1203 (2)	613 (3)	666 (5)
GvHD Prophylaxis			
No GvHD Prophylaxis	176 (<1)	93 (<1)	54 (<1)
TDEPLETION alone	123 (<1)	49 (<1)	64 (1)
TDEPLETION +- other	1101 (2)	304 (1)	392 (3)
CD34 select alone	290 (1)	159 (1)	103 (1)
CD34 select +- other	514 (1)	276 (1)	141 (1)
Cyclophosphamide alone	234 (<1)	88 (<1)	59 (<1)
Cyclophosphamide +- others	3834 (8)	3975 (18)	925 (7)
FK506 + MMF +- others	5440 (11)	2132 (10)	975 (8)
FK506 + MTX +- others(not MMF)	20699 (43)	9116 (42)	3590 (28)
FK506 +- others(not MMF,MTX)	2475 (5)	1310 (6)	486 (4)
FK506 alone	1186 (2)	509 (2)	227 (2)
CSA + MMF +- others(not FK506)	3093 (6)	966 (4)	1044 (8)
CSA + MTX +- others(not MMF,FK506)	6961 (14)	1934 (9)	3484 (27)
CSA +- others(not FK506,MMF,MTX)	1087 (2)	334 (2)	462 (4)
CSA alone	461 (1)	133 (1)	388 (3)
Other GVHD Prophylaxis	758 (2)	292 (1)	216 (2)
Missing	180 (<1)	56 (<1)	135 (1)
Donor/Recipient sex match			
Male-Male	19692 (41)	8442 (39)	4919 (39)
Male-Female	12055 (25)	5123 (24)	2796 (22)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Female-Male	8277 (17)	3895 (18)	2548 (20)
Female-Female	8162 (17)	3546 (16)	2282 (18)
CB - recipient M	18 (<1)	105 (<1)	3 (<1)
CB - recipient F	22 (<1)	90 (<1)	8 (<1)
Missing	386 (1)	525 (2)	189 (1)
Year of transplant			
1986-1990	346 (1)	48 (<1)	103 (1)
1991-1995	1838 (4)	439 (2)	745 (6)
1996-2000	3298 (7)	1184 (5)	1220 (10)
2001-2005	5304 (11)	1084 (5)	1907 (15)
2006-2010	9564 (20)	1926 (9)	1884 (15)
2011-2015	13304 (27)	3591 (17)	2668 (21)
2016-2020	10386 (21)	7188 (33)	2800 (22)
2021-2023	4572 (9)	6266 (29)	1418 (11)
Follow-up among survivors, Months			
N Eval	21810	12456	6004
Median (Range)	55 (0-384)	14 (0-362)	36 (0-385)

Unrelated Cord Blood 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	6329	1790	2251
Source of data			
CRF	4553 (72)	1166 (65)	1090 (48)
TED	1776 (28)	624 (35)	1161 (52)
Number of centers	155	143	227
Disease at transplant			
AML	2405 (38)	618 (35)	733 (33)
ALL	1301 (21)	392 (22)	491 (22)
Other leukemia	98 (2)	30 (2)	37 (2)
CML	136 (2)	37 (2)	58 (3)
MDS	569 (9)	177 (10)	178 (8)
Other acute leukemia	100 (2)	24 (1)	48 (2)
NHL	410 (6)	107 (6)	134 (6)
Hodgkin Lymphoma	103 (2)	27 (2)	36 (2)
Plasma Cell Disorders, MM	38 (1)	12 (1)	13 (1)
Other malignancies	12 (<1)	1 (<1)	3 (<1)
SAA	95 (2)	33 (2)	51 (2)
Inherited abnormalities erythrocyte diff fxn	171 (3)	49 (3)	45 (2)
Inherited bone marrow failure syndromes	6 (<1)	5 (<1)	4 (<1)
Hemoglobinopathies	2 (<1)	1 (<1)	1 (<1)
SCIDs	284 (4)	92 (5)	174 (8)
Inherited abnormalities of platelets	21 (<1)	6 (<1)	10 (<1)
Inherited disorders of metabolism	398 (6)	130 (7)	145 (6)
Histiocytic disorders	108 (2)	30 (2)	53 (2)
Autoimmune disorders	9 (<1)	0	7 (<1)
MPN	53 (1)	16 (1)	20 (1)
Others	10 (<1)	3 (<1)	10 (<1)
AML Disease status at transplant			
CR1	1262 (52)	348 (56)	371 (51)
CR2	642 (27)	158 (26)	192 (26)
CR3+	66 (3)	11 (2)	26 (4)
Advanced or active disease	427 (18)	99 (16)	140 (19)
Missing	8 (<1)	2 (<1)	4 (1)
ALL Disease status at transplant			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CR1	584 (45)	166 (42)	212 (43)
CR2	490 (38)	149 (38)	177 (36)
CR3+	149 (11)	54 (14)	63 (13)
Advanced or active disease	77 (6)	22 (6)	38 (8)
Missing	1 (<1)	1 (<1)	1 (<1)
MDS Disease status at transplant			
Early	175 (31)	42 (24)	72 (40)
Advanced	341 (60)	120 (68)	84 (47)
Missing	53 (9)	15 (8)	22 (12)
NHL Disease status at transplant			
CR1	65 (16)	13 (12)	25 (19)
CR2	76 (19)	24 (22)	35 (26)
CR3+	45 (11)	11 (10)	12 (9)
PR	68 (17)	12 (11)	16 (12)
Advanced	153 (38)	45 (42)	42 (32)
Missing	0	2 (2)	3 (2)
Recipient age at transplant			
0-9 years	1903 (30)	642 (36)	803 (36)
10-17 years	667 (11)	162 (9)	265 (12)
18-29 years	757 (12)	161 (9)	242 (11)
30-39 years	609 (10)	162 (9)	217 (10)
40-49 years	673 (11)	174 (10)	214 (10)
50-59 years	868 (14)	221 (12)	287 (13)
60-69 years	733 (12)	230 (13)	207 (9)
70+ years	119 (2)	38 (2)	16 (1)
Median (Range)	27 (0-85)	24 (0-78)	20 (0-78)
Recipient race			
White	4442 (74)	1250 (74)	1372 (72)
Black or African American	937 (16)	249 (15)	281 (15)
Asian	381 (6)	128 (8)	173 (9)
Native Hawaiian or other Pacific Islander	36 (1)	4 (<1)	19 (1)
American Indian or Alaska Native	59 (1)	17 (1)	23 (1)
Other	1 (<1)	1 (<1)	1 (<1)
More than one race	130 (2)	39 (2)	38 (2)
Unknown	343 (N/A)	102 (N/A)	344 (N/A)
Recipient ethnicity			
Hispanic or Latino	1336 (22)	328 (19)	377 (17)
Non Hispanic or non-Latino	4793 (78)	1367 (80)	1347 (61)
Non-resident of the U.S.	53 (1)	24 (1)	469 (21)
Unknown	147 (N/A)	71 (N/A)	58 (N/A)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Recipient sex			
Male	3511 (55)	1018 (57)	1282 (57)
Female	2818 (45)	772 (43)	969 (43)
Karnofsky score			
10-80	1682 (27)	461 (26)	576 (26)
90-100	4431 (70)	1212 (68)	1479 (66)
Missing	216 (3)	117 (7)	196 (9)
HLA-A B DRB1 groups - low resolution			
<=3/6	167 (3)	93 (7)	63 (3)
4/6	2375 (41)	572 (40)	792 (39)
5/6	2549 (44)	564 (40)	840 (42)
6/6	757 (13)	196 (14)	313 (16)
Unknown	481 (N/A)	365 (N/A)	243 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2990 (55)	651 (55)	929 (54)
6/8	1301 (24)	276 (23)	413 (24)
7/8	785 (14)	168 (14)	249 (14)
8/8	380 (7)	92 (8)	145 (8)
Unknown	873 (N/A)	603 (N/A)	515 (N/A)
HLA-DPB1 Match			
Double allele mismatch	872 (37)	140 (34)	199 (38)
Single allele mismatch	1244 (53)	231 (56)	278 (52)
Full allele matched	228 (10)	44 (11)	53 (10)
Unknown	3985 (N/A)	1375 (N/A)	1721 (N/A)
High resolution release score			
No	4853 (77)	1740 (97)	2226 (99)
Yes	1476 (23)	50 (3)	25 (1)
KIR typing available			
No	5056 (80)	1784 (>99)	2231 (99)
Yes	1273 (20)	6 (<1)	20 (1)
Graft type			
UCB	5940 (94)	1595 (89)	2112 (94)
BM+UCB	1 (<1)	0	0
PBSC+UCB	357 (6)	186 (10)	125 (6)
Others	31 (<1)	9 (1)	14 (1)
Number of cord units			
1	5293 (84)	0	1880 (84)
2	1034 (16)	0	370 (16)
3	1 (<1)	0	0
Unknown	1 (N/A)	1790 (N/A)	1 (N/A)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Conditioning regimen			
Myeloablative	4111 (65)	1137 (64)	1404 (62)
RIC/Nonmyeloablative	2201 (35)	646 (36)	827 (37)
TBD	17 (<1)	7 (<1)	20 (1)
Donor/Recipient CMV serostatus			
+/+	0	0	1 (<1)
+/-	1 (<1)	0	0
-/-	0	0	1 (<1)
CB - recipient +	3967 (63)	1088 (61)	1365 (61)
CB - recipient -	2259 (36)	638 (36)	812 (36)
CB - recipient CMV unknown	102 (2)	64 (4)	72 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	24 (<1)	9 (1)	15 (1)
TDEPLETION alone	1 (<1)	0	0
TDEPLETION +- other	27 (<1)	9 (1)	9 (<1)
CD34 select alone	0	2 (<1)	1 (<1)
CD34 select +- other	274 (4)	140 (8)	78 (3)
Cyclophosphamide alone	0	0	1 (<1)
Cyclophosphamide +- others	14 (<1)	10 (1)	12 (1)
FK506 + MMF +- others	1870 (30)	561 (31)	455 (20)
FK506 + MTX +- others(not MMF)	216 (3)	56 (3)	78 (3)
FK506 +- others(not MMF,MTX)	232 (4)	68 (4)	90 (4)
FK506 alone	145 (2)	44 (2)	27 (1)
CSA + MMF +- others(not FK506)	2883 (46)	704 (39)	1083 (48)
CSA + MTX +- others(not MMF,FK506)	101 (2)	29 (2)	52 (2)
CSA +- others(not FK506,MMF,MTX)	342 (5)	116 (6)	228 (10)
CSA alone	51 (1)	18 (1)	68 (3)
Other GVHD Prophylaxis	137 (2)	21 (1)	43 (2)
Missing	12 (<1)	3 (<1)	11 (<1)
Donor/Recipient sex match			
Male-Female	0	0	1 (<1)
Female-Male	0	0	1 (<1)
CB - recipient M	3511 (55)	1018 (57)	1280 (57)
CB - recipient F	2817 (45)	772 (43)	968 (43)
CB - recipient sex unknown	0	0	1 (<1)
Missing	1 (<1)	0	0
Year of transplant			
1996-2000	1 (<1)	2 (<1)	5 (<1)
2001-2005	112 (2)	85 (5)	34 (2)
2006-2010	1849 (29)	428 (24)	603 (27)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2011-2015	2682 (42)	510 (28)	841 (37)
2016-2020	1340 (21)	528 (29)	551 (24)
2021-2023	345 (5)	237 (13)	217 (10)
Follow-up among survivors, Months			
N Eval	3122	998	1185
Median (Range)	61 (0-196)	43 (0-213)	37 (0-240)

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 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	11911	2051	1001
Source of data			
CRF	3933 (33)	566 (28)	332 (33)
TED	7978 (67)	1485 (72)	669 (67)
Number of centers	93	81	68
Disease at transplant			
AML	3939 (33)	666 (32)	340 (34)
ALL	1968 (17)	405 (20)	191 (19)
Other leukemia	224 (2)	42 (2)	19 (2)
CML	359 (3)	50 (2)	26 (3)
MDS	1600 (13)	249 (12)	130 (13)
Other acute leukemia	180 (2)	37 (2)	10 (1)
NHL	994 (8)	177 (9)	84 (8)
Hodgkin Lymphoma	214 (2)	41 (2)	27 (3)
Plasma Cell Disorders, MM	262 (2)	40 (2)	22 (2)
Other malignancies	24 (<1)	1 (<1)	1 (<1)
Breast cancer	1 (<1)	0	0
SAA	565 (5)	89 (4)	41 (4)
Inherited abnormalities erythrocyte diff fxn	488 (4)	72 (4)	22 (2)
Inherited bone marrow failure syndromes	26 (<1)	4 (<1)	4 (<1)
Hemoglobinopathies	185 (2)	36 (2)	18 (2)
Paroxysmal nocturnal hemoglobinuria	1 (<1)	1 (<1)	0
SCIDs	252 (2)	42 (2)	24 (2)
Inherited abnormalities of platelets	11 (<1)	0	0
Inherited disorders of metabolism	23 (<1)	6 (<1)	2 (<1)
Histiocytic disorders	67 (1)	10 (<1)	5 (<1)
Autoimmune disorders	11 (<1)	0	1 (<1)
MPN	498 (4)	82 (4)	34 (3)
Others	19 (<1)	1 (<1)	0
AML Disease status at transplant			
CR1	2615 (66)	463 (70)	219 (64)
CR2	600 (15)	89 (13)	42 (12)
CR3+	47 (1)	12 (2)	2 (1)
Advanced or active disease	669 (17)	97 (15)	77 (23)
Missing	8 (<1)	5 (1)	0

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
ALL Disease status at transplant			
CR1	1179 (60)	244 (60)	122 (64)
CR2	576 (29)	109 (27)	47 (25)
CR3+	124 (6)	26 (6)	10 (5)
Advanced or active disease	89 (5)	26 (6)	12 (6)
MDS Disease status at transplant			
Early	278 (17)	33 (13)	23 (18)
Advanced	1270 (79)	203 (82)	101 (78)
Missing	52 (3)	13 (5)	6 (5)
NHL Disease status at transplant			
CR1	197 (20)	41 (23)	18 (21)
CR2	188 (19)	35 (20)	11 (13)
CR3+	104 (11)	21 (12)	6 (7)
PR	69 (7)	13 (7)	6 (7)
Advanced	427 (43)	66 (38)	43 (51)
Missing	5 (1)	0	0
Recipient age at transplant			
0-9 years	1245 (10)	194 (9)	94 (9)
10-17 years	1177 (10)	168 (8)	79 (8)
18-29 years	1376 (12)	274 (13)	106 (11)
30-39 years	922 (8)	177 (9)	104 (10)
40-49 years	1424 (12)	249 (12)	112 (11)
50-59 years	2464 (21)	430 (21)	210 (21)
60-69 years	2761 (23)	472 (23)	252 (25)
70+ years	542 (5)	87 (4)	44 (4)
Median (Range)	49 (0-82)	49 (0-77)	51 (0-83)
Recipient race			
White	8882 (79)	1421 (75)	753 (80)
Black or African American	1569 (14)	277 (15)	112 (12)
Asian	566 (5)	155 (8)	55 (6)
Native Hawaiian or other Pacific Islander	45 (<1)	8 (<1)	2 (<1)
American Indian or Alaska Native	81 (1)	9 (<1)	5 (1)
More than one race	139 (1)	16 (1)	11 (1)
Unknown	629 (N/A)	165 (N/A)	63 (N/A)
Recipient ethnicity			
Hispanic or Latino	2227 (19)	481 (24)	215 (22)
Non Hispanic or non-Latino	9345 (80)	1492 (75)	751 (76)
Non-resident of the U.S.	124 (1)	26 (1)	17 (2)
Unknown	215 (N/A)	52 (N/A)	18 (N/A)
Recipient sex			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Male	6979 (59)	1202 (59)	585 (58)
Female	4932 (41)	849 (41)	416 (42)
Karnofsky score			
10-80	4292 (36)	833 (41)	423 (42)
90-100	7224 (61)	1155 (56)	527 (53)
Missing	395 (3)	63 (3)	51 (5)
HLA-A B DRB1 groups - low resolution			
<=3/6	2609 (24)	431 (24)	225 (29)
4/6	775 (7)	143 (8)	81 (10)
5/6	227 (2)	45 (3)	24 (3)
6/6	7279 (67)	1166 (65)	444 (57)
Unknown	1021 (N/A)	266 (N/A)	227 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	3245 (31)	533 (31)	269 (38)
6/8	145 (1)	33 (2)	13 (2)
7/8	164 (2)	29 (2)	18 (3)
8/8	7028 (66)	1098 (65)	405 (57)
Unknown	1329 (N/A)	358 (N/A)	296 (N/A)
HLA-DPB1 Match			
Double allele mismatch	11 (<1)	0	1 (<1)
Single allele mismatch	2722 (29)	315 (30)	173 (39)
Full allele matched	6752 (71)	741 (70)	265 (60)
Unknown	2426 (N/A)	995 (N/A)	562 (N/A)
High resolution release score			
No	5794 (49)	2025 (99)	975 (97)
Yes	6117 (51)	26 (1)	26 (3)
Graft type			
Marrow	3434 (29)	469 (23)	281 (28)
PBSC	8370 (70)	1546 (75)	713 (71)
UCB (related)	2 (<1)	15 (1)	0
BM+PBSC	18 (<1)	4 (<1)	1 (<1)
BM+UCB	45 (<1)	12 (1)	2 (<1)
PBSC+UCB	1 (<1)	1 (<1)	4 (<1)
Others	41 (<1)	4 (<1)	0
Conditioning regimen			
Myeloablative	6607 (55)	1121 (55)	518 (52)
RIC/Nonmyeloablative	5242 (44)	915 (45)	464 (46)
TBD	62 (1)	15 (1)	19 (2)
Donor age at donation			
To Be Determined/NA	16 (<1)	5 (<1)	3 (<1)

Refresh date: Dec 2023

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
0-9 years	828 (7)	129 (6)	47 (5)
10-17 years	928 (8)	148 (7)	66 (7)
18-29 years	2130 (18)	375 (18)	202 (20)
30-39 years	1812 (15)	356 (17)	185 (18)
40-49 years	1911 (16)	335 (16)	148 (15)
50+ years	4286 (36)	703 (34)	350 (35)
Median (Range)	41 (0-82)	40 (0-79)	40 (0-80)
Donor/Recipient CMV serostatus			
+/+	4848 (41)	906 (44)	394 (39)
+/-	1275 (11)	174 (8)	104 (10)
-/+	2998 (25)	494 (24)	260 (26)
-/-	2575 (22)	418 (20)	209 (21)
CB - recipient +	31 (<1)	16 (1)	5 (<1)
CB - recipient -	17 (<1)	12 (1)	1 (<1)
Missing	167 (1)	31 (2)	28 (3)
GvHD Prophylaxis			
No GvHD Prophylaxis	173 (1)	24 (1)	14 (1)
TDEPLETION alone	95 (1)	28 (1)	15 (1)
TDEPLETION +- other	99 (1)	23 (1)	7 (1)
CD34 select alone	83 (1)	23 (1)	11 (1)
CD34 select +- other	91 (1)	28 (1)	9 (1)
Cyclophosphamide alone	76 (1)	11 (1)	8 (1)
Cyclophosphamide +- others	4003 (34)	660 (32)	380 (38)
FK506 + MMF +- others	824 (7)	100 (5)	35 (3)
FK506 + MTX +- others(not MMF)	4204 (35)	641 (31)	344 (34)
FK506 +- others(not MMF,MTX)	839 (7)	306 (15)	72 (7)
FK506 alone	109 (1)	17 (1)	6 (1)
CSA + MMF +- others(not FK506)	241 (2)	43 (2)	19 (2)
CSA + MTX +- others(not MMF,FK506)	731 (6)	95 (5)	53 (5)
CSA +- others(not FK506,MMF,MTX)	82 (1)	10 (<1)	3 (<1)
CSA alone	82 (1)	13 (1)	4 (<1)
Other GVHD Prophylaxis	166 (1)	21 (1)	21 (2)
Missing	13 (<1)	8 (<1)	0
Donor/Recipient sex match			
Male-Male	3957 (33)	728 (35)	338 (34)
Male-Female	2522 (21)	417 (20)	218 (22)
Female-Male	2987 (25)	456 (22)	244 (24)
Female-Female	2393 (20)	421 (21)	195 (19)
CB - recipient M	31 (<1)	17 (1)	3 (<1)
CB - recipient F	17 (<1)	11 (1)	3 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	4 (<1)	1 (<1)	0
Year of transplant			
2006-2010	600 (5)	71 (3)	62 (6)
2011-2015	3668 (31)	508 (25)	229 (23)
2016-2020	5010 (42)	903 (44)	408 (41)
2021-2023	2633 (22)	569 (28)	302 (30)
Follow-up among survivors, Months			
N Eval	7728	1356	657
Median (Range)	25 (0-150)	24 (0-147)	17 (0-148)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Morbidity, Recovery, and Survivorship Working Committee Members

FROM: Rachel Phelan, MD, Scientific Director for the Morbidity, Recovery, and Survivorship Working Committee

RE: Studies in Progress Summary

LE12-03a: Outcomes for patients undergoing solid organ transplants followed by hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) This study aims to report outcomes and compare survival in solid organ transplant recipients prior to receiving HCT. The data derives from both CIBMTR and OPTN (UNOS) databases. This study is currently in manuscript preparation. The goal of this study is to submit by June 2024.

LE12-03b: Outcomes for patients undergoing hematopoietic cell transplantation followed by solid organ transplants (M Gupta/PL Abt/M Levine) This study aims to report outcomes and compare survival in HCT recipients prior to receiving solid organ transplantation. The data derives from both CIBMTR and OPTN (UNOS) databases. This study is currently in manuscript preparation. The goal of this study is to submit by June 2024.

LE17-01a: Late effects after hematopoietic stem cell transplantation for sickle cell disease (E Stenger/L Krishnamurti/S Shenoy) This study aims to describe incidence of late effects after HCT for sickle cell disease (SCD) and the relationship of transplant-related factors to organ dysfunction and SCD-related complications. This study is currently in manuscript preparation. The goal of this study is to submit by June 2024.

LE17-01b: Comparison of survival between transplanted and non-transplanted SCD patients (E Stenger/L Krishnamurti/S Shenoy) This study will compare survival of this transplanted SCD cohort to a cohort of non-transplanted SCD patients. This study is currently in data file preparation. The goal of this study is to be in manuscript preparation by June 2024.

LE18-01: Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) This study aims to evaluate trends in late mortality rates in children and young adults with hematologic malignancies. It will be presented at Tandem. The study is currently in manuscript preparation. The goal of this study is to submit by June 2024.

LE19-01b: Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) This study aims to explore long-term outcomes of pediatric diffuse alveolar hemorrhage (DAH) patients as well as to identify HCT-related risk factors for developing DAH. The study is currently in analysis. Records are cross-matched with the Virtual Pediatric Systems Database and the CIBMTR. The goal of this study is to submit by June 2023.

LE19-02: Incidence and predictors of long-term toxicities and late side effects in elderly patients (>=50 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) This study will evaluate the incidence of late effects within the elderly population and evaluate the association between age and cGVHD with the development of late effects. This study is in analysis. The goal of this study is to submit by June 2024.

LE20-01: Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) This study will utilize linked Childhood Cancer Survivor Study (CCSS) and Center for International Blood and Marrow Transplant Research (CIBMTR) data to enrich our understanding of the relative contributions of clinical factors to cardiometabolic risk among an aging cohort of TBI-exposed HSCT survivors. This study is currently in protocol development. The goal of this study is to submit by July 2024.

LE21-01 Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M-Angel Perales/A Kansagra) This study will compare the outcomes with different patients who used PTCy and who used other CNI-based prophylaxis. This study is currently in data file preparation. The goal of this study is to submit by July 2024.

RT19-01: Analysis of comorbidity-associated toxicity at a regimen-based level (R Shouval/ B Savani/A Nagler). This study aims to 1) evaluate the comorbidity-specific risk of non-relapse mortality and overall mortality within patients receiving pre-defined conditioning regimens, and 2) within patients stratified by conditioning intensity groups (myeloablative, reduced-intensity, and non-myeloablative, and 3) explore toxicities associated with specific conditioning regimen stratified by preexisting comorbidities. This study is currently in data file preparation. The goal of this study is to submit by June 2024.

RT19-02: Hemorrhagic cystitis (HC) as a complication of hematopoietic cell transplantation with post-transplant cyclophosphamide (PTCy)-based graft-versus-host disease prophylaxis compared to other allogeneic transplants (K Adekola/ N Ali/ O Frankfurt/ L Metheny/ J Moreira/ M de Lima). This study aims to determine the incidence and severity of HC in patients who received PTCy as part of GVHD prophylaxis, 2) to describe disease characteristics and pre-transplant regimens in patients that developed HC after receiving PTCy-based GVHD prophylaxis and 3) to evaluate survival outcomes in PTCy patients with HC. This study is currently in protocol development. The goal of this study is to be in analysis by June 2024.

RT20-01: Toxicities of older adults receiving allogeneic hematopoietic cell transplant compared to younger patients. (R Jayani/H Murff). This study aims to determine the incidence of organ toxicities in older and younger adult allo transplants for hematologic malignancies, 2) to describe comorbid conditions in this population and 3) to evaluate survival, progression-free survival, and non-relapse mortality outcome. This study is currently in data file preparation. The goal of this study is to submit by June 2024.

MRS22-01: Racial/ethnic disparities and role of poverty in long-term health outcomes among survivors of allogeneic hematopoietic cell transplant performed in childhood. (N Bhatt/A Sharma/L Jimenez-Kurlander/C Duncan). This study aims to compare the cumulative incidence and risks of malignant and non-malignant late effects by 1) race/ethnicity and 2) neighborhood poverty and

insurance type at time of transplant in survivors of allogeneic HCT who have survived for at least 1 year. This study is currently in protocol development. The goal of this study is to be in analysis by June 2024.

MRS22-02: Incidence, risk factors and outcomes of acute cardiac complications after post-transplant cyclophosphamide based GVHD prophylaxis: A retrospective analysis from the CIBMTR database. (K Poonsombudlert/C Strouse/H Rangarajan/P Satwani/D Modi). This study aims to evaluate the incidence of ACE after use of PT-Cy compared to non-PT-Cy based GVHD prophylaxis regimen and determine pre-transplant factors associated with the development of ACE. This study also aims to evaluate overall survival, disease free survival, and non-relapse mortality in patients who developed ACE compared to patients who did not. This study is currently in protocol development. The goal of this study is to be in analysis by June 2024.

MRS 23-01: Updated Analysis of Long-Term Survival and Late Deaths after Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies and Severe Aplastic Anemia. (M Battiwalla/U Rao). This study aims to determine the probability of survival at 10 years after HCT. It will further investigate risk factors of late mortality, change in late mortality over time, and comparing relative mortality after HCT with the general population. This study is currently in protocol development. The goal of this study is to be in analysis by June 2024.

TITLE: Defibrotide prophylaxis for hepatic sinusoidal obstructive syndrome in hematopoietic cellular therapy recipients: real-world outcomes and health care utilization implications

PIs: Michelle L Schoettler, MD, MS, Merve Pamukcuoglu, MD, Kirsten M Williams, MD

RESEARCH QUESTION: In the real world setting, does defibrotide prophylaxis result in significant differences in the incidence of severe sinusoidal obstructive syndrome (SOS) incidence, measured by organ failure, and non-relapse related mortality and what are the early post HCT health care utilization (HCU) implications of defibrotide prophylaxis?

RESEARCH HYPOTHESIS: Patients who receive defibrotide prophylaxis will have a significantly lower cumulative incidence of severe SOS as defined by multiorgan dysfunction compared to matched cohort who did not receive prophylaxis in both children and adults. We hypothesize there will be no differences in health care utilization (HCU) in those who received defibrotide prophylaxis and the matched cohort; costs of drug in the defibrotide cohort will be attenuated by costs of critical illness in severe SOS in the cohort without prophylaxis.

SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED

Objective 1: To determine the following comparing children (age ≤18 years old) who received defibrotide prophylaxis for SOS to a matched cohort who did not receive defibrotide prophylaxis:

A. The difference in cumulative incidence of severe SOS (defined as multi-organ dysfunction) by day 100 post HCT
B. The difference in the following clinical secondary endpoints: SOS, non-relapsed related mortality (NRM), overall survival (OS), and hospital admission days.
C. The difference in health care utilization as measured by standardized inpatient costs from time HCT admission day 100 post HCT

Objective 2: To determine the following comparing adults (age >19 years old) who received defibrotide prophylaxis for SOS to a matched cohort who did not receive defibrotide prophylaxis:

A. The difference in cumulative incidence of severe SOS (defined as multi-organ dysfunction) by day 100 post HCT
B. The difference in the following clinical secondary endpoints: SOS, non-relapsed related mortality (NRM), overall survival (OS), and hospital admission days.

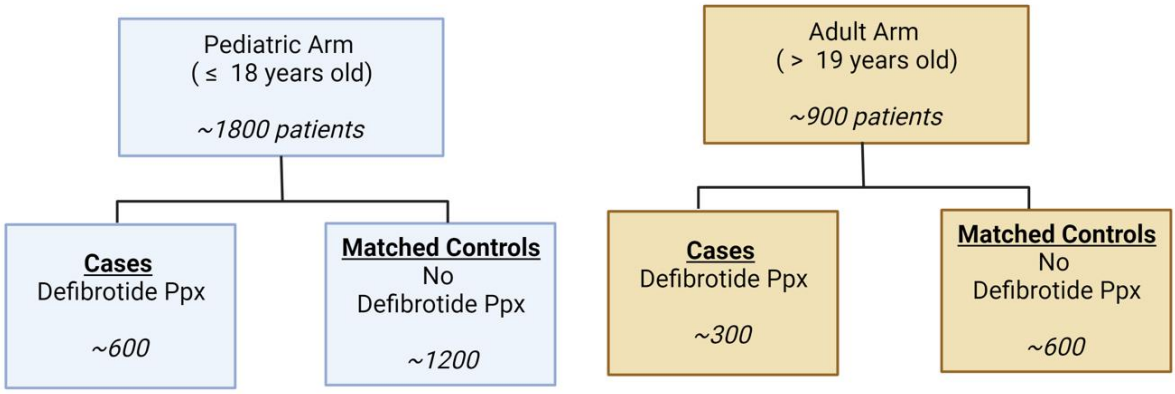
SCIENTIFIC IMPACT: Reporting real-world outcomes of defibrotide prophylaxis can immediately inform clinical practice for practitioners caring for these patients. In addition to clinical outcomes, reporting HCU of this expensive therapy can help hospitals and programs evaluate the value of this therapy.

SCIENTIFIC JUSTIFICATION: A randomized phase 3 clinical trial in children demonstrated a significant difference in cumulative incidence of SOS on day 30 post HCT[1]. However, the study was not powered to detect differences in multi-organ failure or non-relapse related mortality. A follow up randomized, open-label phase 3 multicenter trial evaluating the efficacy of SOS-free survival at day 30 in children and adults was closed early after an interim analysis determined that the study met protocol-specified futility[2]. Given these recent results, there is unlikely to be a follow up clinical trial. However, it remains unclear whether defibrotide prophylaxis impacts SOS incidence or the severity of disease, particularly in very high-risk children for whom a prior study

demonstrated some benefit, or adults for whom there are scant data. Because death within 30 days of HCT is a rare event, and mitigation of severe SOS would still be of value even if defibrotide failed to avert disease, the role of defibrotide prophylaxis in these outcomes merits investigation. Severe SOS remains a life-threatening complication of HCT, especially for those at highest risk (e.g. disease indication of osteopetrosis, recent exposure to inotuzumab, or infants with leukemia). There is no data to guide practitioners on whether to use defibrotide prophylaxis to avert severe disease.

In addition to uncertainty regarding the efficacy of defibrotide prophylaxis, there are cost considerations. Several analyses have demonstrated that defibrotide is cost effective for the treatment of VOD[3,4]. However, there are no data on the impact of costs for VOD prophylaxis. Merging data from the Pediatric Health Information System (PHIS) and CIBMTR database is the best way to way to answer the research question in children and is a secondary endpoint.

PARTICIPANT SELECTION CRITERIA: This is a case-control study with a pediatric and adult arm.



CASES (defibrotide prophylaxis)

Inclusion:

- Patients who underwent allogeneic or autologous HCT and received defibrotide prophylaxis from 2009-2022.

Exclusion:

- Defibrotide administration for treatment of VOD

CONTROLS (no defibrotide prophylaxis)

Inclusion:

- Patients who underwent allogeneic or autologous HCT who did not receive defibrotide prophylaxis from 2009-2022 and will be matched to the SOS group on the following characteristics:
    - Underlying disease
    - Prior gemtuzumab/inotuzumab exposure
    - Known prior liver injury
    - Age

  - Preparative regimen

Exclusion:

- Missing data on defibrotide prophylaxis
- Defibrotide for the treatment of SOS

We intend on matching cases and controls (1:2) to improve power.

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/DataCollectionForms/Pages/index.aspx Outline any supplementary data required. Additional data collection is extremely difficult and will make your proposal less feasible.

No additional data collection is necessary. Variables needed for the analysis include:

Patient Related:

- HCT indication
- Age
- Sex
- Prior HCT (yes/no)
- Receipt of gemtuzumab or inotuzumab prior to HCT
- Prior liver disease
- DRI (hematologic malignancy only)

Transplant Related

- Transplant type (autologous/allogeneic)
- HLA mismatch
- Stem Cell Source
- Donor related/unrelated
- Preparative regimen
  - Myeloablative/ non and TBI vs busulfan
  - Busulfan and AUC
- Acute GVHD prophylaxis

Transplant complications

- Sinusoidal obstructive syndrome (SOS)
  - Date SOS
  - Maximum severity (maximum bilirubin, organ function as below)
  - Management of late sequelae required (variceal banding, TIPS, paracentesis, thoracentesis)
- TA-TMA
  - Date TA-TMA
- Defibrotide prophylaxis (yes/no)
- Acute GVHD, maximum stage and grade
- Relapsed disease (yes/no)
  - Date relapse
- Significant organ impairment in the first 100 days:

  - Acute renal failure requiring dialysis
  - Intubation/Mechanical Ventilation
  - Diffuse alveolar hemorrhage
  - Intensive care admission and days *(PHIS data)*
- Dead/Alive, date
  - NRM or relapse
  - Estimates on: day 100, 180 and 1 year

Cost Data (PHIS)

- Standardized costs from day of HCT admission to day 100
- Cost subcategory costs

NON-CIBMTR DATA SOURCE: Pediatric Health Information System (PHIS) data will be linked to obtain a standardized unit cost in the pediatric cohort. The standardized cost accounts for differences in geographic areas, inflation, and hospital cost- it is not what patients are charged, but is a measure of health care utilization. Linkage is required because CIBMTR does not collect cost data. Linkage with PHIS is feasible and has been done in a prior CIBMTR study[5]. Between data from the CIBMTR and PHIS data systems, we will have all the data necessary to answer the study questions.

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Characteristics for adult patients with data on defibrotide prophylaxis, 2009-2020 (TED Retrieval)

Characteristic	Defibr. Proph.	No Defibr. Proph.
No. of patients	215	86539
No. of centers	83	300
Patient related		
Age - no. (%)		
19-29	72 (33.5)	6482 (7.5)
30-39	26 (12.1)	6554 (7.6)
40-49	26 (12.1)	10754 (12.4)
50-59	51 (23.7)	22883 (26.4)
60-69	32 (14.9)	30822 (35.6)
70+	8 (3.7)	9044 (10.5)
Sex- no. (%)		
Male	131 (60.9)	51208 (59.2)
Female	84 (39.1)	35331 (40.8)
Race - no. (%)		
White	164 (76.3)	63434 (73.3)
Black or African American	14 (6.5)	9289 (10.7)
Asian	9 (4.2)	2969 (3.4)
Native Hawaiian or other Pacific Islander	1 (0.5)	232 (0.3)
American Indian or Alaska Native	0 (0.0)	410 (0.5)
More than one race	1 (0.5)	282 (0.3)
Not reported	26 (12.1)	9923 (11.5)
Ethnicity - no. (%)		
Hispanic or Latino	37 (17.2)	8021 (9.3)
Not Hispanic or Latino	121 (56.3)	64734 (74.8)
Non-resident of the U.S.	54 (25.1)	11788 (13.6)
Not reported	3 (1.4)	1996 (2.3)
Karnofsky score prior to HCT - no. (%)		
90-100%	129 (60.0)	47771 (55.2)
< 90%	80 (37.2)	36816 (42.5)
Not reported	6 (2.8)	1952 (2.3)
HCT-CI - no. (%)		
0	48 (22.3)	23359 (27.0)
1	39 (18.1)	11893 (13.7)
2	29 (13.5)	13805 (16.0)
3+	97 (45.1)	36933 (42.7)

Characteristic	Defibr. Proph.	No Defibr. Proph.
TBD	1 (0.5)	290 (0.3)
Missing	1 (0.5)	259 (0.3)
Moderate/Severe Hepatic - no. (%)		
No	164 (76.3)	77111 (89.1)
Yes	22 (10.2)	1162 (1.3)
Not reported	29 (13.5)	8266 (9.5)
TBI - no. (%)		
No	11 (5.1)	4462 (5.2)
Yes	73 (34.0)	12208 (14.1)
Not reported	131 (60.9)	69869 (80.8)
Busulfan - no. (%)		
No	104 (48.4)	63154 (73.0)
Yes	87 (40.5)	14761 (17.1)
Not reported	24 (11.2)	8624 (9.9)
Disease related		
Primary disease - no. (%)		
Acute myelogenous leukemia or ANLL	61 (28.4)	12912 (14.9)
Acute lymphoblastic leukemia	53 (24.7)	4410 (5.1)
Other leukemia	2 (1.0)	1013 (1.1)
Chronic myelogenous leukemia	4 (1.9)	957 (1.1)
Myelodysplastic/myeloproliferative disorders	39 (18.1)	7347 (8.5)
Non-Hodgkin lymphoma	19 (8.8)	15041 (17.4)
Hodgkin lymphoma	5 (2.3)	4321 (5.0)
Plasma cell disorder/Multiple Myeloma	5 (2.3)	36826 (42.5)
Other Malignancies	8 (3.8)	1595 (1.8)
Severe aplastic anemia	5 (2.3)	1027 (1.2)
Inherited abnormalities erythrocyte differentiation or function	9 (4.2)	432 (0.5)
SCID and other immune system disorders	5 (2.3)	141 (0.2)
Inherited abnormalities of platelets	0 (0.0)	4 (0.0)
Inherited disorders of metabolism	0 (0.0)	20 (0.0)
Histiocytic disorders	0 (0.0)	81 (0.1)
Autoimmune Diseases	0 (0.0)	412 (0.5)
Transplant related		
Type of transplant - no. (%)		
Allogeneic	193 (89.8)	32142 (37.1)
Autologous	22 (10.2)	54397 (62.9)
Graft type - no. (%)		

Characteristic	Defibr. Proph.	No Defibr. Proph.
Bone marrow	53 (24.7)	4723 (5.5)
Peripheral blood	148 (68.8)	80401 (92.9)
Umbilical cord blood	10 (4.7)	957 (1.1)
BM + PB	2 (0.9)	102 (0.1)
BM + UCB	0 (0.0)	2 (0.0)
PB + UCB	2 (0.9)	200 (0.2)
Other	0 (0.0)	154 (0.2)
Donor type - no. (%)		
Autologous	22 (10.2)	54382 (62.8)
HLA-identical sibling	49 (22.8)	8779 (10.1)
Twin	1 (0.5)	115 (0.1)
Other related	36 (16.7)	6330 (7.3)
Partially-matched unrelated (7/8)	0 (0.0)	1 (0.0)
Multi-donor	0 (0.0)	19 (0.0)
Unrelated (matching TBD)	95 (44.2)	15742 (18.2)
Cord blood	12 (5.6)	1169 (1.4)
Not reported	0 (0.0)	2 (0.0)
Conditioning regimen intensity - no. (%)		
MAC	95 (44.2)	9886 (11.4)
RIC	9 (4.2)	2425 (2.8)
NMA	16 (7.4)	5052 (5.8)
TBD	61 (28.4)	27895 (32.2)
Missing	34 (15.8)	41281 (47.7)
GVHD prophylaxis - no. (%)		
None	28 (13.0)	54717 (63.2)
Ex-vivo T-cell depletion	3 (1.4)	161 (0.2)
CD34 selection	9 (4.2)	653 (0.8)
PtCy + other(s)	45 (20.9)	8215 (9.5)
PtCy alone	0 (0.0)	204 (0.2)
TAC + MMF +- other(s) (except PtCy)	13 (6.0)	3004 (3.5)
TAC + MTX +- other(s) (except MMF, PtCy)	54 (25.1)	10764 (12.4)
TAC + other(s) (except MMF, MTX, PtCy)	4 (1.9)	1676 (1.9)
TAC alone	5 (2.3)	661 (0.8)
CSA + MMF +- other(s) (except PtCy,TAC)	25 (11.6)	1905 (2.2)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	21 (9.8)	3618 (4.2)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	0 (0.0)	39 (0.0)
CSA alone	1 (0.5)	466 (0.5)

Characteristic	Defibr. Proph.	No Defibr. Proph.
Other(s)	7 (3.3)	438 (0.5)
Missing	0 (0.0)	18 (0.0)
Did VOD SOS develop since the date of last report? - no. (%)		
No	113 (52.6)	69981 (80.9)
Yes	60 (27.9)	464 (0.5)
Not reported	42 (19.5)	16094 (18.6)
TX year - no. (%)		
2009	0 (0.0)	317 (0.4)
2010	1 (0.5)	689 (0.8)
2011	3 (1.4)	1053 (1.2)
2012	2 (0.9)	1291 (1.5)
2013	1 (0.5)	1653 (1.9)
2014	1 (0.5)	1999 (2.3)
2015	2 (0.9)	2805 (3.2)
2016	21 (9.8)	12293 (14.2)
2017	29 (13.5)	18414 (21.3)
2018	50 (23.3)	19735 (22.8)
2019	66 (30.7)	17811 (20.6)
2020	39 (18.1)	8479 (9.8)

Characteristics for pediatric patients with data on defibrotide prophylaxis, 2009-2020 (TED Retrieval)

Characteristic	Defibr. Proph.	No Defibr. Proph.
No. of patients	517	11788
No. of centers	70	199
Patient related		
Age - no. (%)		
0-9	339 (65.6)	7757 (65.8)
10-18	178 (34.4)	4031 (34.2)
Sex- no. (%)		
Male	306 (59.2)	7075 (60.0)
Female	211 (40.8)	4713 (40.0)
Race - no. (%)		
White	349 (67.5)	6671 (56.6)
Black or African American	38 (7.4)	1387 (11.8)
Asian	33 (6.4)	966 (8.2)
Native Hawaiian or other Pacific Islander	8 (1.5)	62 (0.5)
American Indian or Alaska Native	3 (0.6)	100 (0.8)
More than one race	14 (2.7)	267 (2.3)
Not reported	72 (13.9)	2335 (19.8)
Ethnicity - no. (%)		
Hispanic or Latino	126 (24.4)	1979 (16.8)
Not Hispanic or Latino	223 (43.1)	6316 (53.6)
Non-resident of the U.S.	153 (29.6)	3116 (26.4)
Not reported	15 (2.9)	377 (3.2)
Karnofsky score prior to HCT - no. (%)		
90-100%	357 (69.1)	9022 (76.5)
< 90%	124 (24.0)	2138 (18.1)
Not reported	36 (7.0)	628 (5.3)
HCT-CI - no. (%)		
0	234 (45.3)	7651 (64.9)
1	122 (23.6)	1887 (16.0)
2	47 (9.1)	628 (5.3)
3+	110 (21.3)	1548 (13.1)
TBD	1 (0.2)	13 (0.1)
Missing	3 (0.6)	61 (0.5)
Moderate/Severe Hepatic - no. (%)		
No	425 (82.2)	10842 (92.0)

Characteristic	Defibr. Proph.	No Defibr. Proph.
Yes	45 (8.7)	603 (5.1)
Not reported	47 (9.1)	343 (3.0)
TBI - no. (%)		
No	28 (5.4)	854 (7.2)
Yes	122 (23.6)	2489 (21.1)
Not reported	377 (71.0)	8445 (71.6)
Busulfan - no. (%)		
No	259 (50.1)	7710 (65.4)
Yes	199 (38.5)	3495 (29.6)
Not reported	59 (11.4)	583 (4.9)
Disease related		
Primary Disease - no. (%)		
Acute myelogenous leukemia or ANLL	124 (24.0)	1274 (10.8)
Acute lymphoblastic leukemia	90 (17.4)	1526 (12.9)
Other leukemia	6 (1.2)	128 (1.1)
Chronic myelogenous leukemia	1 (0.2)	89 (0.8)
Myelodysplastic/myeloproliferative disorders	29 (5.6)	358 (3.1)
Non-Hodgkin lymphoma	7 (1.4)	183 (1.6)
Hodgkin lymphoma	2 (0.4)	340 (2.9)
Plasma cell disorder/Multiple Myeloma	0 (0.0)	3 (0.0)
Other Malignancies	129 (25.0)	3508 (29.7)
Severe aplastic anemia	8 (1.5)	965 (8.2)
Inherited abnormalities erythrocyte differentiation or function	45 (8.7)	1610 (13.7)
SCID and other immune system disorders	28 (5.4)	1117 (9.5)
Inherited abnormalities of platelets	0 (0.0)	40 (0.3)
Inherited disorders of metabolism	20 (3.9)	341 (2.9)
Histiocytic disorders	28 (5.4)	280 (2.4)
Autoimmune Diseases	0 (0.0)	26 (0.2)
Transplant related		
Type of transplant - no. (%)		
Allogeneic	385 (74.5)	7860 (66.7)
Autologous	132 (25.5)	3928 (33.3)
Graft type - no. (%)		
Bone marrow	198 (38.3)	4762 (40.4)
Peripheral blood	257 (49.7)	6010 (51.0)
Umbilical cord blood	56 (10.8)	909 (7.7)
BM + PB	0 (0.0)	17 (0.1)

Characteristic	Defibr. Proph.	No Defibr. Proph.
BM + UCB	2 (0.4)	54 (0.5)
PB + UCB	0 (0.0)	5 (0.0)
Other	4 (0.8)	31 (0.2)
Donor type - no. (%)		
Autologous	132 (25.5)	3928 (33.3)
HLA-identical sibling	89 (17.2)	2399 (20.4)
Twin	1 (0.2)	10 (0.1)
Other related	107 (20.7)	1782 (15.1)
Multi-donor	0 (0.0)	9 (0.1)
Unrelated (matching TBD)	128 (24.8)	2680 (22.7)
Cord blood	60 (11.6)	979 (8.3)
Not reported	0 (0.0)	1 (0.0)
Conditioning regimen intensity - no. (%)		
MAC	305 (59.0)	4821 (40.9)
RIC	11 (2.1)	272 (2.3)
NMA	19 (3.7)	1053 (8.9)
TBD	141 (27.3)	4667 (39.6)
Missing	41 (7.9)	975 (8.3)
GVHD prophylaxis - no. (%)		
None	154 (29.8)	4116 (34.9)
Ex-vivo T-cell depletion	19 (3.7)	321 (2.7)
CD34 selection	30 (5.8)	421 (3.6)
PtCy + other(s)	43 (8.3)	1252 (10.6)
PtCy alone	0 (0.0)	10 (0.1)
TAC + MMF +- other(s) (except PtCy)	42 (8.1)	562 (4.8)
TAC + MTX +- other(s) (except MMF, PtCy)	55 (10.6)	1313 (11.1)
TAC + other(s) (except MMF, MTX, PtCy)	4 (0.8)	79 (0.7)
TAC alone	10 (1.9)	118 (1.0)
CSA + MMF +- other(s) (except PtCy,TAC)	52 (10.1)	1034 (8.8)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	72 (13.9)	1933 (16.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	10 (1.9)	221 (1.9)
CSA alone	15 (2.9)	256 (2.2)
Other(s)	11 (2.1)	146 (1.2)
Missing	0 (0.0)	6 (0.1)
Did VOD SOS develop since the date of last report? - no. (%)		
No	302 (58.4)	7965 (67.6)
Yes	107 (20.7)	501 (4.3)

Characteristic	Defibr. Proph.	No Defibr. Proph.
Not reported	108 (20.9)	3322 (28.2)
TX year - no. (%)		
2009	0 (0.0)	56 (0.5)
2010	0 (0.0)	113 (1.0)
2011	1 (0.2)	161 (1.4)
2012	1 (0.2)	180 (1.5)
2013	2 (0.4)	209 (1.8)
2014	2 (0.4)	327 (2.8)
2015	13 (2.5)	458 (3.9)
2016	44 (8.5)	1910 (16.2)
2017	102 (19.7)	2846 (24.1)
2018	120 (23.2)	2710 (23.0)
2019	145 (28.0)	2265 (19.2)
2020	87 (16.8)	553 (4.7)

Field	Response
Proposal Number	2310-28-TIJAROOVALLE
Proposal Title	Toxicity profile and survival of patients with BMI >30 undergoing allogeneic stem cell transplantation
Key Words	Allogeneic stem cell transplant, conditioning, obesity
Principal Investigator #1: - First and last name, degree(s)	Natalia Tijaro Ovalle, MD
Principal Investigator #1: - Email address	tijaroon@mskcc.org
Principal Investigator #1: - Institution name	Memorial Sloan Kettering Cancer Center
Principal Investigator #1: - Academic rank	Hematology/Oncology Fellow
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Ann Jakubowski, MD
Principal Investigator #2 (If applicable): - Email address:)	jakubowa@mskcc.org
Principal Investigator #2 (If applicable): - Institution name:	Memorial Sloan Kettering Cancer Center
Principal Investigator #2 (If applicable): - Academic rank:	Bone Marrow Transplant Specialist
Junior investigator status (defined as ≤5 years from fellowship)	No
Do you identify as an underrepresented/minority?	No
We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:	Ann Jakubowski
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	None
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Morbidity, Recovery and Survivorship
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Does increasing obesity impact outcomes in individuals with body mass index ≥ 30 undergoing allogeneic stem cell transplant?
RESEARCH HYPOTHESIS:	Morbidly obese patients (BMI 40+) with MDS and AML have significantly poorer outcomes in allogeneic transplant compared to patients with BMI 30+ and those 25-29.9.

Field	Response
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	- Primary objective: determine 100-day and 1-year incidence of post-transplant toxicities (defined as any grade 3 or 4 non-hematological toxicity, incidence of renal, pulmonary, hepatic, and cardiac toxicity), incidence and grade of GVHD, and mortality in allogeneic stem cell transplant patients with BMI 25-29.99 vs 30-39.99 vs 40+. - Secondary objectives: A) determine the 1-year incidence of relapse in patient with BMI 25-29.99 vs. 30-39.99 vs 40+. B) describe the causes of death at 1-year, and overall survival in the 3 groups of patients. C) describe comorbidities and association with survival at 1-year in the 3 groups of patients. D) describe gender, race, and geographical location of patient in each of the 3 groups and association with outcomes.
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	According to the Centers for Disease Control and Prevention (CDC), by March of 2020 the prevalence of obesity in America was approximately 42% (1). Even though cancer-induced cachexia frequently leads to weight loss in patients who undergo stem cell transplantation (2), obesity defined as a body mass index (BMI) 30+ is still common among transplant recipients at the time of their conditioning, affecting anywhere from 6 to 18 % of patients (3,4). Obesity is frequently associated with higher HCT-CI scores, which often leads to the use of reduced-intensity conditioning prior to allogeneic stem cell transplant in this population (5,6). A frequently adopted practice by transplant centers in the United States is to use adjusted body weight dosing if the patient's weight is ≥ 125% of their ideal body weight. However, there is no consensus in the literature regarding the safety of using adjusted body weight-based dosing of the drugs used in transplant, as opposed to using ideal-body-weight dosing in this population (7). This study aims to provide evidence that will help support the decision-making process of appropriate dosing of conditioning regimens used for obese allogeneic stem cell transplant recipients, in addition to illustrate the toxicity profile of conditioning in patients with obesity (BMI 30-39.99) and morbid obesity (BMI 40+).

Field	Response
SCIENTIFIC JUSTIFICATION: Provide a background summary of previous related research and their strengths and weaknesses, justification of your research and why your research is still necessary.	In 2014, the American Society for Blood and Marrow Transplantation (ASBMT), now known as American Society for Transplantation and Cellular Therapy (ASTCT), released a literature review on the dosing of conditioning chemotherapy prior to autologous or allogeneic stem cell transplant in obese individuals. After analyzing the existing evidence, they reported that dose adjustments for obese patients were mostly empiric or adapted from data coming from non-transplant populations (8). Unfortunately, due to the lack of sufficient evidence in obese stem cell transplant recipients, the practice guideline committee was unable to propose level I or II recommendations on the appropriate dosing for conditioning chemotherapy in this population. Since then, scattered studies have addressed this gap in the knowledge. Hunter et al showed that obese individuals who received adjusted body weight dosing (calculated as (total body weight – ideal body weight) x 0.4 + ideal body weight) of high-dose cyclophosphamide as part of their allogeneic stem cell transplant conditioning suffered higher overall toxicity, particularly renal dysfunction, compared to non-obese patients (9). Most recently, studies have focused on describing the importance of pharmacokinetic-based dosing of melphalan and busulfan in stem cell transplantation of adult recipients (10, 11, 12), but these have not been universally accepted and furthermore fludarabine pharmacokinetic models have generally not been adopted as standard practice (13). More so, many transplant centers cannot follow pharmacokinetic-based dosing of conditioning regimens given its cost and complexity. As the number of obese patients continues to rise in the US, evidence is needed to assist physicians in appropriately informing patients of their risks of toxicity with conditioning regimens, and to potentially justify studies to improve their management. In the current era of health equity, this is especially important for the minority racial groups where the highest incidence of obesity is found.

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion criteria: • Patients aged ≥ 18 years old. • Patients with any of the following hematologic malignancies for which allogeneic stem cell transplant is indicated, including: o Acute nonlymphocytic leukemia in CR1 or in ≥ CR2, relapsed/refractory o Myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), or MDS/MPN overlap syndromes • Patients with Body mass index (BMI) 25-29.99 (group 1), 30-39.99 (group 2) and 40+ (group 3) • Patients who received any chemotherapy conditioning regimen • Patients undergoing first allogeneic stem cell transplant only • Patients transplanted in years 2000-2020 Exclusion criteria: • Patients who received radiation containing conditioning • Patients lost to follow up within the first-year post-transplant • Patients undergoing cord blood transplant
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	N/A
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	- Variables of interest: Age, sex, race, KPS/ECOG at the time of transplant, HCT-CI, pre-transplant comorbidities, transplant indication/diagnosis/status of disease, donor type (MRD, MUD, MMUD), graft type (PBSC vs. BM), chemotherapy dosing, presence/absence of dosing adjustment based on ≥125% ideal body weight, BMI at the time of transplant, GVHD prophylaxis regimen, duration of follow up to 1 year , baseline creatinine/CrCl/eGFR, AST/ALT/AP/total bilirubin, FEV1/DLCO, LV ejection fraction, overall toxicity incidence (defined as any grade 3 or 4 non-hematological toxicity, incidence of renal, pulmonary, hepatic, or cardiac toxicity), non-relapse mortality, progression free-survival, overall survival, grade 3-4 acute GVHD, any grade of chronic GVHD, cause of death.
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A desc	N/A
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A

Field	Response
SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary o	N/A
NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required.	N/A

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

Characteristics of first allo adult HCT patients for AML, MDS, and MPN from 2000-2020 (CRF) (by BMI group)

Characteristic	25-29	30-39	40+
No. of patients	9887	7174	1226
No. of centers	288	259	154
Patient related			
Age at Transplant - no. (%)			
18-29	775 (7.8)	581 (8.1)	161 (13.1)
30-39	903 (9.1)	672 (9.4)	166 (13.5)
40-49	1449 (14.7)	1207 (16.8)	297 (24.2)
50-59	2743 (27.7)	2065 (28.8)	335 (27.3)
60-69	3220 (32.6)	2225 (31.0)	241 (19.7)
70+	797 (8.1)	424 (5.9)	26 (2.1)
Sex - no. (%)			
Male	6606 (66.8)	4390 (61.2)	568 (46.3)
Female	3281 (33.2)	2784 (38.8)	658 (53.7)
Race - no. (%)			
White	8518 (86.2)	6189 (86.3)	1021 (83.3)
Black or African American	509 (5.1)	523 (7.3)	131 (10.7)
Asian	402 (4.1)	104 (1.4)	13 (1.1)
Native Hawaiian or other Pacific Islander	34 (0.3)	33 (0.5)	6 (0.5)
American Indian or Alaska Native	27 (0.3)	32 (0.4)	11 (0.9)
Other	61 (0.6)	43 (0.6)	7 (0.6)
More than one race	37 (0.4)	36 (0.5)	6 (0.5)
Not reported	299 (3.0)	214 (3.0)	31 (2.5)
Ethnicity - no. (%)			
Hispanic or Latino	718 (7.3)	566 (7.9)	101 (8.2)
Non Hispanic or non-Latino	7698 (77.9)	5818 (81.1)	992 (80.9)
Non-resident of the U.S.	807 (8.2)	335 (4.7)	31 (2.5)
Not reported	664 (6.7)	455 (6.3)	102 (8.3)
Karnofsky score prior to HCT - no. (%)			
90-100%	5772 (58.4)	3944 (55.0)	651 (53.1)
< 90%	3769 (38.1)	2989 (41.7)	532 (43.4)
Not reported	346 (3.5)	241 (3.4)	43 (3.5)
HCT-CI - no. (%)			
0	2015 (20.4)	1083 (15.1)	49 (4.0)
1	1021 (10.3)	774 (10.8)	134 (10.9)
2	944 (9.5)	785 (10.9)	120 (9.8)

Characteristic	25-29	30-39	40+
3+	3140 (31.8)	2716 (37.9)	545 (44.5)
TBD	164 (1.6)	111 (1.5)	20 (1.6)
Not reported	2603 (26.4)	1705 (23.8)	358 (29.2)
Disease related			
Primary disease - no. (%)			
Acute myelogenous leukemia or anll	4299 (43.5)	3160 (44.0)	609 (49.7)
Acute lymphoblastic leukemia	1279 (12.9)	1018 (14.2)	210 (17.1)
Other leukemia	668 (6.8)	457 (6.4)	73 (6.0)
MDS/MPN	3641 (36.9)	2539 (35.4)	334 (27.2)
Transplant related			
Graft type in merge - no. (%)			
Bone marrow	1776 (18.0)	1272 (17.7)	187 (15.3)
Peripheral blood	8079 (81.7)	5884 (82.0)	1037 (84.6)
BM + PB	17 (0.2)	7 (0.1)	2 (0.2)
Other	13 (0.1)	11 (0.2)	0 (0.0)
Not reported	2 (0.0)	0 (0.0)	0 (0.0)
Donor type - no. (%)			
HLA-identical sibling	2715 (27.5)	1832 (25.5)	297 (24.2)
Twin	43 (0.4)	19 (0.3)	4 (0.3)
Other related	1186 (12.0)	1000 (13.9)	184 (15.0)
Well-matched unrelated (8/8)	1189 (12.0)	795 (11.1)	176 (14.4)
Partially-matched unrelated (7/8)	491 (5.0)	376 (5.2)	70 (5.7)
Mis-matched unrelated (<= 6/8)	178 (1.8)	115 (1.6)	26 (2.1)
Multi-donor	16 (0.2)	18 (0.3)	1 (0.1)
Unrelated (matching TBD)	4062 (41.1)	3013 (42.0)	466 (38.0)
Not reported	7 (0.1)	6 (0.1)	2 (0.2)
Conditioning regimen intensity - no. (%)			
MAC	5046 (51.0)	3785 (52.8)	757 (61.7)
RIC	3379 (34.2)	2309 (32.2)	279 (22.8)
NMA	1141 (11.5)	868 (12.1)	149 (12.2)
TBD	177 (1.8)	121 (1.7)	30 (2.4)
Not reported	144 (1.5)	91 (1.3)	11 (0.9)
Cyclophosphamide in preparative regimen - no. (%)			
No	5781 (58.5)	3978 (55.5)	622 (50.7)
Yes	3748 (37.9)	2911 (40.6)	573 (46.7)
Not reported	358 (3.6)	285 (3.9)	31 (2.5)
Busulfan in preparative regimen - no. (%)			
No	4911 (49.7)	3510 (48.9)	593 (48.4)

Characteristic	25-29	30-39	40+
Yes	4659 (47.1)	3413 (47.6)	601 (49.0)
Not reported	317 (3.2)	251 (3.5)	33 (2.6)
Fludarabine in preparative regimen - no. (%)			
No	2533 (25.6)	1989 (27.7)	418 (34.1)
Yes	6488 (65.6)	4644 (64.7)	695 (56.7)
Not reported	866 (8.7)	541 (7.5)	113 (9.1)
Melphalan in preparative regimen - no. (%)			
No	7742 (78.3)	5734 (79.9)	1051 (85.7)
Yes	1821 (18.4)	1167 (16.3)	139 (11.3)
Not reported	324 (3.3)	273 (3.8)	36 (2.9)
Thiotepa in preparative regimen - no. (%)			
No	9214 (93.2)	6612 (92.2)	1145 (93.4)
Yes	254 (2.6)	208 (2.9)	38 (3.1)
Not reported	419 (4.2)	354 (4.9)	43 (3.5)
GVHD prophylaxis - no. (%)			
Ex-vivo T-cell depletion/ CD34 selection	337 (3.4)	254 (3.5)	51 (4.1)
PtCy + other(s)	1237 (12.5)	1047 (14.6)	180 (14.7)
PtCy alone	24 (0.2)	28 (0.4)	3 (0.2)
TAC + MMF +- other(s) (except PtCy)	1256 (12.7)	980 (13.7)	164 (13.4)
TAC + MTX +- other(s) (except MMF, PtCy)	3951 (40.0)	2936 (40.9)	515 (42.0)
TAC + other(s) (except MMF, MTX, PtCy)	476 (4.8)	341 (4.8)	50 (4.1)
TAC alone	243 (2.5)	183 (2.6)	31 (2.5)
CSA + MMF +- other(s) (except PtCy,TAC)	677 (6.8)	414 (5.8)	67 (5.5)
CSA + MTX +- other(s) (except PtCy,TAC,MMF)	1142 (11.6)	660 (9.2)	115 (9.4)
CSA + other(s) (except PtCy,TAC,MMF,MTX)	63 (0.6)	42 (0.6)	10 (0.8)
CSA alone	177 (1.8)	80 (1.1)	12 (1.0)
Other(s)	286 (2.9)	194 (2.7)	27 (2.2)
Missing	18 (0.2)	15 (0.2)	1 (0.1)
TX year - no. (%)			
2000	257 (2.6)	168 (2.3)	30 (2.4)
2001	311 (3.1)	166 (2.3)	33 (2.7)
2002	288 (2.9)	182 (2.5)	40 (3.3)
2003	318 (3.2)	197 (2.7)	40 (3.3)
2004	394 (4.0)	252 (3.5)	49 (4.0)
2005	409 (4.1)	281 (3.9)	55 (4.5)
2006	441 (4.5)	317 (4.4)	61 (5.0)
2007	454 (4.6)	352 (4.9)	84 (6.9)
2008	641 (6.5)	453 (6.3)	79 (6.4)

Characteristic	25-29	30-39	40+
2009	520 (5.3)	389 (5.4)	66 (5.4)
2010	330 (3.3)	263 (3.7)	49 (4.0)
2011	245 (2.5)	200 (2.8)	23 (1.9)
2012	293 (3.0)	195 (2.7)	31 (2.5)
2013	585 (5.9)	408 (5.7)	78 (6.4)
2014	719 (7.3)	562 (7.8)	92 (7.5)
2015	693 (7.0)	546 (7.6)	84 (6.9)
2016	717 (7.3)	529 (7.4)	69 (5.6)
2017	707 (7.2)	464 (6.5)	95 (7.7)
2018	705 (7.1)	498 (6.9)	77 (6.3)
2019	604 (6.1)	517 (7.2)	64 (5.2)
2020	256 (2.6)	235 (3.3)	27 (2.2)
Follow-up of survivors - median (range)	73.6 (1.3-206.5)	73.5 (1.6-192.0)	86.4 (3.2-10861.4)

Study title: Incidence, risk factors, and characteristics of subsequent neoplasms in CAR-T recipients and its impact on survival

Proposed working committee: Morbidity, Recovery and Survivorship Working Committee

Research question: Defining the incidence, risk factors, and pattern of subsequent neoplasms (SN) and second hematological malignancies (SHM) following CAR-T therapy and its impact on progression-free (PFS) and overall survival (OS).

Research hypothesis:

1. Patient- and disease-related factors available prior to CAR-T therapy are associated with the risk for second primary neoplasms developing after CAR-T therapy.
2. A higher grade of inflammatory complications such as cytokine release syndrome or neurotoxicity are associated with increased risk for subsequent neoplasms post CAR-T.

Specific objectives/outcomes to be investigated:

Primary:

1. To characterize the cumulative incidences and characteristics of
    a. Subsequent neoplasms (SN)
    b. Myeloid neoplasms post-CART therapy
    c. T-cell lymphoma in CD19 and BCMA CAR-T therapy recipients.

Secondary:

1. Impact of SN/SHM development on 2-year PFS and OS
2. Identify pre- and post-CAR-T therapy related factors associated with a higher risk of developing SN

Scientific impact: CAR-T cell therapy is currently FDA approved for relapsed, refractory B-cell non-Hodgkin Lymphoma (NHL), multiple myeloma (MM), and B-cell acute lymphoblastic leukemia (B-ALL). SN/SHM developing after day +100 are a significant deterrent to life expectancy and/or quality of life—even more so in whom CART therapy is 'successful.' The rationale for our approach is as follows.

Second primary malignancies and second hematological malignancies: Multiple studies indicate higher-than-expected incidences of SN and SHM following CAR-T therapy. For example, Cordeiro *et al* (Transplant and Cellular Therapy, 2020) reported a 15% incidence of SN that included 7% non-melanoma skin cancer, 5% myelodysplastic syndrome (MDS), 1% melanoma, 1% non-invasive bladder cancer, and 1% MM. In a cohort of 189 patients treated with commercially available CAR-T therapy for relapsed/refractory NHL, 10 (5.3%) patients developed myeloid neoplasms post cytotoxic therapy (MN-pCT) (Alkhateeb *et al*, Blood Cancer Journal, 2022). Median time to develop t-MN was 9.1 months and 6 (60%) patient developing t-MN within 1 year from CAR-T. At MN-pCART diagnosis, 4 (40%) had complex karyotype and *TP53* mutation. When compared to t-MN developing after autologous stem cell transplant, there was short latency of post CAR-T t-MN as median MN free survival was 22 *vs.* 44 months (p=0.01), and MN-pCAR-T continues to have comparable worse survival compared to t-MN following other forms of therapy (9 *vs.* 16 months, p=0.11). Finally, MD Anderson/Moffitt groups also noted a 2-year cumulative incidence of 12% (Saini *et al*, Blood Cancer Discovery, 2022). The presence of clonal hematopoiesis prior to CAR-T therapy was associated with a higher incidence of t-MN (19% *vs*. 4.2%).

There is renewed interest in characterizing the scope of T-cell lymphoma developing in CAR-T recipients. The U.S. Food and Drug Administration announced that it will be investigating serious risk of T-cell malignancies following anti-BCMA and anti-CD-19 CAR-T cell therapies based on initial reports received from post-marketing analysis of these products (FDA Biologic Safety and Availability Report, 11/28/2023).

In contrast, the reported incidence of SN varies widely among clinical trials. For example, in the CARTITUDE-1 study (Martin *et al*, Journal of Clinical Oncology, 2022), 20 SN were reported in 16 patients. Nine patients had

SHM, including one case of low-grade B-cell lymphoma, 6 MDS, and 3 acute myeloid leukemia (AML). Four patients had squamous cell carcinoma; one of these also had basal cell carcinoma. One patient each had malignant melanoma, adenocarcinoma, or myxofibrosarcoma, and one patient had prostate cancer in addition to his squamous cell carcinoma and AML reported above. Whereas the pivotal CAR-T studies in NHL including ZUMA-7, TRANSFORM, and BELINDA did not report the development of SN including t-MN.

In summary, while CAR-T therapy is a life-saving option for many patients, unique and serious adverse events are being recognized with longer follow up. This CIBMTR database will allow us to comprehensively characterize the burden of secondary malignancies in CAR T cell recipients. As the utilization of CAR-T therapy is expected to rise exponentially, it is critical to further our understanding of long-term complications, which will inform the choice and sequencing of therapies and monitoring.

Patient selection criteria:

1. All adult patients who underwent CAR-T therapy for NHL and MM
2. Achieved remission at day+100
3. Subsequently diagnosed with a malignancy unrelated to the primary indication for CAR-T therapy including—
    a. solid malignancies
    b. unrelated hematological malignancies including MN-pCT and T-cell lymphomas

Does this study include pediatric patients? No

Data requirements: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses.

<u>Patient and disease related (at baseline):</u>

- Age at CAR-T, as a categorical variable (18-60, 60-70, and >70)
- Performance status - KPS prior to CAR-T therapy
- HCT-CI (if available for most)
- Sex
- Ethnicity
- Primary indication for CAR-T therapy
- Disease status at CART infusion
- Prior lines of therapy
    - Use of alkylator (yes *vs*. no)
    - Use of nucleoside analogue (yes *vs*. no)
    - Use of radiation (yes *vs*. no)
    - Use of immunosuppressive therapy (yes *vs*. no)
- Prior autologous stem cell transplant (yes vs. no)
    - Type of conditioning chemotherapy
- Prior malignancy (yes *vs*. no)
    - If yes, type (SN, SHM other than MN-pCT, MN-pCT)
- Ferritin
- LDH
- C-reactive protein

<u>CAR-T related:</u>

- Bridging chemotherapy utilized (yes *vs*. no)
- Lymphodepletion chemotherapy (drug and dose)
- CAR-T Product name and construct
- Time from collection to infusion
- Time to neutrophil and platelet recovery

- Max grade of cytokine release syndrome (CRS) and neurotoxicity grade (using immune effector cell-associated neurotoxicity syndrome or ICANS score)
- Use of immunosuppressive therapy to treat CRS/neurotoxicity (steroids vs tocilizumab vs. anakinra vs. others)

Long-term complication related:

- CBC at day +100, 6 months, 1 year
- Diagnosis and type of SN (pathology review whenever feasible)
- Time to develop SN/SHM
- Vital status at last follow-up
- Primary cause of death

Study population: Patients who underwent first CAR-T therapy for any of the following approved indications: relapsed/refractory lymphomas including diffuse large B-cell lymphoma, transformed low-grade lymphomas, high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma, relapsed/refractory multiple myeloma alive at +100 days after CAR-T therapy.

Statistical analysis: The study population will be summarized using descriptive statistics. While the cumulative incidence of LPD and MM appears to be similar; the patient, disease, and treatment related factors are likely different. For that reason, we will analyze the risk factors for SN/SHM development as stratified by the primary indication (LPD *vs*. MM).

For the purpose of this study, SN will be defined as any solid tumor malignancy that develops >3 months from CAR-T infusion. SHM will defined as the development of an unrelated hematological malignancy that develops >3 months from CAR-T infusion. Finally, MN-pCART will be defined as the development of MDS, AML, or MDS/MPN malignancy that develops >3 months from CAR-T infusion according to the 5th edition of the WHO criteria (Khoury et al, Leukemia 2022).

Cumulative incidence of SN/SHM will be calculated using landmark analysis from day +100 to the development of the first SN/SHM with death from any cause as a competing risk. The incidence of SN/SHM will be stratified according to the diagnosis before or after the relapse of the primary malignancy. Uni- and multivariate Cox regression model will be performed using patient, disease, and CAR-T related variables for the development of SN/SHM. Kaplan-Meier method and log-rank testing for univariate comparisons will be used to determine probabilities of OS and PFS. Multivariate analysis (MVA) will be performed using a Cox proportional hazards regression model using both the variables as time-dependent covariates to determine the impact of SN and SHM on PFS or OS. A stepwise model building approach will be adopted and variables that attain a *P*-value <5% were retained in the final model.

Population characteristics for adult patients with NHL or MM who underwent CAR-T and achieved remission at day 100

Characteristic	Non-Hodgkin lymphoma (NHL)	Plasma cell disorder/multiple myeloma (PCD/MM)
No. of patients	3783	926
No. of centers	136	68
Patient related		
Level Age at CT Treatment - median (min-max)	64.9 (18.2-91.2)	66.0 (35.0-90.3)
Recipient Sex - no. (%)		
Male	2333 (61.7)	520 (56.2)
Female	1448 (38.3)	406 (43.8)
Not reported	2 (0.1)	0 (0.0)
Ethnicity - no. (%)		
Hispanic or Latino	373 (9.9)	50 (5.4)
Non Hispanic or non-Latino	3042 (80.4)	851 (91.9)
Non-resident of the U.S.	246 (6.5)	1 (0.1)
Unknown	122 (3.2)	24 (2.6)
Recipient race - no. (%)		
White	3034 (80.2)	748 (80.8)
Black or African American	166 (4.4)	130 (14.0)
Asian	184 (4.9)	14 (1.5)
Native Hawaiian or other Pacific Islander	5 (0.1)	1 (0.1)
American Indian or Alaska Native	11 (0.3)	5 (0.5)
Other	11 (0.3)	4 (0.4)
More than one race	180 (4.8)	17 (1.8)
Missing	192 (5.1)	7 (0.8)
CT-CI - no. (%)		
0	1094 (28.9)	245 (26.5)
1	804 (21.3)	159 (17.2)
2	535 (14.1)	127 (13.7)
3+	1297 (34.3)	389 (42.0)
TBD	15 (0.4)	5 (0.5)
Not reported	38 (1.0)	1 (0.1)
Karnofsky performance score prior to CT - no. (%)		
90-100	1708 (45.1)	336 (36.3)
80	1136 (30.0)	354 (38.2)
< 80	572 (15.1)	175 (18.9)
Not reported	367 (9.7)	61 (6.6)

Characteristic	Non-Hodgkin lymphoma (NHL)	Plasma cell disorder/multiple myeloma (PCD/MM)
Patient had a prior ALLO HCT - no. (%)		
No	3572 (94.4)	897 (96.9)
Yes	211 (5.6)	29 (3.1)
Patient had a prior AUTO HCT - no. (%)		
No	2784 (73.6)	146 (15.8)
Yes	999 (26.4)	780 (84.2)
Disease Related		
Disease status at infusion (NHL only) - no. (%)		
PIF	1123 (29.7)	0 (0.0)
CR1	86 (2.3)	0 (0.0)
CR2	176 (4.7)	0 (0.0)
CR3+	100 (2.6)	0 (0.0)
First relapse	1140 (30.1)	0 (0.0)
Second relapse	764 (20.2)	0 (0.0)
Third or more relapse	376 (9.9)	0 (0.0)
Disease untreated	14 (0.4)	0 (0.0)
Not reported	4 (0.1)	926 (100)
Specify the new malignancy - no. (%)		
Acute myeloid leukemia (AML/ANLL)	15 (0.4)	1 (0.1)
Breast cancer	3 (0.1)	2 (0.2)
Central nervous system (CNS) malignancy	1 (0.0)	1 (0.1)
Clonal cytogenetic abnormality without leukemia or MDS	2 (0.1)	0 (0.0)
Gastrointestinal malignancy (GI)	11 (0.3)	0 (0.0)
Genitourinary malignancy (GU)	11 (0.3)	0 (0.0)
Hodgkin disease	2 (0.1)	0 (0.0)
Lung cancer	7 (0.2)	0 (0.0)
Melanoma	12 (0.3)	1 (0.1)
Myelodysplasia (MDS)/Myeloproliferative (MPS) disorder	98 (2.6)	8 (0.9)
Oropharyngeal cancer	1 (0.0)	0 (0.0)
Thyroid cancer	1 (0.0)	0 (0.0)
Other malignancy	10 (0.3)	0 (0.0)
Non-Hodgkin lymphoma	3 (0.1)	0 (0.0)
Basal cell malignancy	32 (0.8)	9 (1.0)
Squamous cell skin malignancy	46 (1.2)	13 (1.4)
Acute lymphoblastic leukemia	1 (0.0)	0 (0.0)
Soft tissue sarcoma	3 (0.1)	0 (0.0)
TBD	4 (0.1)	0 (0.0)

Characteristic	Non-Hodgkin lymphoma (NHL)	Plasma cell disorder/multiple myeloma (PCD/MM)
Not reported	3520 (93.0)	891 (96.2)
Time to develop subsequent neoplasm, months - median (min-max)	11.0 (1.0-50.8)	5.8 (1.6-20.0)
Cellular Therapy Related		
Product - no. (%)		
Kymriah	572 (15.1)	0 (0.0)
Yescarta	2457 (64.9)	0 (0.0)
Tecartus	427 (11.3)	0 (0.0)
Breyanzi	327 (8.6)	0 (0.0)
Abecma	0 (0.0)	696 (75.2)
Carvykti	0 (0.0)	230 (24.8)
Time from initial diagnosis to CT, months - median (min-max)	20.4 (0.4-446.2)	76.8 (0.2-293.4)
Lymphodepleting regimen - no. (%)		
Yes	3781 (99.9)	926 (100)
Bendamustine	297 (7.9)	64 (6.9)
Bendamustine + Cyclophosphamide + Fludarabine	1 (0.0)	0 (0.0)
Bendamustine + Other	14 (0.4)	0 (0.0)
Carboplatin + Fludarabine	1 (0.0)	0 (0.0)
Cyclophosphamide	12 (0.3)	11 (1.2)
Cyclophosphamide + Cytarabine + Fludarabine	1 (0.0)	0 (0.0)
Cyclophosphamide + Fludarabine	3404 (90.0)	826 (89.2)
Cyclophosphamide + Fludarabine + Other	7 (0.2)	0 (0.0)
Cyclophosphamide + Melphalan	1 (0.0)	0 (0.0)
Cyclophosphamide + Other	14 (0.4)	20 (2.2)
Cytarabine + Fludarabine	8 (0.2)	1 (0.1)
Etoposide + Other	1 (0.0)	0 (0.0)
Fludarabine	15 (0.4)	2 (0.2)
Other	3 (0.1)	0 (0.0)
None specified	2 (0.1)	2 (0.2)
No	2 (0.1)	0 (0.0)
Bridging therapy - no. (%)		
No	2098 (55.5)	355 (38.3)
Yes	1389 (36.7)	484 (52.3)
Not reported	296 (7.8)	87 (9.4)
Year of CT - no. (%)		
2017	1 (0.0)	0 (0.0)
2018	240 (6.3)	0 (0.0)
2019	443 (11.7)	0 (0.0)

Characteristic	Non-Hodgkin lymphoma (NHL)	Plasma cell disorder/multiple myeloma (PCD/MM)
2020	536 (14.2)	0 (0.0)
2021	909 (24.0)	207 (22.4)
2022	1248 (33.0)	502 (54.2)
2023	406 (10.7)	217 (23.4)
Follow-up of survivors - median (range)	12.8 (1.0-62.3)	6.7 (1.4-26.7)

Note: This data will become available in 2 years (or with company approval) after the end of the data embargo. With this embargo applied, we currently have 3312 NHL patients and 128 MM/PCD patients eligible.

Field	Response
Proposal Number	2310-45-WUDHIKARN
Proposal Title	The impact of obesity and body weight on immune mediated toxicities and outcomes of patients with relapsed/refractory large B cell lymphoma treated with CD19 CAR T cells
Key Words	Obesity, toxicity, Chimeric antigen receptor T cell
Principal Investigator #1: - First and last name, degree(s)	Kitsada Wudhikarn, MD
Principal Investigator #1: - Email address	kitsada.w@chula.ac.th
Principal Investigator #1: - Institution name	Chulalongkorn University
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	Infection in patients with r/r large B cell lymphoma treated with CD19 CAR T cells
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Lymphoma
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	Does obesity have an effect on the toxicity and outcome after CD19 CAR T cell in patients with r/r large B cell lymphoma?
RESEARCH HYPOTHESIS:	1. Obese patients with large B cell non Hodgkin lymphoma have higher incidence of CAR T cell immune-mediated toxicities compared to non-obese patients 2. Obese patients with large B cell non Hodgkin lymphoma have inferior response rate and outcome after CD19 CAR T cell therapy compared to non-obese patients
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	1. To compare immune mediated toxicities of large B cell NHL treated with FDA approved CART between obese and non-obese patients 2. To compare clinical response and survival of large B cell NHL treated with FDA approved CAR T product between obese and non-obese patients Interested outcomes: - Incidence of immune mediated complication: CRS and ICANS - Incidence of hemophagocytic syndromes - Incidence of grade ≥3 adverse events - Response rate at 3 and 6 months post-CAR T cell therapy - Non Relapse Mortality - Progression Free Survival - Overall Survival

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	The result of our study will give us better understanding about the effect of obesity on toxicities and response to CAR T cell therapy. It will provide insights about the association of LD chemotherapy dose intensity and CAR T cell dose on toxicity and response after CD19 CAR T cell products. This data can serve as foundation to inform optimization of CAR T cell delivery for patients with extreme body weight.

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.	Over the recent years, CD19 chimeric antigen receptor T cell has transformed the treatment armamentarium of relapsed/refractory B lymphoid malignancy providing an unprecedented response rate and potential durable disease remission in these difficult-to-treat patients (1, 2). Notably, in exchange for its impressive efficacy, CD19 CAR T cells induce unique immune-mediated toxicities including cytokine release syndrome, immune effector cell associated neurotoxicity syndrome, B cell aplasia and prolonged cytopenia (3). Factors determining the efficacy and toxicities of CD19 CAR T cells are highly complicated involving several aspects, not only CAR T cell associated features but also patient-related factors (4) such as CAR T dose or underlying host immune systems. Obesity is a public health concern in the United States. The age-adjusted prevalence of obesity among U.S. adults in 2017-2018 was 42.4% (5). Data from preclinical models and early phase clinical trials demonstrated correlation between cell dose of CAR T cells and immune-mediated adverse events. Axicabtagene ciloleucel (axi-cel; Yescarta) is an FDA-approved CD19 CAR T cell product authorized for patients with relapsed/refractory large B cell lymphoma. According to the pivotal ZUMA-1 study and the prescribing information of axi-cel, the recommended dose of axi-cel is 2.0x106 cells/kg with a maximum of 2×108 CAR-positive viable T cells (2). Notably, patients with body weight over 100 kg will receive lower weight-based CAR T cell dose (<2x106 cells/kg). For tisagenlecleucel (Tisa-cel; Kymriah), the FDA approved dose is 0.5 to 6 x 108 CAR-positive cells for lymphoma. The median dose infused in standard of care practice was 0.6 to 3 x 108 CAR-positive cells (6). These findings demonstrate wide ranges of infused CAR T cell dose and highlights potential impact of obesity on delivered CAR T cell dose (per kg), toxicities and outcomes. Besides, the effect of body weight on CAR T cell dose, an extreme body weight can influence the dosing pattern of lymphodepletion chemotherapy and may alter pharmacokinetic of chemotherapy. The LD chemotherapy dose adjustment can result in under-exposure of lymphodepletion agents which leads to suboptimal host immune suppression and CAR T cell persistence. Data from CIBMTR in autologous hematopoietic stem cell transplant (HSCT) indicated comparable toxicities between patients receiving conditioning regimen dosing based on adjusted and actual body weight. The result of this study did not support dose adjustment of conditioning regimen (7) in HSCT, however, there is currently no available data in CAR T cell therapy. Lastly, obesity is demonstrated to be associated with endothelial injury, chronic inflammation

Field	Response
	and immune dysregulation in pre-clinical studies (8, 9) which may impact the phenotypes of CAR T cells and host immune response to CAR T cell therapy. Data from allogeneic (HSCT) indicated that obesity was associated with high aGVHD rate, higher transplant related mortality and worse survival after allogeneic HSCT (10-12). In contrast, obesity may be associated with improved survival in patients treated with immune checkpoint blockade therapy (13). In keeping with all these potential plausible mechanisms, we propose to look at the impact of obesity on toxicities and outcomes in patients treated with FDA approved CAR T products and compare with non-obese patients.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Adult patients with aggressive large B-NHL who received tisagenlecleucel, lisocabtagene maraleucel and axicabtagene ciloleucel from the October 2017 to July 2023
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Focusing on LBCL

Field	Response
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	1. Body weight 2. Height 3. Body Mass Index 4. Ethnicity 5. Date of birth and date of CAR T infusion (to calculate age at CAR T cell therapy) 6. Gender: Male VS Female 7. Disease stage prior to CAR T cell therapy 8. Disease status prior to CAR T cell therapy 9. Karnofsky Performance Status 10. Hematopoietic Cell Transplant Comorbidity Index: 0-2 VS 3-4, vs high risk group (≥ 5) 11. Number of prior lines of treatments: 12. Prior hematopoietic stem cell transplantation 13. Lymphodepletion therapy regimens for CAR T cell (Given or not) a. Dose of cyclophosphamide b. Dose of fludarabine c. Dose of bendamustine 14. CAR T cell product (axicabtagene xiloleucel, tisagenlecleucel) 15. CAR T cell dose total dose (if available) 16. Peak Cytokine Level a. CRP b. Ferritin 17. CAR T Related Complication a. CRS: Yes vs. No. Time to onset. b. ICANs: Yes vs. No. Time to onset. c. Grade ≥3 adverse events: Yes vs. No. Time to onset. 18. Steroid for CRS or ICANS: Yes or No including indication (for CRS and/or ICANS), number of dose 19.Tocilizumab: Yes or No including indication (for CRS and/or ICANS), number of doses 20. Other interventions for CRS: other medications, vasopressor use, O2 requirement, intubation, etc. 21. Other interventions for ICANS; other medications, intubation, ICP monitoring 22. Best response to CAR T cell therapy at 6 months post CAR T cell infusion 23. Disease status (relapse) for PFS/EFS and Cumulative incidence of relapse a. Relapse date if relapse b. Last FU date if non relapse 24. Live/Death Status at last contact for OS 25. Cause of death
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A desc	No
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	No

Field	Response
SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary o	No
NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required.	No

Field	Response
REFERENCES:	1. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56. 2. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-44. 3. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-30. 4. Wudhikarn K, Park JH. Dissecting factors influencing response to CAR T cell therapy in B lymphoid hematologic malignancies: from basic to practice. Leuk Lymphoma. 2020:1-11. 5. Hales CM, Carroll MD, Fryar CD, Odgen CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. In: Statistics NCfHa, editor. 2020. 6. Jaglowski S, Hu Z-H, Zhang Y, Kamdar M, Ghosh M, Lulla P, et al. Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry. Blood. 2019;134(Supplement_1):766-. 7. Brunstein CG, Pasquini MC, Kim S, Fei M, Adekola K, Ahmed I, et al. Effect of Conditioning Regimen Dose Reduction in Obese Patients Undergoing Autologous Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2019;25(3):480-7. 8. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med. 2019;25(1):141-51. 9. Aguilar EG, Murphy WJ. Obesity induced T cell dysfunction and implications for cancer immunotherapy. Curr Opin Immunol. 2018;51:181-6. 10. Nakao M, Chihara D, Niimi A, Ueda R, Tanaka H, Morishima Y, et al. Impact of being overweight on outcomes of hematopoietic SCT: a meta-analysis. Bone Marrow Transplant. 2014;49(1):66-72. 11. Aplenc R, Zhang MJ, Sung L, Zhu X, Ho VT, Cooke K, et al. Effect of body mass in children with hematologic malignancies undergoing allogeneic bone marrow transplantation. Blood. 2014;123(22):3504-11. 12. Doney K, McMillen K, Buono L, Deeg HJ, Gooley T. Impact of Body Mass Index on Outcomes of Hematopoietic Stem Cell Transplantation in Adults. Biol Blood Marrow Transplant. 2019;25(3):613-20. 13. Woodall MJ, Neumann S, Campbell K, Pattison ST, Young SL. The Effects of Obesity on Anti-Cancer Immunity and Cancer Immunotherapy. Cancers (Basel). 2020;12(5).

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

Population characteristics for adult patients with Large B-cell NHL who underwent CAR-T from 2018 to Jul. 2023, stratified by BMI

Characteristic	<25	25-29	30+
No. of patients	1495	1384	1169
No. of centers	130	130	124
Patient related			
Level Age at CT Treatment - median (min-max)	66.1 (18.3-89.1)	66.3 (19.1-91.2)	61.6 (19.5-86.8)
Recipient Sex - no. (%)			
Male	801 (53.6)	965 (69.7)	781 (66.8)
Female	693 (46.4)	419 (30.3)	388 (33.2)
Missing	1 (0.1)	0 (0.0)	0 (0.0)
Ethnicity - no. (%)			
Hispanic or Latino	153 (10.2)	154 (11.1)	127 (10.9)
Non Hispanic or non-Latino	1086 (72.6)	1008 (72.8)	891 (76.2)
Non-resident of the U.S.	225 (15.1)	174 (12.6)	117 (10.0)
Unknown	31 (2.1)	48 (3.5)	34 (2.9)
Recipient race - no. (%)			
White	1069 (71.5)	1017 (73.5)	890 (76.1)
Black or African American	56 (3.7)	69 (5.0)	92 (7.9)
Asian	148 (9.9)	70 (5.1)	24 (2.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.1)	1 (0.1)
American Indian or Alaska Native	2 (0.1)	7 (0.5)	6 (0.5)
Other	9 (0.6)	6 (0.4)	5 (0.4)
More than one race	78 (5.2)	87 (6.3)	68 (5.8)
Missing	133 (8.9)	127 (9.2)	83 (7.1)
CT-CI - no. (%)			
0	540 (36.1)	451 (32.6)	247 (21.1)
1	280 (18.7)	281 (20.3)	259 (22.2)
2	196 (13.1)	194 (14.0)	211 (18.0)
3+	471 (31.5)	446 (32.2)	445 (38.1)
TBD	5 (0.4)	9 (0.6)	4 (0.3)
Not reported	3 (0.2)	3 (0.2)	3 (0.3)
Karnofsky performance score prior to CT - no. (%)			
90-100	558 (37.3)	565 (40.8)	459 (39.3)
80	462 (30.9)	432 (31.2)	397 (34.0)
< 80	357 (23.9)	274 (19.8)	222 (19.0)
Not reported	118 (7.9)	113 (8.2)	91 (7.8)

Characteristic	<25	25-29	30+
Prior HCT - no. (%)			
No	1219 (81.5)	1098 (79.3)	983 (84.1)
Yes	270 (18.1)	280 (20.2)	185 (15.8)
Unknown	1 (0.1)	1 (0.1)	0 (0.0)
Not reported	5 (0.3)	5 (0.4)	1 (0.1)
Total number of lines of therapy received - no. (%)			
1	101 (6.8)	116 (8.4)	116 (9.9)
2	467 (31.2)	460 (33.2)	410 (35.1)
3	916 (61.3)	797 (57.6)	637 (54.5)
Not reported	11 (0.7)	11 (0.8)	6 (0.5)
Disease related			
Disease status at infusion - no. (%)			
PIF	635 (42.5)	578 (41.8)	487 (41.7)
CR1	23 (1.5)	20 (1.4)	21 (1.8)
CR2	45 (3.0)	53 (3.8)	50 (4.3)
CR3+	25 (1.7)	32 (2.3)	19 (1.6)
First relapse	434 (29.0)	405 (29.3)	347 (29.7)
Second relapse	211 (14.1)	204 (14.7)	180 (15.4)
Third or more relapse	116 (7.8)	85 (6.1)	60 (5.1)
Disease untreated	4 (0.3)	6 (0.4)	5 (0.4)
Not reported	2 (0.1)	1 (0.1)	0 (0.0)
Cellular Therapy Related			
Product - no. (%)			
Kymriah	342 (22.9)	297 (21.5)	185 (15.8)
Yescarta	929 (62.1)	880 (63.6)	803 (68.7)
Breyanzi	224 (15.0)	207 (15.0)	181 (15.5)
Time from initial diagnosis to CT, months - median (min-max)	12.6 (1.1-446.2)	13.4 (0.9-391.6)	13.7 (0.4-395.2)
Lymphodepleting regimen - no. (%)			
Yes	1495 (100)	1384 (100)	1169 (100)
Bendamustine	170 (11.4)	160 (11.6)	155 (13.3)
Bendamustine + Cyclophosphamide	1 (0.1)	0 (0.0)	0 (0.0)
Bendamustine + Cyclophosphamide + Fludarabine	0 (0.0)	0 (0.0)	2 (0.2)
Bendamustine + Other	8 (0.5)	5 (0.4)	8 (0.7)
Carboplatin + Fludarabine	2 (0.1)	0 (0.0)	0 (0.0)
Cyclophosphamide	8 (0.5)	6 (0.4)	3 (0.3)
Cyclophosphamide + Fludarabine	1277 (85.4)	1193 (86.2)	984 (84.2)

Characteristic	<25	25-29	30+
Cyclophosphamide + Melphalan	1 (0.1)	0 (0.0)	0 (0.0)
Cyclophosphamide + Other	9 (0.6)	8 (0.6)	6 (0.5)
Cytarabine + Fludarabine	6 (0.4)	4 (0.3)	3 (0.3)
Etoposide + Other	1 (0.1)	0 (0.0)	0 (0.0)
Fludarabine	12 (0.8)	8 (0.6)	7 (0.6)
None specified	0 (0.0)	0 (0.0)	1 (0.1)
Bridging therapy - no. (%)			
No	628 (42.0)	622 (44.9)	566 (48.4)
Yes	636 (42.5)	552 (39.9)	431 (36.9)
Not reported	231 (15.5)	210 (15.2)	172 (14.7)
Year of CT - no. (%)			
2018	2 (0.1)	2 (0.1)	0 (0.0)
2019	1 (0.1)	10 (0.7)	7 (0.6)
2020	93 (6.2)	91 (6.6)	58 (5.0)
2021	419 (28.0)	365 (26.4)	314 (26.9)
2022	621 (41.5)	617 (44.6)	491 (42.0)
2023	359 (24.0)	299 (21.6)	299 (25.6)
Follow-up of survivors - median (range)	12.1 (1.0-47.1)	12.0 (0.5-48.7)	12.0 (1.1-42.7)

Note: This data will become available in 2 years (or with company approval) after the end of the data embargo. With this embargo applied, we currently have 1107 BMI <25 patients, 1045 BMI 25-29 patients, and 922 BMI 30+ patients eligible.

Study Title

Combined proposals: **2310-53 and 2310-232**

"Impact of renal insufficiency before CAR-T cell therapy"

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Research Hypothesis

Renal insufficiency (RI) predicts for increase in toxicities and inferior survival in patients receiving CD19-directed and BCMA-directed Chimeric Antigen Receptor T-cell (CAR-T) therapy.

Specific Aims

Primary aim:

1. To determine the cumulative incidence of non-relapse mortality (NRM) and overall survival (OS) for patients with renal insufficiency (RI) compared to patients without RI who receive CAR-T cell therapy.

Secondary aims:

1. Compare incidence of relapse and progression free survival (PFS) between patients with or without RI who receive CAR-T cell therapy.
2. To analyze incidence of CAR-T related toxicities (CRS and ICANS) in patients with RI who receive CAR-T therapy.
3. Correlate choice and dose of lymphodepleting drug in patients with RI prior to CAR-T cell therapy with outcomes after CAR-T cell therapy.
4. To analyze incidence of other non-CAR-T related toxicities including but not limited to infection, organ dysfunction and others in patients with RI.
5. Report causes of death among patients with RI who receive CAR-T cell therapy

Scientific Justification

Chimeric Antigen Receptor (CAR) T-cell therapy has had dramatic responses in certain hematologic malignancies and revolutionized treatment paradigms in the modern era.[1-5] Although initial trials have reported long-term data with durable remissions, patients with renal impairment were excluded.[6, 7] CAR-T therapy is associated with its unique toxicities such as cytokine release syndrome (CRS) and immune effector associated cell neurotoxicity (ICANS) that may require management in the ICU where a number of renal injuries are both associated with preceding hypotension, respiratory failure and seizures and exacerbated by the use of vasopressors, mechanical ventilation, among other life-saving measures.[8]

While CAR-T therapy is FDA approved for treatment of B cell lymphoma (r/r BCL) which includes relapsed or refractory large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma, patients enrolled on pivotal clinical trials of CAR-T therapy had adequate kidney function, defined as serum creatinine ≤1.5 mg/dl or creatinine clearance ≥ 60 ml/min/1.73 m2. In the real world, patients with renal dysfunction receive CAR-T therapy per FDA approval guidelines but the impact of renal dysfunction is unknown. Comparatively renal dysfunction is a recognized risk factor for mortality in patients receiving allogeneic hematopoietic cell transplantation (Allo-HCT) and is a component of the Hematopoietic Cell Transplantation

Comorbidity Index (HCT CI). Currently, HCT-CI assigns a score of 2 for moderate-severe renal dysfunction based on serum creatinine (Cr) > 2 [9]. Recently a large center for international blood and marrow transplant research (CIBMTR) analysis demonstrated that degree of renal dysfunction defined by glomerular filtration rate (GFR), independently predicted both overall survival and treatment related mortality in those who received allo-HCT [10].

The purine analog fludarabine (Flu) is immunosuppressive and has activity against many hematological malignancies. It is widely utilized with cyclophosphamide as the lymphodepletion (LD) regimen administered prior to CAR-T infusion. Patients who receive lymphodepletion without Flu have lower CAR-T expansion and subsequent responses compared to those who received LD with Flu [11]. Flu has a half-life of about 20 hours, and it is largely eliminated by renal excretion (60% during first 24 hours). A cancer and leukemia group B(CALGB) study suggested that reduced creatinine clearance is a risk factor for Flu toxicity notably neurotoxicity [12, 13] [14]. One of the largest reported series of neurotoxicity attributed to patients receiving allo-HCT treated at the University of Minnesota over a 10-year period identified 39 patients who developed neurotoxicity secondary to Flu, including acute toxic leukoencephalopathy, other leukoencephalopathy, and posterior reversible encephalopathy syndrome. Risk factors identified include older age, poor renal function, Flu dose, and previously treated central nervous system (CNS) disease [14].Flu dose is often adjusted in real world practice for reduced creatinine clearance based on guidelines that recommend 20-25% dose reduction in the setting of mild to moderate renal impairment and 50% dose adjustment in severe renal impairment [15]. But these practices are not universally accepted, and it is unclear if reduced Flu dose is affecting disease related outcomes in CAR-T recipients.

Alternatively, cytokines released with CAR-T are associated with delayed clearance in patients with renal disease who have altered vascular tone which can exacerbate renal function further. In support of this observation CRS and ICANS was found to be more significant with impaired renal clearance in a study at Moffitt, where peak cytokines were higher in patients with AKI.[16] Retrospective studies on the incidence of AKI after CAR-T and impact of CKD prior to CAR-T are limited to single institution experiences.[16-18] Administering CAR-T cell therapy in patients with ESRD on dialysis has only been reported in case reports; although durable remission has been reported, these are low numbers, experience is limited, and long-term follow-up is lacking.[18]

CAR-T utilization is expected to increase with recent studies evaluating the efficacy and safety of CART in the second line setting in multiple diseases [19]. Even less is known about response and outcomes of CAR-T cell therapy in patients with multiple myeloma where incidence of renal pathology and impaired creatinine clearance is significant and related to disease burden. There remains a lack of patients with renal dysfunction enrolled in registration studies, highlighting the need to better refine and predict for outcomes and toxicities based on pre-CAR-T comorbidities.

Scientific impact

Patients with RI who receive CAR-T cell therapy may be more at risk for CRS, ICANS, inferior overall survival and may require dose reductions in lymphodepleting regimens. Currently, only single institution studies have reported limited experiences and registration trials excluded patients with significant renal impairment, thus real-world registry data is warranted. The CIBMTR is well positioned to perform such a study given the limited efforts in investigating effect of GFR on outcomes of allo-HCT in smaller heterogenous samples. The impact of this

proposal involves predicting CAR-T related toxicities and outcomes in patients with RI. **The results of this study will provide guidance in treatment of patients with renal insufficiency.**

Patient Eligibility Population

Any patient (any age) with the diagnosis of B-ALL, non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM) receiving commercial, FDA-approved CD19 or BCMA directed autologous CAR-T cell product.

Data Requirements

Variables to be described:

Best response – Pre and post CAR-T as reported to CIBMTR

Relapse/progression: Progressive disease or recurrence of disease would be counted as an event. Treatment related death, defined as death without relapse or progression, is the competing event. Those who survive without recurrence or progression would be censored at the time of last contact.

Progression-free survival (PFS): Survival without recurrence or tumor progression. Recurrence of progression of disease and death would be counted as events. Those who survive without recurrence or progression would be censored at the time of last contact.

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

Causes of death and immune reconstitution in those with infections will be described

Non-relapse mortality (NRM): Death without relapse or progression, where relapse or progression would be competing risks. Those who survive without recurrence or progression would be censored at the time of last contact.

Patient-related:

- Age at receipt of CAR-T therapy:
- Patient sex: male vs. female
- Race: Caucasian vs. others vs. missing
- Ethnicity: Hispanic vs. non-Hispanic
- Karnofsky performance prior to CAR-T: ≥ 90 vs. < 90 vs. missing
- ECOG performance score prior to CAR-T
- HCT-CI (comorbidity index) prior to CAR-T
- **Renal insufficiency (Cr > 2) as defined by HCT-CI (yes/no)**
- **Baseline creatinine pre-CAR-T (pre-LD)**
- ***GFR –(calculated using age, gender, and race (yes/no African-American/Black)***
- ***Categorize RI by Cr: mild RI (1.0-1.5), moderate RI (1.5-1.9), severe RI (> 2.0)***

Disease-related:

- Diagnosis: DLBCL, transformed FL, B-ALL, Multiple Myeloma
- Lugano and ISS staging
- LDH

- B2 macroglobulin
- IMWG best response pre and post CART
- Disease risk index
- High risk cytogenetics: yes vs.no
- Number of prior therapies (before transplant an dCAR-T): 1 vs. 2 vs. ≥ 3
- Type of prior therapies (chemo vs radiation vs other)
- Sites of disease
- Tumor size/bulk (in cm)
- Dose/fraction of radiation (2 Gy vs 3-Gy vs 4-Gy vs other)
- Field of radiation
- Sites of radiation
- Proximity of disease sites to crucial/essential structures/tissues
- Timing of radiation prior to apheresis
- Timing of radiation prior to CAR-T
- Time from transplant to CAR-T (<12 mo vs > 12 mo)
- Name of salvage therapies (including number of cycles and number of lines)
- History of local radiation prior to bridging therapy
- Disease status at the time of each salvage therapy: complete remission vs partial response vs. stable disease vs progressive disease
- CNS involvement at diagnosis and prior to CAR-T infusion
- Response to First line therapy (Lugano versus IMWG)
- Therapies given before HCT and CAR-T
- Remission status prior to HCT
- MM stage, ISS
- MRD status by NGS if available
- Immunoglobulin and light chain data

CAR-T related:

- **Axicabtagene Ciloleucel (Axi-cel) vs. Tisagenlecleucel(tisa-cel) vs. brexucabtagene autoleucel (brexu-cel) vs. Lisocabtagene Maraleucel (Liso-cel) vs. idecabtagene vicleucel (ide-cel) vs ciltacabtagene autoleucel (cilta-cel**)
- Time from diagnosis to CAR-T
- Year of administration of CAR-T
- Bridging therapy pre-CAR T
- Fludarabine dose (mg/m2) as part of lymphodepletion regimen
- Prophylaxis administered for CRS (Y vs. N)
- Maximum grade of CRS
- Number of doses of tocilizumab prescribed for CRS
- Steroid for management of CRS (yes/no)
- Cumulative steroid dose for the management of CRS
- Other agents used for the management of CRS
- Maximum grade of ICANS
- Steroids for management of ICANS (yes/no)
- Cumulative steroid dose for the management of ICANS
- Best response to CAR-T
- Relapse post CAR-T
- Time to relapse from CAR-T

- Receipt of IVIG (immunoglobulins) post CAR-T

Statistical analysis

A retrospective multicenter study will be conducted utilizing CIBMTR dataset. Patients will be eligible if they satisfied the criteria detailed in the "Patient Eligibility" section. **The impact of renal comorbidity as assessed by the HCT-CI (defined as serum creatinine > 2) on CAR-T related outcomes will be assessed.** This patient population will be compared by match-pair analysis to patients who receive CAR-T therapy and do not have renal comorbidity per HCT-CI depending on available data in a 2:1 or 3:1 ratio between control and experimental arm.

If **robust/complete** data on individual pre-LD serum creatinine levels are available, GFR can be calculated and patients will be stratified by GFR, calculated using CKD-EPI (CKD-epidemiology collaboration) method. GFR could potentially be utilized as a variable of interest for survival outcomes if data is available. Otherwise, serum creatinine levels can be compared between mild, moderate, or severe levels of RI: **mild RI (1.0-1.4), moderate RI (1.5-1.9), severe RI (> 2.0).**

Descriptive tables of patient, disease-, and transplant-related factors will be created. The tables will list median and range for continuous variables and proportions for categorical variables. Cumulative incidence of relapse/progression, NRM will be calculated while accounting for competing events. Univariate analysis of neutrophil and platelet recovery, prolonged cytopenias (neutrophil, platelets, and both), overall survival, CRS and ICANS and their respective grading and treatment will be calculated

Probabilities of OS will be calculated using the Kaplan-Meier estimator. If Sample size and number of events allow, multivariate analysis will be performed using Cox proportional hazards models for outcomes for CRS, ICANS, cytopenias, relapse/progression, NRM, PFS, and OS and logistic regression for acute GVHD. A stepwise model building approach will then be used to identify the significant risk factors associated with the outcomes. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. The proportional hazards assumption will be checked for the Cox model. If violated, it will be added as time-dependent covariates.

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Population characteristics for adult patients that underwent CAR-T, stratified by moderate/severe renal injury

Characteristic	No	Yes
No. of patients	11724	296
No. of centers	214	80
Patient related		
Level Age at CT Treatment - median (min-max)	62.7 (0.3-91.2)	64.4 (19.7-83.9)
Recipient Sex - no. (%)		
Male	7327 (62.5)	207 (69.9)
Female	4392 (37.5)	89 (30.1)
Not reported	5 (0.0)	0 (0.0)
Ethnicity - no. (%)		
Hispanic or Latino	1552 (13.2)	25 (8.4)
Non-Hispanic or non-Latino	8980 (76.6)	243 (82.1)
Non-resident of the U.S.	836 (7.1)	20 (6.8)
Unknown	355 (3.0)	8 (2.7)
Missing	1 (0.0)	0 (0.0)
Recipient race - no. (%)		
White	8966 (76.5)	208 (70.3)
Black or African American	794 (6.8)	41 (13.9)
Asian	548 (4.7)	16 (5.4)
Native Hawaiian or other Pacific Islander	23 (0.2)	1 (0.3)
American Indian or Alaska Native	44 (0.4)	2 (0.7)
Other	83 (0.7)	1 (0.3)
More than one race	622 (5.3)	10 (3.4)
Missing	644 (5.5)	17 (5.7)
CT-CI - no. (%)		
0	3690 (31.5)	0 (0.0)
1	2393 (20.4)	0 (0.0)
2	1605 (13.7)	47 (15.9)
3+	3994 (34.1)	249 (84.1)
TBD	42 (0.4)	0 (0.0)
Karnofsky performance score prior to CT - no. (%)		
90-100	4946 (42.2)	86 (29.1)
80	3540 (30.2)	92 (31.1)
< 80	2211 (18.9)	92 (31.1)
Not reported	1027 (8.8)	26 (8.8)
Prior HCT - no. (%)		

Characteristic	No	Yes
No	7894 (67.3)	180 (60.8)
Yes	3780 (32.2)	116 (39.2)
Unknown	4 (0.0)	0 (0.0)
Not reported	46 (0.4)	0 (0.0)
Prior radiation therapy - no. (%)		
No	6880 (58.7)	175 (59.1)
Yes	3092 (26.4)	64 (21.6)
Not reported	1752 (14.9)	57 (19.3)
eGFR - no. (%)		
< 60 ml/min/1.73 m2	595 (5.1)	103 (34.8)
>= 60 ml/min/1.73 m2	3082 (26.3)	14 (4.7)
Not reported	8047 (68.6)	179 (60.5)
Serum creatinine - no. (%)		
< 1.0 mg/dL	2650 (22.6)	9 (3.0)
1.0-1.4 mg/dL	1008 (8.6)	13 (4.4)
1.5-1.9 mg/dL	170 (1.5)	10 (3.4)
>= 2.0 mg/dL	25 (0.2)	85 (28.7)
Not reported	7871 (67.1)	179 (60.5)
Disease Related		
Disease - no. (%)		
Acute lymphoblastic leukemia (ALL)	1508 (12.9)	2 (0.7)
Non-Hodgkin lymphoma (NHL)	8236 (70.2)	172 (58.1)
Plasma cell disorder/multiple myeloma (PCD/MM)	1804 (15.4)	114 (38.5)
Not reported	176 (1.5)	8 (2.7)
Cellular Therapy Related		
Product - no. (%)		
Kymriah	2731 (23.3)	44 (14.9)
Yescarta	5338 (45.5)	96 (32.4)
Tecartus	1034 (8.8)	15 (5.1)
Breyanzi	771 (6.6)	21 (7.1)
Abecma	1223 (10.4)	85 (28.7)
Carvykti	627 (5.3)	35 (11.8)
Time from initial diagnosis to CT, months - median (min-max)	21.0 (0.2-446.2)	33.3 (1.3-331.1)
Lymphodepleting regimen - no. (%)		
Yes	11701 (99.8)	296 (100)
Bendamustine	901 (7.7)	35 (11.8)
Bendamustine + Cyclophosphamide	1 (0.0)	0 (0.0)
Bendamustine + Cyclophosphamide + Fludarabine	2 (0.0)	0 (0.0)

Characteristic	No	Yes
Bendamustine + Cytarabine	0 (0.0)	1 (0.3)
Bendamustine + Other	25 (0.2)	1 (0.3)
Carboplatin + Fludarabine	2 (0.0)	0 (0.0)
Clofarabine + Fludarabine	1 (0.0)	0 (0.0)
Cyclophosphamide	52 (0.4)	8 (2.7)
Cyclophosphamide + Cytarabine + Etoposide + Fludarabine	2 (0.0)	0 (0.0)
Cyclophosphamide + Cytarabine + Fludarabine	3 (0.0)	0 (0.0)
Cyclophosphamide + Cytarabine + Fludarabine + Other	1 (0.0)	0 (0.0)
Cyclophosphamide + Etoposide	1 (0.0)	0 (0.0)
Cyclophosphamide + Fludarabine	9858 (84.1)	226 (76.4)
Cyclophosphamide + Fludarabine + Other	16 (0.1)	0 (0.0)
Cyclophosphamide + Gemcitabine	1 (0.0)	0 (0.0)
Cyclophosphamide + Melphalan	1 (0.0)	0 (0.0)
Cyclophosphamide + Other	64 (0.5)	0 (0.0)
Cyclophosphamide + Thiotepa	1 (0.0)	0 (0.0)
Cytarabine	1 (0.0)	0 (0.0)
Cytarabine + Etoposide	4 (0.0)	0 (0.0)
Cytarabine + Fludarabine	21 (0.2)	2 (0.7)
Etoposide + Other	1 (0.0)	0 (0.0)
Fludarabine	45 (0.4)	1 (0.3)
Other	24 (0.2)	0 (0.0)
None specified	673 (5.7)	22 (7.4)
No	23 (0.2)	0 (0.0)
Bridging Therapy – no. (%)		
No	4894 (41.7)	118 (39.9)
Yes	4499 (38.4)	109 (36.8)
Not reported	2331 (19.9)	69 (23.3)
Year of CT - no. (%)		
2017	16 (0.1)	0 (0.0)
2018	604 (5.2)	5 (1.7)
2019	1171 (10.0)	23 (7.8)
2020	1413 (12.1)	32 (10.8)
2021	2121 (18.1)	52 (17.6)
2022	3326 (28.4)	100 (33.8)
2023	3073 (26.2)	84 (28.4)
Follow-up of survivors - median (range)	12.7 (0.4-69.4)	12.1 (1.5-50.4)

Note: This data will become available in 2 years (or with company approval) after the end of the data embargo. With this embargo applied, we currently have 8365 patients without renal injury and 146 patients with renal injury eligible.

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TITLE:

Immune effector cell associated HLH-like Syndrome (IEC-HS) in patients undergoing CAR T cell therapy

RESEARCH QUESTION:

Hemophagocytic lymphohistiocytosis (HLH)-like toxicities have been reported, usually with a poor outcome, following chimeric antigen receptor T cell therapy (CAR T) and are now termed as IEC-HS.[1] This proposal aims to evaluate the incidence, patterns of presentation, and clinical outcomes of IEC-HS in CAR T recipients. Upon successful completion, this work will guide clinical practice on recognition of risk factors and decisions on management strategies for IEC-HS, a rare yet consequential complication after CAR T cell therapy. Ultimately, this is critical to improve outcomes following CAR T.

RESEARCH HYPOTHESIS:

The incidence of IEC-HS varies by underlying disease and CAR T product, and contributes to prolonged morbidity and inferior outcomes following CAR T cell therapy.

SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.) *Suggested word limit of 200 words:*

Primary objective: To describe reported real-world incidence, and clinical outcomes (response and survival) of IEC-HS

Secondary objectives:

(1) Identify risk factors associated with IEC-HS following CAR T for B cell lymphoma (BCL), multiple myeloma, and B-cell acute lymphoblastic leukemia (B-ALL)
(2) To describe management options used for treatment of IEC-HS and related improvement and complications.
(3) To describe characteristics and patterns of hematopoietic recovery in patients with IEC-HS
(4) To describe characteristics and patterns of infectious complications in patients with IEC-HS
(5) Describe causes of death in patients experiencing IEC-HS

Exploratory objectives:

(1) To evaluate overall survival of patients who developed IEC-HS
(2) To evaluate the feasibility of applying the recently published IEC-HS criteria[1]
(3) Develop a risk score that predicts the risk of developing IEC-HS

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

This study will provide contemporary real-world evidence on the incidence, patterns of clinical presentation, risk factors, therapeutic options and related outcomes i.e. response and overall

survival across different disease types in CAR T recipients experiencing IEC-HS. **With the increasing use and promising outcomes with CAR T, addressing the safety and management of complications like IEC-HS, is a critical need – one we will address in this study.**

IEC-HS has been associated with severe and life-threatening complications following CAR T[2-6]. Our group recently led the effort to define IEC-HS to guide clinical practice.[1] Yet, existing reports of IEC-HS have included limited numbers of patients and have mostly focused on a single underlying malignancy. Through this CIBMTR proposal, we will be able to aid clinical practice by characterizing high-risk factors to consider in clinical management, incidence and outcomes of IEC-HS across B-ALL, lymphoma, and multiple myeloma and the respective CAR T constructs. Additionally, defining predictors of IEC-HS will inform prospective clinical trials of pre-emptive anti-inflammatory therapies for high-risk groups. **Lastly, compiling management approaches has the potential to inform treatment strategies in clinical care and for prospective clinical trial design for future patients.**

There is a critical need to refine the ability to diagnose patients who experience IEC-HS. If feasible based on sample size and available data, we will explore validation of the recently published IEC-HS criteria (**Figure 1**).[1] With the application of this new definition, upon completion of this study, we will be able to further elaborate on the performance of the IEC-HS criteria. **Altogether, this effort will provide the much-needed information and guidance for clinical practice on IEC-HS.**

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.

IEC-HS refers to HLH-like toxicities following CAR T infusion which can result in life-threatening organ dysfunction. With the increased use of CAR T cell therapy in recent years, IEC-HS has been described anecdotally with the use of commercially approved and investigational products, but findings have been limited by varying criteria used to define this toxicity and/or focus on a single disease type or CAR T-cell product.[3,4,7-9] Therefore, to address the unmet need for a uniform definition of HLH-like toxicities following CAR T-cell therapy, a panel of experts in diverse fields including adult and pediatric oncology, infectious disease, critical care, and rheumatology proposed definitions and diagnostic criteria (**Figure 1**), and established this as an entity distinct from cytokine release syndrome **(Figure 2**).[1] These criteria have helped identify patients in practice. **However, much of the existing literature on IEC-HS has been limited to single CAR T-cell constructs or single institution studies. Therefore, there remains an unmet need in characterization of the incidence of IEC-HS by CAR T construct and underlying disease, of severity, and recommendation of treatment options.**

Mortality from IEC-HS can be high, with higher rates of infection, non-relapse mortality, progressive disease, and relapse described in patients with this toxicity, although findings have varied by disease and CAR construct[2,3,5-7]. Given that outcomes in this group have been described as poor, validating these findings across underlying diagnoses in a larger cohort, and identifying the main drivers of poor outcomes, could help to target interventions that could lead to improved outcomes of CAR T-cell recipients overall. Further, identifying and validating risk factors for the development of IEC-HS has the potential to inform prospective studies that will aim at

curtailing inflammation in high-risk populations through prospective and pre-emptive anti-inflammatory treatment approaches, as has been described for prevention of severe CRS or ICANS[10-12].

Cytopenias are a primary feature of IEC-HS in addition to rapidly rising ferritin, coagulopathy, and often severe organ dysfunction. While hematopoietic recovery in the context of CAR T cell therapy has been well-defined[13-15], recovery and clinical implications of cytopenias in the context of IEC-HS are not well-understood. Given the prior correlations of prolonged cytopenias with higher-grade inflammatory toxicities of CRS and ICANS, one could hypothesize that cytopenias developing in the context of IEC-HS would be more persistent and possibly result in clinical consequences such as infections or bleeding. **Hence, an improved understanding of cytopenias and risk of infections will guide clinical practice of infection prophylaxis and management.**

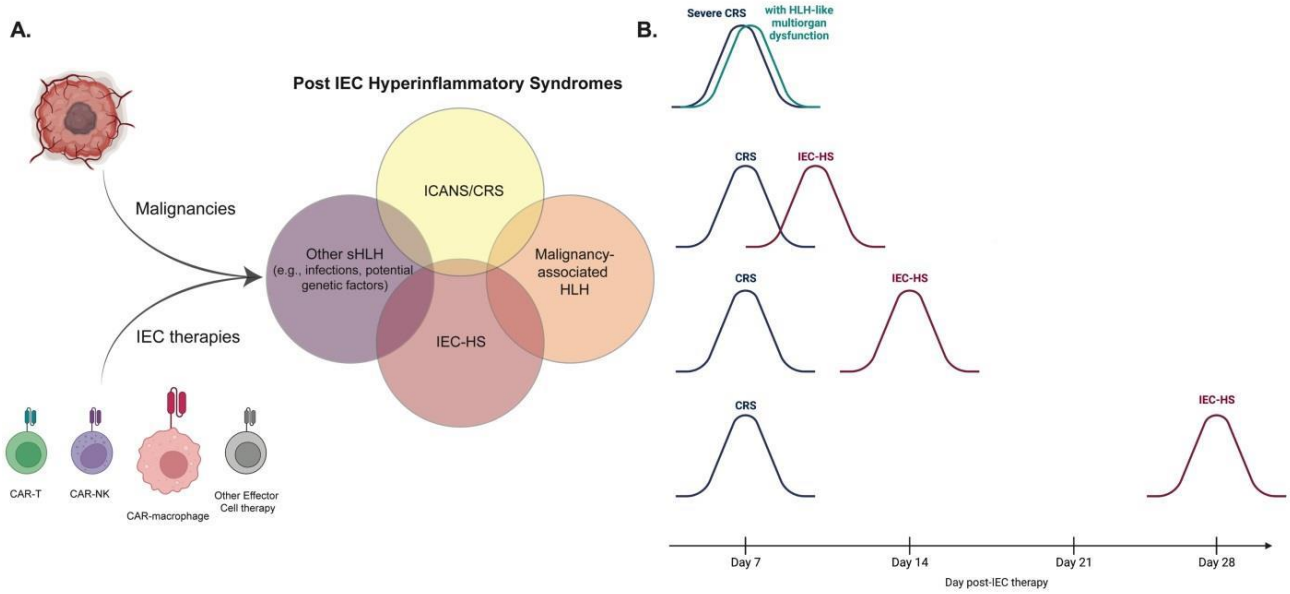
CIBMTR registry data involves data from all cellular therapy centers and is likely the most reliable resource to capture most patients who receive CAR T cell therapy. **Given that IEC-HS is expected to be a relatively rare entity, a resource such as the CIBMTR registry data would be the most optimal opportunity to evaluate the true incidence and clinical outcomes related to IEC-HS**, as well as to compare the incidence and clinical data of those with IEC-HS across disease subtypes and CAR T constructs. Hence, we hereby propose to use the CIBMTR registry data to identify patients who developed IEC-HS following CAR T cell therapy, irrespective of the product or the disease diagnosis.

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

Figure 1. IEC definitions and classifications

Definition of IEC-HS	The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis
Criteria for Identifying IEC-HS*	**Clinical/Laboratory Manifestations**
Most common manifestations†	Required: elevated ferritin (>2 × ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)
	Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS-directed therapy‡
	Hepatic transaminase elevation§ (>5 × ULN (if baseline was normal) or >5 × baseline if baseline was abnormal)
	Hypofibrinogenemia (<150 mg/dL or <LLN)‖
	Hemophagocytosis in bone marrow or other tissue‖
	Cytopenias (new onset, worsening, or refractory¶)
Other manifestations that may be present	Lactate dehydrogenase elevations (>ULN)
	Other coagulation abnormalities (eg, elevated PT/PTT)
	Direct hyperbilirubinemia
	New-onset splenomegaly
	Fever (new# or persistent)‖
	Neurotoxicity
	Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, pulmonary edema)
	Renal insufficiency (new onset)
	Hypertriglyceridemia (fasting level, >265 mg/dL‖)

Figure 2. Biology and correlation of timing of IEC-HS and CRS



PATIENT ELIGIBILITY POPULATION:

For the primary analysis, we will include all adult and pediatric patients who received CAR T cell therapy for any hematological malignancy using a commercially available or an investigational product (within the limits of protocol allowance) and reported as having developed IEC-HS (or CAR-HLH or MAS). If the exploratory analysis is permitted, we will include all CAR T recipients with peak ferritin of 3000 ng/mL for additional data collection.

DATA REQUIREMENTS:

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

Patient and disease details:

-age/sex
-race/ethnicity
-diagnosis (BCL, multiple myeloma, ALL)
-subtype (transformed FL, double-hit BCL, triple-hit BCL, MCL, Ph Positive B-ALL, Ph negative B-ALL, MM)
-number of prior lines of therapy
-prior CNS disease involvement
-current active CNS involvement
-prior autologous stem cell transplantation (yes/no)
-days from prior autologous transplant
-prior allogeneic stem cell transplantation (yes/no)
-days from prior allogeneic transplant (4101-R1 #11)
-baseline organ dysfunction (yes/no)
-if yes, which organ dysfunction
-cellular therapy comorbidity index (CT-CI) if available

-baseline (pre-lymphodepletion chemotherapy) counts (ANC, WBC, ALC, HGB, PLT)
-baseline marrow blast percentage (for B-ALL)
-Baseline inflammatory markers and markers of cellular turnover (CRP, Ferritin, LDH)
- Disease burden prior to CAR T-cell (progressive /relapsed disease, CR, responding to bridging)

CAR T details:

-product name
-was the product a clinical trial product (4000 R10 #8)
-Was the entire product infused ? (4006 R6, #7)
-Did the recipient receive a subsequent infusion ? (4101-R1 #4)
-Any prior engineered T cell therapy
-lymphodepletion chemotherapy
-time from diagnosis
-cell dose, viability, percent of genetically modified cells, and was target percent of genetically modified cells achieved (if available)
-bridging therapy (yes/no)
-type of bridging therapy
-disease status at the time of CAR (active disease or CR)
-Therapy given for the prevention of CRS, if any
-Therapy given for prevention of neurotoxicity (ICANS), if any

Outcomes details:

-peak ferritin
-days from CAR T to peak ferritin
-peak C-reactive protein
-days from CAR T to peak C-reactive protein
-peak IL-6 (if available)
-onset, duration and severity of CRS
-treatment used for CRS
-onset, duration and severity of ICANS
-treatment used for ICANS
-duration of hospitalization
-ICU transfer (yes/no)
-duration of ICU stay
-was IEC-HS (or HLH/MAS) diagnosed? (form 4101-R1 #68)
-features related to HLH/MAS (Form 4100 R8.0#110-120)
-Specific therapy given for MAS/HLH-like toxicity (form 4100 R9 #70)
-Soluble IL2Ralpha level
-organ involvement (hepatic, pulmonary, renal, coagulopathy)
-fibrinogen levels
-triglyceride levels if available
-was IEC-HS or HLH/MAS treated? (yes/no)
-treatment used for IEC-HS or HLH/MAS
-overall response of IEC-HS or HLH/MAS
-days to ANC recovery from CAR T (4101-R1 #16, 29)

-days to platelet recovery from CAR T (4101-R1 #20, 23)
-Blood counts available post-CAR T (WBC, ANC, ALC, HGB, PLT)
-transfusions of PRBCs
-transfusion of platelets
-use of growth factors
-use of TPO-RA/stem cell boost/other treatments for cytopenias
-infections complications post CAR T
-type of infection(s)
-bleeding complications
-severity of bleeding complication
-nadir fibrinogen levels
-use of cryoprecipitate/FFP
-peak liver enzymes
-peak creatinine
-disease response (best)
-disease response day 30
-relapse/progression
-death/survival/last follow up
-cause of death (will evaluate if IEC-HS related or not)
-Duration of hospitalization requirement (Form 4100 R8.0 #204-205)
-Persistence of CAR T-cells, if available (Form 4100 R8.0 #44-68)

SAMPLE REQUIREMENTS: Not applicable
If the study requires biologic samples from the NMDP Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology; 2) A summary of the investigator's previous experience with the proposed assay systems; 3) A biosketch or brief curriculum vitae documenting experience in the laboratory methods proposed.

STUDY DESIGN:
We will evaluate the reported incidence of IEC-HS in the overall CAR T cohort. We will use descriptive statistics to describe the characteristics and treatment-specific outcomes of patients who develop IEC-HS. We will evaluate for clinical outcomes including overall response rate, cumulative incidence of non-relapse mortality and relapse, progression-free survival at 2 years, and overall survival at 2 years in patients with reported IEC-HS. Kaplan Meier curves will be used to depict survival outcomes. Cox proportional hazards will be used to evaluate factors associated with the development of IEC-HS and the severity of cytopenias.

If the patient number allows for the exploratory outcome, we will use ferritin of 3000 ng/mL as screening and then evaluate patients who meet 2 of the following criteria using additional data (refer to **Table 1**) for evaluation of IEC-HS patients. Using this "post-hoc diagnosed IEC-HS cohort, we will identify the actual incidence of IC-HS using defined criteria and clinical outcomes in this post-hoc cohort.

Table 1: Case Definition of IEC-HS:

Patients must experience a ferritin of >1000 ng/ml and least **2** of the following supportive criteria:	Form 4100 R9.0 #176 and 177 (maximum ferritin and date of maximum ferritin)
Onset of symptoms with resolving/resolved CRS or worsening inflammatory response	**Form 4100 R9.0 Question #67-68**

after initial improvement with CRS-directed therapies	
Hepatic transaminase (AST/ALT) elevation ≥ Grade 3	**Form 4100 R8.0 #182 or 189**
Hypofibrinogenemia (<150 mg/dL)	**Form 4100 R8.0 # 115**
Cytopenias (new onset, worsening, or refractory)	**Form 4100 R8.0 #16-24**
Hemophagocytosis in bone marrow or other tissue	**Form 4100 R8.0 # 113**
Elevated bilirubin levels	**Form 4100 R9.0 #156**
Splenomegaly	**Form 4100 R9.0 #72**
Neurotoxicity	**Form 4100 R8.0 #121**
Pulmonary Manifestations (hypoxia, pulmonary infiltrates, pulmonary edema)	**Form 4100 R9.0 #156 or #163 (Grade 3 or 4 pulmonary edema or respiratory failure)**
Renal insufficiency	**Form 4100 R9.0 #156 or #163 (Grade 3 or 4 acute kidney injury)**
Hypertriglyceridemia	**Form 4100 R9.0 #77 and 78**

NON-CIBMTR DATA SOURCE: Not applicable

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; 3) A list of the data elements available in both data sources that will be used to link the CIBMTR record with the external record; 4) The methodology used to link the datasets.

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Population characteristics for patients who underwent CAR-T, stratified by known IEC-HS

Characteristic	No	Yes
No. of patients	8338	143
No. of centers	203	65
Patient related		
Level Age at CT Treatment - median (min-max)	62.6 (0.5-91.2)	57.4 (4.4-82.7)
Recipient Sex - no. (%)		
Male	5220 (62.6)	92 (64.3)
Female	3115 (37.4)	51 (35.7)
Missing	3 (0.0)	0 (0.0)
Ethnicity - no. (%)		
Hispanic or Latino	1109 (13.3)	21 (14.7)
Non Hispanic or non-Latino	6359 (76.3)	96 (67.1)
Non-resident of the U.S.	634 (7.6)	22 (15.4)
Unknown	235 (2.8)	4 (2.8)
Missing	1 (0.0)	0 (0.0)
Recipient race - no. (%)		
White	6388 (76.6)	91 (63.6)
Black or African American	558 (6.7)	12 (8.4)
Asian	374 (4.5)	8 (5.6)
Native Hawaiian or other Pacific Islander	14 (0.2)	0 (0.0)
American Indian or Alaska Native	30 (0.4)	1 (0.7)
Other	58 (0.7)	4 (2.8)
More than one race	432 (5.2)	14 (9.8)
Missing	484 (5.8)	13 (9.1)
CT-CI - no. (%)		
0	2538 (30.4)	48 (33.6)
1	1680 (20.1)	25 (17.5)
2	1181 (14.2)	17 (11.9)
3+	2872 (34.4)	51 (35.7)
TBD	35 (0.4)	1 (0.7)
Not reported	32 (0.3)	1 (0.7)
Karnofsky performance score prior to CT - no. (%)		
90-100	3655 (43.8)	28 (19.6)
80	2526 (30.3)	45 (31.5)
< 80	1508 (18.1)	55 (38.5)
Not reported	649 (7.8)	15 (10.5)
Patient had a prior ALLO HCT - no. (%)		

Characteristic	No	Yes
No	7252 (87.0)	117 (81.8)
Yes	1086 (13.0)	26 (18.2)
Patient had a prior AUTO HCT - no. (%)		
No	5956 (71.4)	106 (74.1)
Yes	2382 (28.6)	37 (25.9)
Total number of lines of therapy received - no. (%)		
1	341 (4.1)	0 (0.0)
2	1729 (20.7)	20 (14.0)
3	3777 (45.3)	75 (52.4)
Not reported	2491 (29.9)	48 (33.6)
Serum ferritin value known prior to infusion - no. (%)		
No	6528 (78.3)	108 (75.5)
Yes	1810 (21.7)	35 (24.5)
C-Reactive protein value known prior to infusion - no. (%)		
No	6523 (78.2)	106 (74.1)
Yes	1815 (21.8)	37 (25.9)
LDH value known prior to infusion - no. (%)		
No	3117 (37.4)	33 (23.1)
Yes	5221 (62.6)	110 (76.9)
C-reactive protein reported at follow-up- no. (%)		
No	1058 (12.7)	11 (7.7)
Yes	7280 (87.3)	132 (92.3)
Total serum ferritin - no. (%)		
No	939 (11.3)	8 (5.6)
Yes	7399 (88.7)	135 (94.4)
Disease Related		
Disease - no. (%)		
Acute lymphoblastic leukemia (ALL)	1102 (13.2)	30 (21.0)
Non-Hodgkin lymphoma (NHL)	5892 (70.7)	95 (66.4)
Plasma cell disorder/multiple myeloma (PCD/MM)	1300 (15.6)	17 (11.9)
Not reported	44 (0.5)	1 (0.7)
Cellular Therapy Related		
Product - no. (%)		
Kymriah	2001 (24.0)	43 (30.1)
Yescarta	3675 (44.1)	50 (35.0)
Tecartus	822 (9.9)	20 (14.0)
Breyanzi	527 (6.3)	13 (9.1)
Abecma	1005 (12.1)	10 (7.0)

Characteristic	No	Yes
Carvykti	308 (3.7)	7 (4.9)
Was the entire volume of product infused? - no. (%)		
No	145 (1.7)	3 (2.1)
Yes	8147 (97.7)	140 (97.9)
Not reported	46 (0.6)	0 (0.0)
Total number of CT infusion(s) - no. (%)		
1	7929 (95.1)	138 (96.5)
2	348 (4.2)	5 (3.5)
3	44 (0.5)	0 (0.0)
4	12 (0.1)	0 (0.0)
5	5 (0.1)	0 (0.0)
Therapy given for the prevention of CRS - no. (%)		
No	5908 (70.9)	123 (86.0)
Yes	661 (7.9)	13 (9.1)
Not reported	1769 (21.2)	7 (4.9)
Therapy given for neurotoxicity (during follow-up for this CT) - no. (%)		
No	353 (4.2)	5 (3.5)
Yes	2646 (31.7)	87 (60.8)
Not reported	5339 (64.0)	51 (35.7)
Time from initial diagnosis to CT, months - median (min-max)	22.3 (0.2-446.2)	16.4 (1.6-214.1)
Lymphodepleting regimen - no. (%)		
Yes	8324 (99.8)	143 (100)
Bendamustine	704 (8.4)	13 (9.1)
Bendamustine + Cyclophosphamide	1 (0.0)	0 (0.0)
Bendamustine + Cyclophosphamide + Fludarabine	2 (0.0)	0 (0.0)
Bendamustine + Cytarabine	1 (0.0)	0 (0.0)
Bendamustine + Other	26 (0.3)	0 (0.0)
Carboplatin + Fludarabine	2 (0.0)	0 (0.0)
Clofarabine + Fludarabine	1 (0.0)	0 (0.0)
Cyclophosphamide	48 (0.6)	0 (0.0)
Cyclophosphamide + Cytarabine + Fludarabine	1 (0.0)	0 (0.0)
Cyclophosphamide + Cytarabine + Fludarabine + Other	1 (0.0)	0 (0.0)
Cyclophosphamide + Etoposide	1 (0.0)	0 (0.0)
Cyclophosphamide + Fludarabine	7325 (87.9)	128 (89.5)
Cyclophosphamide + Fludarabine + Other	9 (0.1)	0 (0.0)
Cyclophosphamide + Gemcitabine	1 (0.0)	0 (0.0)
Cyclophosphamide + Melphalan	1 (0.0)	0 (0.0)
Cyclophosphamide + Other	57 (0.7)	0 (0.0)

Characteristic	No	Yes
Cyclophosphamide + Thiotepa	1 (0.0)	0 (0.0)
Cytarabine + Etoposide	4 (0.0)	0 (0.0)
Cytarabine + Fludarabine	16 (0.2)	0 (0.0)
Etoposide + Other	1 (0.0)	0 (0.0)
Fludarabine	38 (0.5)	1 (0.7)
Other	10 (0.1)	0 (0.0)
None specified	73 (0.9)	1 (0.7)
No	13 (0.2)	0 (0.0)
None specified	1 (0.0)	0 (0.0)
Bridging therapy - no. (%)		
No	3858 (46.3)	40 (28.0)
Yes	3457 (41.5)	83 (58.0)
Not reported	1023 (12.3)	20 (14.0)
Year of CT - no. (%)		
2017	6 (0.1)	0 (0.0)
2018	278 (3.3)	0 (0.0)
2019	555 (6.7)	1 (0.7)
2020	1035 (12.4)	11 (7.7)
2021	2076 (24.9)	42 (29.4)
2022	3269 (39.2)	56 (39.2)
2023	1119 (13.4)	33 (23.1)
Follow-up of survivors - median (range)	12.5 (0.5-69.4)	11.1 (1.5-30.4)

Note: This data will become available in 2 years (or with company approval) after the end of the data embargo. With this embargo applied, we currently have 5931 patients without IEC-HS and 93 with IEC-HS eligible.

Field	Response
Proposal Number	2310-160-REJESKI
Proposal Title	Determinants of Immune Effector Cell-Associated Hematotoxicity (ICAHT) following CAR-T therapy across Disease Entities
Key Words	hematotoxicity, prediction, large B-cell lymphoma, CAR-T
Principal Investigator #1: - First and last name, degree(s)	Kai Rejeski, MD PhD
Principal Investigator #1: - Email address	k.rejeski@gmail.com
Principal Investigator #1: - Institution name	Memorial Sloan Kettering Cancer Center
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
Principal Investigator #2 (If applicable): - First and last name, degree(s):	Roni Shouval, MD PhD
Principal Investigator #2 (If applicable): - Email address:)	shouval@gmail.com
Principal Investigator #2 (If applicable): - Institution name:	Memorial Sloan Kettering Cancer
Principal Investigator #2 (If applicable): - Academic rank:	Assistant Attending
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	No
We encourage a maximum of two Principal Investigators per study. If more than one author is listed, please indicate who will be identified as the corresponding PI below:	Roni Shouval
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	RT19-01: RS is the PI for a study on the interaction between comorbidities, conditioning regimens, and outcomes in patients receiving an allogeneic hematopoietic cell transplantation. LY22-02: RS is an investigator in a study on CAR-T outcomes in rare lymphoma subtypes.
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Infection and Immune Reconstitution
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No

Field	Response
RESEARCH QUESTION:	i) Can we identify predictive markers for immune effector cell-associated hematotoxicity (ICAHT) at time of leukapheresis and lymphodepletion in patients treated with CD19- and BCMA-directed chimeric antigen receptor T-cells (CAR-T)? ii) Is the CAR-HEMATOTOX score a valid tool to determine the risk of hematotoxicity in CAR-T recipients? iii) What is the comparative incidence of early and late ICAHT across disease entities and comparing treatment lines (e.g. third or further line vs. second line)? iv) What are the clinical implications of severe hematotoxicity in regards to infections, nonrelapse mortality and treatment outcomes?
RESEARCH HYPOTHESIS:	Baseline (pre-CAR-T) patient-, disease-, and treatment-related features are predictive of hematological toxicities in patients treated with CAR-T therapy.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary outcome: ICAHT grades according to novel EHA/EBMT consensus grading (Rejeski et al. Blood 2023).1 Secondary outcomes: Hematotoxicity: Phenotypes of neutrophil recovery (quick vs. intermittent vs. aplastic as defined in Rejeski et al. Blood 2021),2 CTCAE Grading of Cytopenia (v5.0), Transfusion use (pRBC, platelets) Other: Infection rate, nonrelapse mortality, overall response, overall survival, progression-free survival
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Hematotoxicity stands as one of the primary complications associated with CAR-T cell therapy. The extent of hematotoxicity resulting from CAR-T therapy carries implications for infection risk, quality of life, and the patients' ability to undergo subsequent treatments post-CAR-T. The success of our proposal, which centers around hematotoxicity, could facilitate the following: 1. Risk stratification of hematotoxicity in patients with LBCL/MM treated with CAR-T. 2. The design of clinical trials and risk-adapted interventions for supportive therapies such as G-CSF and anti-infective prophylaxis. 3. The identification of ultra-high-risk candidates during leukapheresis, necessitating prophylactic stem cell collection for the safe administration of CAR-T. 4. Patient counseling regarding expected incidence rates across different disease entities.

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.	Autologous CD19 and BCMA CAR T-cells represent a practice-changing immunotherapy platform for multiple advanced B-cell malignancies (e.g. LBCL, MM, MCL, FL, BCP-ALL).3-8 While response rates have been encouraging, CAR-T is associated with a unique side effect profile that imposes a considerable burden on patients with potentially long-lasting sequelae and reduced quality of life. We and others have attempted first forays into risk modeling CAR-T toxicity, including modified versions of the EASIX score for the prediction of neurotoxicity and CRS (Pennisi and Greenbaum et al, Blood Adv 2021)9,10 and the CAR-HEMATOTOX score for predicting hematotoxicity and infections across several disease entities (Rejeski et al. Blood 2021; JITC 2022; Hemasphere 2023; JHO 2023; AJH 2023).11-15 However, these models are hampered by their low positive predictive value and are currently not broadly implemented to guide decisions in clinical routine – particularly in regard to G-CSF and anti-infective use. As a result, there is a critical need to understand what factors govern CAR-T related hematological toxicity. Hematologic toxicity represents the most common CTCAE grade 3 or higher side effect within the first year following CAR-T infusion.16 Profound neutropenia can predispose for severe infections, which represent the main determinant of non-relapse mortality in cell therapy patients.11 Cytopenias are also often long-lasting, lasting weeks to months, and can be biphasic in nature (e.g. recurrent neutrophil dips).17 In previous work, we established that there are three typical trajectories of neutrophil recovery following CAR-T infusion: quick vs. intermittent vs. aplastic (Fig. 1a).12,14,15,18 The aplastic phenotype in particular, remains clinically challenging and is closely associated with infectious complications and poor treatment outcomes (Fig 1b).18 In contrast, a phenotype characterized by recurrent neutrophil dips (“intermittent”) was associated with excellent treatment outcomes, high CAR-T expansion/persistence and decreasing systemic inflammation over time. Recently, an international survey of >50 CAR-T centers across 18 countries was performed to better understand current management of hematotoxicity – demonstrating a high degree of heterogeneity in terms of current grading and highly variable management practices.19 For this reason, an international panel of experts from EHA and EBMT convened to define Immune Effector Cell-Associated Hematotoxicity (ICAHT) as a distinct toxicity category of cell therapy and to issue best practice recommendations (Rejeski et al, Blood 2023).1 The novel grading separates early (day 0-30) vs. late ICAHT (beyond day +30) (Fig. 1c). Importantly, early

Field	Response
	ICAHT incorporates not only depth but also duration of neutropenia, which is based on the rationale that this represents the main driver of infection risk and is clinically more relevant than current CTCAE criteria.20,21 By clearly defining severity grades of ICAHT, the panel was able to issue severity-based recommendations for both the diagnostic work-up and management of ICAHT (Fig. 1d). Our preliminary results highlight the clinical importance of ICAHT and point towards close interactions between host hematopoiesis and CAR-T function and efficacy. While the EHA/EBMT consensus grading represents a first blueprint to examine the true severity of ICAHT using a unified nomenclature, the comparative incidence across disease entities and CAR products remains unclear. Furthermore, the clinical relevance of ICAHT in regards to infections, transfusion use and treatment outcomes is still ill-defined. Therefore, a larger registry analysis could better define whether reporting of ICAHT grades should be mandidatory in clinical trials examining novel CAR products in new indications. Figure 1. Immune Effector Cell-Associated Hematotoxicity (ICAHT) as a distinct toxicity category of cell therapy. (A) Three typical trajectories of neutrophil recovery are observed following CAR-T therapy: quick vs. intermittent vs. aplastic. The externally validated CAR-HEMATOTOX score incorporates factors associated with pre-lymphodepletion hematopoietic reserve (e.g. ANC, platelet count, hemoglobin) and inflammatory state (e.g. ferritin, CRP) to predict patients at high risk for hematological toxicity. The model identifies patients with a high risk for severe neutropenia ≥14 days (“aplastic“ phenotype: 40% vs. 2%). (B) The phenotypes of neutrophil recovery are associated with survival outcomes in a cohort of 344 patients treated with Axi-cel or Tisa-cel for R/R LBCL in a real-world setting. (C) The new EHA/EBMT consensus grading for early (day 0-30) vs. late (after day 30) ICAHT. (D) The grading system enables first severity-based recommendations for diagnostic work-up and management of ICAHT.
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Id	F_4ZmQ762QpQRfyTf
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Name	Heme Tox Figure.jpg
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Size	5139958
SCIENTIFIC JUSTIFICATION: If applicable, upload graphic as a single file (JPG, PNG, GIF) - Type	image/jpeg

Field	Response
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Adult patients (age ≥ 18 years of age) who underwent 1st infusion of commercially available CAR-T (Axi-cel, Tisa-cel, Liso-cel, Ide-cel, Cilta-cel, Brexu-cel) for advanced B-cell malignancies (large B-cell lymphoma [LBCL], follicular lymphoma [FL], B-cell precursor acute lymphoblastic leukemia [BCP-ALL], mantle cell lymphoma [MCL], multiple myeloma [MM]) between 2015-2023.
Does this study include pediatric patients?	No
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient related: - Age at CAR-T treatment - Sex - Race - Ethnicity - ECOG performance status/Karnofsky performance status Disease related: - Diagnosis by WHO classification - Date of diagnosis and relapse - LDH at diagnosis and pre-CART/ASCT - Extranodal involvement - Bone marrow involvement (incl. percentage if available) - Prior lines of therapy (Form 2018/166-222) including prior SCT CART related: - Date of CAR-T - Disease status at CART: CR vs PR vs SD vs PD - CAR-T product (clinical trial/SOC; within/outside specification; cell dose) - Bridging therapy pre-CART: yes/no - Lymphodepleting drugs and dose - Any concomitant therapy with CART Hematotoxicity Endpoints: - Early/Late ICAHT Grading (Rejeski et al. Blood 2023) - CTCAE Grading Cytopenia (Neutropenia, Anemia, Thrombocytopenia) - Neutrophil Recovery Phenotype (Rejeski et al. Blood 2021) - Date of neutrophil/platelet recovery relative to CART infusion - Tranfusion Use (pRBC and PLT) - G-CSF Use - Thrombopoietin Receptor Agonist Use (e.g. Eltrombopag, Romiplostim) - Stem Cell Boost Use Follow-up: - Patient status at D100, 6 months, 1 year and last contact - Best objective response (CR/PR/SD/PD) - Maximum CRS grade (CAR-T only) - Maximum ICANS grade (CAR-T only) - Infections day 0-90 - Infections after day 90 - Date of disease relapse /progression - Cause of death
PATIENT REPORTED OUTCOME (PRO) REQUIREMENTS: If the study requires PRO data collected by CIBMTR, the proposal should include: 1) A detailed description of the PRO domains, timepoints, and proposed analysis of PROs; 2) A desc	N/A

Field	Response
MACHINE LEARNING: Please indicate if the study requires methodology related to machine-learning and clinical predictions.	N/A
SAMPLE REQUIREMENTS: If the study requires biologic samples from the CIBMTR Repository, the proposal should also include: 1) A detailed description of the proposed testing methodology and sample requirements; 2) A summary o	N/A
NON-CIBMTR DATA SOURCE: If applicable, please provide: 1) A description of external data source to which the CIBMTR data will be linked; 2) The rationale for why the linkage is required.	N/A

REFERENCES:	1. Rejeski K, Subklewe M, Aljurf M, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142(10):865-877. 2. Stein-Thoeringer CK, Saini NY, Zamir E, et al. A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy. Nat Med. 2023. 3. Rejeski K, Jain MD, Smith EL. Mechanisms of Resistance and Treatment of Relapse after CAR T-cell Therapy for Large B-cell Lymphoma and Multiple Myeloma. Transplant Cell Ther. 2023. 4. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-654. 5. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. J Clin Oncol. 2022:JCO2200842. 6. Wang M, Munoz J, Goy A, et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. J Clin Oncol. 2022:JCO2102370. 7. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103. 8. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491-502. 9. Pennisi M, Sanchez-Escamilla M, Flynn JR, et al. Modified-EASIX predicts severe cytokine release syndrome and neurotoxicity after Chimeric Antigen Receptor (CAR) T cells. Blood Adv. 2021. 10.Greenbaum U, Strati P, Saliba RM, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021;5(14):2799-2806. 11. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. J Immunother Cancer. 2022;10(5). 12. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499-2513. 13. Rejeski K, Blumenberg V, Iacoboni G, et al. Identifying Early Infections in the Setting of CRS With Routine and Exploratory Serum

Field	Response
	Proteomics and the HT10 Score Following CD19 CAR-T for Relapsed/Refractory B-NHL. Hemasphere. 2023;7(4):e858. 14. Rejeski K, Hansen DK, Bansal R, et al. The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma. J Hematol Oncol. 2023;16(1):88. 15. Rejeski K, Wang Y, Albanyan O, et al. The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene autoleucel for relapsed or refractory MCL. Am J Hematol. 2023. 16. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. Blood Adv. 2020;4(13):3024-3033. 17. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant. 2019;54(10):1643-1650. 18. Rejeski K, Perez A, Iacoboni G, et al. Severe hematotoxicity after CD19 CAR-T therapy is associated with suppressive immune dysregulation and limited CAR-T expansion. Sci Adv. 2023;9(38):eadg3919. 19. Rejeski K, Greco R, Onida F, et al. An International Survey on Grading, Diagnosis, and Management of Immune Effector Cell-Associated Hematotoxicity (ICAHT) Following CAR T-cell Therapy on Behalf of the EBMT and EHA. Hemasphere. 2023;7(5):e889. 20. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36(14):1443-1453. 21. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol. 2018;36(30):3043-3054.
CONFLICTS OF INTEREST: Do you have any conflicts of interest pertinent to this proposal concerning?	Yes, I have conflicts of interest pertinent to this proposal
If yes, provide detail on the nature of employment, name of organization, role, entity, ownership, type of financial transaction or legal proceeding and whether renumeration is >$5000 annually.	K.R. Kite/Gilead: Research Funding, Consultancy, Honoraria and travel support; Novartis: Honoraria; BMS/Celgene: Consultancy, Honoraria; Pierre-Fabre: travel support. Renumeration <5000 Dollars.

Population characteristics for adult patients who underwent 1st infusion of commercial CAR-T for B-cell lymphoma between 2015-2023

Characteristic	N (%)
No. of patients	8294
No. of centers	168
Patient related	
Level Age at CT Treatment - median (min-max)	64.4 (18.0-91.2)
Recipient Sex - no. (%)	
Male	5329 (64.3)
Female	2963 (35.7)
NA	2 (0.0)
Ethnicity - no. (%)	
Hispanic or Latino	834 (10.1)
Non-Hispanic or non-Latino	6510 (78.5)
N/A - Not a resident of the U.S.	683 (8.2)
Unknown	266 (3.2)
Not reported	1 (0.0)
Recipient race - no. (%)	
White	6454 (77.8)
African-American	418 (5.0)
Asian	416 (5.0)
Pacific Islander	12 (0.1)
Native American	30 (0.4)
More than one race	37 (0.4)
Unknown	415 (5.0)
Not reported	512 (6.2)
CT-CI - no. (%)	
0	2490 (30.0)
1	1681 (20.3)
2	1136 (13.7)
3+	2896 (34.9)
TBD, unclear lineage of prior hematologic malignancies	28 (0.3)
TBD, inconsistencies between parent and child-questions	5 (0.1)
Not reported	58 (0.7)
Karnofsky performance score prior to CT - no. (%)	
90-100	3307 (39.9)
80	2531 (30.5)

Characteristic	N (%)
< 80	1644 (19.8)
Not reported	812 (9.8)
Prior HCT - no. (%)	
No	6471 (78.0)
Yes	1804 (21.8)
Unknown	2 (0.0)
Not reported	17 (0.2)
Total number of lines of therapy received - no. (%)	
1 line	517 (6.2)
2 lines	2397 (28.9)
3+ lines	5321 (64.2)
Not reported	59 (0.7)
Serum ferritin prior to infusion (ng/mL) - no. (%)	
< 650	1267 (15.3)
650-1999	326 (3.9)
>= 2000	96 (1.2)
Not reported	6605 (79.6)
C-Reactive protein prior to infusion (mg/dL) - no. (%)	
< 3	1278 (15.4)
>= 3	378 (4.6)
Not reported	6638 (80.0)
ANC per µL - no. (%)	
< 1200	453 (5.5)
>= 1200	4753 (57.3)
Not reported	3088 (37.2)
Platelet count (G/L) - no. (%)	
< 75	579 (7.0)
75-174	2145 (25.9)
>= 175	2582 (31.1)
Not reported	2988 (36.0)
Hemoglobin (g/dL) - no. (%)	
< 9.0	767 (9.2)
>= 9.0	4656 (56.1)
Not reported	2871 (34.6)
Neutrophil recovery (ANC >= 500/mm^3 achieved and sustained for 3 lab values) (at 100-day reporting) - no. (%)	
Known	7006 (84.5)
Unknown	1288 (15.5)

Characteristic	N (%)
Disease related	
Disease Type - no. (%)	
Large B-cell lymphoma	6945 (83.7)
Follicular lymphoma	613 (7.4)
Mantle cell lymphoma	736 (8.9)
Disease status at infusion - no. (%)	
PIF	3284 (39.6)
CR1	115 (1.4)
CR2	259 (3.1)
CR3+	137 (1.7)
REL1	2401 (28.9)
REL2	1372 (16.5)
REL3	687 (8.3)
Untreated	32 (0.4)
Not reported	7 (0.1)
Cellular Therapy Related	
Product - no. (%)	
Kymriah	1489 (18.0)
Yescarta	5326 (64.2)
Tecartus	728 (8.8)
Breyanzi	751 (9.1)
Time from initial diagnosis to CT, months - median (min-max)	15.4 (0.8-446.2)
Lymphodepleting regimen - no. (%)	
Yes	8284 (99.9)
Bendamustine	702 (8.5)
Bendamustine + Cyclophosphamide	1 (0.0)
Bendamustine + Cyclophosphamide + Fludarabine	2 (0.0)
Bendamustine + Cytarabine	1 (0.0)
Bendamustine + Other	26 (0.3)
Carboplatin + Fludarabine	2 (0.0)
Cyclophosphamide	30 (0.4)
Cyclophosphamide + Cytarabine + Fludarabine	1 (0.0)
Cyclophosphamide + Fludarabine	6921 (83.4)
Cyclophosphamide + Fludarabine + Other	14 (0.2)
Cyclophosphamide + Melphalan	1 (0.0)
Cyclophosphamide + Other	32 (0.4)
Cytarabine + Fludarabine	17 (0.2)

Characteristic	N (%)
Etoposide + Other	1 (0.0)
Fludarabine	33 (0.4)
Other	22 (0.3)
None specified	478 (5.8)
No	10 (0.1)
Bridging therapy - no. (%)	
No	3916 (47.2)
Yes	2966 (35.8)
Not reported	1412 (17.0)
Year of CT - no. (%)	
2017	5 (0.1)
2018	479 (5.8)
2019	948 (11.4)
2020	1182 (14.3)
2021	1610 (19.4)
2022	2210 (26.6)
2023	1860 (22.4)
Follow-up of survivors - median (range)	13.0 (0.5-62.3)

Note: This data will become available in 2 years (or with company approval) after the end of the data embargo. With this embargo applied, we currently have 7098 patients eligible.

Field	Response
Proposal Number	2310-173-KHAN
Proposal Title	Return to work among adolescent and young adult survivors of autologous stem cell transplantation in the US
Key Words	survivorship, adolescent and young adult, AYA
Principal Investigator #1: - First and last name, degree(s)	Niloufer Khan, MD, MSCE
Principal Investigator #1: - Email address	nikhan@coh.org
Principal Investigator #1: - Institution name	City of Hope
Principal Investigator #1: - Academic rank	Assistant Professor
Junior investigator status (defined as ≤5 years from fellowship)	Yes
Do you identify as an underrepresented/minority?	Yes
If you are a junior investigator and would like assistance identifying a senior mentor for your project please click below:	Yes, I am a junior investigator and would like assistance identifying a senior mentor for my project
Please list any ongoing CIBMTR projects that you are currently involved in and briefly describe your role.	NA
Do any of the PI(s) within this proposal have a CIBMTR WC study in manuscript preparation >6 months?	No
PROPOSED WORKING COMMITTEE:	Morbidity, Recovery and Survivorship
Please indicate if you have already spoken with a scientific director or working committee chair regarding this study.	No
RESEARCH QUESTION:	What patient, disease, and transplant related factors are associated with not returning to work after autologous HCT?
RESEARCH HYPOTHESIS:	We hypothesize that gender, pre-transplant educational attainment and pre-transplantation comorbidities may be associated with a lower rate of return to work after autologous stem cell transplantation.
SPECIFIC OBJECTIVES/OUTCOMES TO BE INVESTIGATED (Include Primary, Secondary, etc.):	Primary outcome: Percentage of patients who have returned to work (full or part time) vs unemployed (unemployed or claiming medical disability) at 1 year after autoSCT Secondary outcomes: Patient-related factors associated with unemployment at 1 year after autoSCT Disease-related factors associated with unemployment at 1 year after autoSCT Transplant-related factors associated with unemployment at 1 year after autoSCT

Field	Response
SCIENTIFIC IMPACT: Briefly state how the completion of the aims will impact participant care/outcomes and how it will advance science or clinical care.	Financial toxicity refers to the negative effects of the cost of cancer treatment on a person's quality of life (Hussaini, Gupta, and Dusetzina 2022). More than one-third of cancer patients experience financial toxicity. This results in increased risk for asset depletion, medical debt, and high levels of finance-related anxiety, worry, and stress (Tangka et al. 2010; Yabroff et al. 2016; Azzani, Roslani, and Su 2015). Severe financial distress is associated with earlier mortality in long-term cancer survivors (Azzani, Roslani, and Su 2015; Ramsey et al. 2016). Disparities also exist among cancer survivors, with non-white patients significantly more likely to bear a financial burden and be denied subsequent insurance due to cancer when compared to white patients (Panzone et al. 2022). Acknowledging and measuring the financial toxicity of treatment is a critical component of care for cancer survivors. Adolescent and young adult (AYA) patients, defined as patients aged 15-39 years at diagnosis (Sankaran et al. 2022), are particularly vulnerable to financial toxicity. They are diagnosed with cancer at a formative time in their lives, during transition from childhood to adulthood, and are likely to have fewer assets than older patients (Carrera, Kantarjian, and Blinder 2018). They may need to interrupt their careers or education to undergo treatment, hampering their earning capability later in life (Meernik et al. 2021; Kirchhoff et al. 2010). US health insurance is often linked to employment, and unemployment can affect AYA survivors' ability to seek health insurance in the future (Smith et al. 2013). Identification of barriers to employment and risks for unemployment among AYA survivors is a critically important and understudied component of understanding financial toxicity in this population.

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.	Autologous stem cell transplant is a key treatment modality for many hematologic malignancies, including Hodgkin lymphoma which has a peak incidence among the AYA population. With advances in diagnosis and treatment, survival among patients with HL has greatly improved, with cure rates exceeding 95% in early-stage disease. For the approximately 20% of patients who relapse, remission can be achieved in more than 70% if patients have access to salvage therapies, which involve combination chemotherapy followed by autologous stem-cell transplant (Cole et al. 2017; LaCasce et al. 2018; Moskowitz et al. 2021) Late effects of older high-intensity salvage therapy include negative impacts on quality of life, specifically in the domains of social and cognitive functioning, as well as fatigue, insomnia, and, importantly, financial problems (Goodman et al. 2007). For AYAs with HL specifically, population-based and single-institution studies have previously revealed race-based health disparities, demonstrating relapse and survival disadvantages in non-white vs white patients(Evens et al. 2012; Grubb, Neboori, and Diaz 2016; Metzger et al. 2008; Khullar et al. 2020). A recent pooled analysis of Children's Oncology Group (COG) data found that when controlling for disease and treatment characteristics, these racial disparities were driven by post-relapse mortality(Kahn et al. 2019). Racial disparities in post-relapse mortality may partially reflect biologic differences, but event-free survival was found to be equivalent between non-white and white patients. It is more likely that these data reveal disparities in clinical trial enrollment, supportive care, or access to and care after salvage therapy (Majhail et al. 2012). The impact of disparities is amplified in AYA patients who undergo high-intensity treatment at a pivotal time in life, interrupting key developmental transitions and milestones (e.g., educational pursuits, graduation, workforce entry, and financial independence from parents). While disparities in treatment have been identified and described in the literature, disparities in financial toxicity and return to work have not been fully identified in this population. CIBMTR has previously led an analysis of return to work patterns in young adult survivors of allogeneic stem cell transplantation (Bhatt et al. 2021). Here, 50% of patients were unemployed or on medical disability at 1 year after HCT. Patient, disease, and transplant related characteristics were all associated with unemployment or medical disability. These factors included female sex (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.40 to 0.77), HCT Comorbidity Index score ≥3 (OR, 0.57; 95% CI, 0.39 to 0.82), pre-HCT unemployment (OR, 0.37; 95% CI, 0.24 to 0.56), medical

Field	Response
	disability (OR, 0.44; 95% CI, 0.28 to 0.70), and relapse within 1 year post-HCT (OR, 0.34; 95% CI, 0.21 to 0.56) (Bhat et al. 2021). Though these are not modifiable characteristics, they may allow providers to identify patients at risk and support effective interventions for return to work in patients with these risk factors. There is limited data on return to work after autologous stem cell transplantation, and most published studies are based at single centers with both autologous and allogeneic stem cell transplant survivors. A self-administered questionnaire study administered to patients with multiple myeloma reported that 30% of 145 patients with a full-time job at diagnosis returned to work. These patients were older than AYA patients and treated with a single (bortezomib-based) induction regimen(Granell et al. 2021). In another single center study (n = 38 autologous HCT survivors, n=159 allogeneic HCT survivors), 36% of all patients returned to work by 1 year(Kirchhoff et al. 2010). Another analysis from the Mayo Clinic reported a 62% return to work rate at 1 year post HCT among allogenic and autologous stem cell transplant survivors (Morrison et al. 2016). Given that more autologous stem cell transplants are performed annually than allogeneic stem cell transplants in the US, and that autologous stem cell transplant is a key treatment modality for Hodgkin lymphoma, a prototypical AYA cancer, understanding return to work in young adults who receive autologous stem cell transplant is critical.
PARTICIPANT SELECTION CRITERIA: State inclusion and exclusion criteria.	Inclusion: Patients who underwent autologous stem cell transplant at ages 18-39 years of age in the US for malignant conditions All conditioning regimens Timepoint: January 1, 2008 – December 31, 2020 (or most recently available) Exclusion: Patients with insufficient data Patients who were students prior to autologous stem cell transplant Patients with missing work status at all timepoints
Does this study include pediatric patients?	No
If this study does not include pediatric patients, please provide justification:	Would not be employed full time prior to autologous stem cell transplant
DATA REQUIREMENTS: After reviewing data on CIBMTR forms, list patient-, disease- and infusion- variables to be considered in the multivariate analyses. Outline any supplementary data required.	Patient-related: Age at HCT Sex Race/ethnicity pre-HCT Karnofsky Performance Status Hematopoietic Cell Transplantation Comorbidity Index [HCT-CI] pre-HCT marital status pre-HCT work status pre-HCT highest education grades work status at 6 months, 1 year, 2 years, and 3 years post transplant Disease-related: Disease type Transplant related: Regimen Year of transplantation Disease relapse

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

Characteristics of U.S. auto HCT patients at ages 18-39 years for malignant conditions (CRF retrieval up to 2020)

Characteristic	N (%)
No. of patients	862
No. of centers	111
Patient related	
Age at transplant - no. (%)	
18-24	84 (9.7)
25-29	186 (21.6)
30-34	232 (26.9)
35-39	360 (41.8)
Sex - no. (%)	
Male	472 (54.8)
Female	390 (45.2)
Race - no. (%)	
White	517 (60.0)
Black or African American	260 (30.2)
Asian	48 (5.6)
Native Hawaiian or other Pacific Islander	5 (0.6)
American Indian or Alaska Native	2 (0.2)
More than one race	7 (0.8)
Not reported	23 (2.7)
Ethnicity - no. (%)	
Hispanic or Latino	117 (13.6)
Non Hispanic or non-Latino	727 (84.3)
Non-resident of the U.S.	4 (0.5)
Not reported	14 (1.6)
Karnofsky score prior to HCT - no. (%)	
90-100%	554 (64.3)
< 90%	275 (31.9)
Not reported	33 (3.8)
HCT-CI - no. (%)	
0	295 (34.2)
1	106 (12.3)
2	158 (18.3)
3+	273 (31.7)
TBD, review needed for history of malignancies	3 (0.3)
NA, f2400 (pre-TED) not completed	26 (3.0)

Characteristic	N (%)
Missing	1 (0.1)
Marital status at transplant - no. (%)	
Single, never married	350 (40.6)
Married or living with a partner	438 (50.8)
Separated	11 (1.3)
Divorced	36 (4.2)
Widowed	1 (0.1)
Not reported	26 (3.0)
Highest level of education - no. (%)	
Primary education	3 (0.3)
Lower secondary education	32 (3.7)
Upper secondary education	271 (31.4)
Post-secondary, non-tertiary education	79 (9.2)
Tertiary education	206 (23.9)
Advanced research qualification	61 (7.1)
Unknown	20 (2.3)
Not reported	190 (22.0)
Last reported occupation - no. (%)	
Professional/technical	201 (23.3)
Manager, administrator, or proprietor	66 (7.7)
Clerical	65 (7.5)
Sales	50 (5.8)
Service	126 (14.6)
Skilled craft	85 (9.9)
Equipment/vehicle operator	39 (4.5)
Laborer	58 (6.7)
Farmer	1 (0.1)
Military	10 (1.2)
Homemaker	36 (4.2)
Not previously employed	41 (4.8)
Other	49 (5.7)
Not reported	35 (4.1)
Most recently reported work status after transplant - no. (%)	
Full time	458 (53.1)
Part time	46 (5.3)
Unemployed	158 (18.3)
Medical disability	159 (18.4)
TBD	41 (4.8)

Characteristic	N (%)
Disease related	
Primary disease - no. (%)	
Acute myelogenous leukemia	26 (3.0)
Acute lymphoblastic leukemia	6 (0.7)
Non-Hodgkin lymphoma	217 (25.2)
Hodgkin lymphoma	373 (43.3)
Plasma cell disorder, multiple myeloma	240 (27.8)
Transplant related	
Graft type in merge - no. (%)	
Bone marrow	1 (0.1)
Peripheral blood	856 (99.3)
BM + PB	3 (0.3)
PB + UCB	1 (0.1)
PB + OTH	1 (0.1)
Reported preparative regimen - no. (%)	
Myeloablative	357 (41.4)
Non-myeloablative (NST)	16 (1.9)
Reduced intensity (RIC)	7 (0.8)
Not reported	482 (55.9)
TX year - no. (%)	
2008	163 (18.9)
2009	64 (7.4)
2010	27 (3.1)
2011	36 (4.2)
2012	38 (4.4)
2013	83 (9.6)
2014	65 (7.5)
2015	81 (9.4)
2016	74 (8.6)
2017	53 (6.1)
2018	90 (10.4)
2019	72 (8.4)
2020	16 (1.9)
Follow-up of survivors - median (range)	72.3 (0.4-179.8)